Pluralism, values and context:

understanding the boundaries of plurality in scientific practices in the case of neglected tropical diseases

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I, Erman Sozudogru, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

In this thesis, I give a philosophical account of pluralities in scientific inquiry. The pluralist argument I present here is the rejection of the monist assumption that the aim of science is to provide a single, complete and coherent account of phenomena. Instead, I argue that monist assumptions must be challenged and replaced with the following pluralist tenets: there are multiple aims in science; different approaches have distinct aims, focusing on different aspects of phenomena; and each account is particular to the specific questions and aims of an approach.

Herein I focus on current efforts of the World Health Organisation to eliminate Human African Trypanosomiasis – in particular, the development of new anti-parasitic drugs. I argue that drug discovery and development requires a plurality of approaches, each focusing on different aspects of phenomena. The pluralist argument I present here is normative in the sense that scientific inquiry ought to be pluralist (instead of monistic), in which a multiplicity of accounts and approaches is necessary to explain and explore different aspects of phenomena. Moreover, I argue that the plurality of approaches and accounts employed to achieve a certain aim is bounded by pragmatic values. I argue that pragmatic values determine the best way to achieve a specific aim within the broader socio-economic and political context of scientific inquiry. In my thesis, I argue that the extent of plurality in scientific practices involved in developing new drugs to eliminate HAT must be understood with respect to the pragmatic values that define the best way to eliminate HAT in its current socio-economic and political context.

In this thesis, I provide a normative argument for pluralism, challenging monist assumptions about scientific practices and their aims. Moreover, I provide a pragmatic framework within which to understand and explain the extent of pluralities in scientific practices.

For my parents, Mukaddes and Esen

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List of Abbreviations

DNDi: Drugs for Neglected Tropical Diseases Initiative

DST: Developmental Systems Theory

HAT: Human African Trypanosomiasis

MSF: Médecins Sans Frontières

NECT: Nifurtimox-Eflornithine

NTD: Neglected Tropical Diseases

PEPFAR: President’s Emergency Plan for AIDS relief

PNLTHA: Programme National de Lutte contre la Trypanosomiase Humaine Africaine

TPP: Target Product Profile

UNDP: United Nations Development Programme

WHO: World Health Organisation

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Chapter 1

Introduction

In this thesis, I wish to provide a philosophical account of pluralities in scientific inquiry, by studying scientific practices with respect to their broader context. Using several case studies from scientific practices, I argue that multiple approaches (each with distinct aims and sets of questions) focus on multiple aspects of phenomena, providing partial accounts. Moreover, I build a normative argument for pluralism, where I argue that scientific inquiry ought to be pluralistic to explain and explore different aspects of phenomena.

The pluralist thesis I present here is motivated by the apparent pluralities in scientific practices. Herein, I follow the philosophy of science in practice approach, arguing that the subject matter of philosophy of science must include all aspects of scientific inquiry, including scientific practices and scientific accounts of the world. I argue that in order to build a philosophical account to understand scientific inquiry and scientific knowledge, it is necessary to consider scientific practices. Moreover, I argue that broadening the subject matter of philosophy of science to include scientific practices reveals that the there are multiple approaches and accounts in scientific inquiry, as well as revealing that there are multiple aims and sets of values shaping that inquiry. Herein, I argue that the apparent multiplicities in scientific practices are an important characteristic of scientific inquiry.

Coupled with the acceptance of pluralities as an important characteristic of scientific inquiry, herein I present an argument against monism. I take monism to be the notion that the aim of scientific inquiry is to provide a single, complete and coherent account of the world, from which all knowledge can be derived. While it is difficult to find a proponent of monism, I argue that monist assumptions about science are prevalent in how scientific inquiry is understood by philosophers,

historians, scientists etc. In this thesis, I identify three monist assumptions (metaphysical, epistemic and methodological) that lead to a monist understanding of scientific inquiry, in which pluralities in scientific practices are seen as temporary states of affairs, resulting in different accounts and approaches being eliminated in pursuit of the monist account. Here, I argue that the monist assumptions about science unnecessarily restrict the ability of scientific practices to explain and explore different aspects of phenomena. Thus, I argue that it is necessary to challenge monist assumptions from a philosophy of science point of view, given that the plurality of approaches is an important characteristic of scientific practices.

The pluralist thesis I develop here focuses on three pluralist arguments put forward by Kellert et al. (2006), Chang (2012) and Mitchell (2002). These three pluralist theses focus on scientific practices, aiming to provide a philosophical account of pluralities in scientific practices. Kellert et al. put forward the pluralist stance as an empirical account of the pluralities in scientific practices. Kellert et al. define pluralities as the state of affairs in scientific practices, in which the pluralist stance is the philosophical interpretation of such a state. In building the pluralist stance, Kellert et al. reject monism in scientific inquiry in favour of 'openness to the ineliminability of multiplicity in some scientific contexts' (Kellert et al., 2006: xiii). Similarly to Kellert et al., Mitchell (2002) argues that a plurality of accounts and approaches scientific practices is an important characteristic of scientific inquiry. She further argues in favour of the way in which multiple approaches and accounts interact with each other to address particular questions. Chang (2012) goes further, arguing for the benefits of pluralism and stating that plurality is more beneficial to science when one considers the aims and values of science. Chang's argument focuses on actively promoting plurality in scientific practices in order to reap the benefits of having multiple systems with which to explore and explain phenomena. For Chang, the role of pluralists is to challenge monism by actively promoting plurality, either through pluralist historiography (studying forgotten systems of practices, such as phlogiston), or removing

obstacles to existing systems of practices that are limited by monist assumptions.

Similar to Chang, I wish to argue that scientific inquiry ought to be pluralistic in order to explain and explore different aspects of phenomena. However, I also argue that the extent of plurality is bounded by pragmatic values. I argue that pragmatic values are specific to the broader context of scientific practices and determine the best way to achieve an aim in that context. The extent of pluralism must be understood, taking the particular aims of science and pragmatic values into consideration. Thus, I argue that scientific inquiry must be understood with respect to its broader context, proposing a pragmatic framework of values that can be used to assess the benefits of pluralities in scientific practices.

The main question I wish to address is how we make sense of pluralities in scientific practices with respect to their broader context. Here I use several case studies, mainly from life sciences, to illustrate my argument. However, I mainly focus on the current efforts organised by the World Health Organisation to eliminate Human African Trypanosomiasis by the year 2030. Human African Trypanosomiasis (HAT) is a parasitic disease prevalent in sub-Saharan Africa, mostly affecting rural areas. In this thesis, I argue that eliminating HAT can be achieved in multiple ways, presenting historical approaches through which near-elimination was achieved using vector controls or other environmental approaches (such as displacement of population from disease-endemic areas). Current efforts to eliminate HAT organised by the WHO rely on mobile screening teams that are tasked with screening populations in disease-endemic areas and treating patients with HAT. The rationale behind the deployment of the active screening campaigns is that HAT is epidemiologically vulnerable and thus the transmission cycle of the parasite can be disrupted through effective treatment of the human population with HAT. However, there are multiple barriers to the implementation of the active screening campaigns, mostly due to inadequacies of the current diagnostic and

therapeutic tools available to the screening teams. Thus, anti-parasitic drug discovery and development research are prioritised over other approaches that can be used to eliminate HAT. Moreover, anti-parasitic drug discovery and development is managed and regulated carefully to ensure that the end product matches patients' needs and can be used effectively by mobile screening teams.

In the first part of my argument, I focus on the benefits of multiple approaches in anti-parasitic drug discovery processes to develop new drugs to treat HAT. I argue that, by employing multiple approaches, scientists can study different aspects of the parasite's metabolism and drug interactions, allowing them to develop drugs that match patients' needs. In the second part of my argument, I broaden my approach to look at the extent of plurality involved in the scientific practices employed to eliminate HAT. Here, I argue that there is a limit to the extent of plurality, where anti-parasitic drug discovery approaches are prioritised over alternatives (such as environmental approaches or vector control approaches). Furthermore, I explore the limits of plurality in scientific practices employed to fulfil the WHO's aim, using pragmatic values that originate in the socio-economic and political context of HAT. I argue that the socio-economic and political context of HAT determine the aims of scientific practices, and the extent of plurality in scientific inquiry.

In chapter 2, I outline the philosophy of science in practice approach, arguing for a broadening of the subject matter of philosophy of science, asserting that this is necessary and will allow closer attention to be paid to scientific practices. Moreover, I present preliminary arguments for pluralism and values in science.

In chapter 3, I focus on the clinical and epidemiological details of HAT, as well as providing an overview of the historical attempts to combat HAT and the current efforts to eliminate it. The aim of this chapter to provide my reader with the necessary background on HAT, arguing for the need to prioritise anti-parasitic drug discovery.

In chapter 4, I provide a detailed argument for pluralism, with detailed overviews of Kellert et al. (2006), Chang (2012) and Mitchell (2002). In this chapter I develop the argument that pluralities are an important characteristic of scientific practices. Moreover, I argue against possible monist objections to pluralities in science.

In chapter 5, I further my discussion of the normative aspects of pluralism, arguing that scientific practices ought to be pluralistic in order to explain and explore different aspects of phenomena. In this chapter, I identify three assumptions that lead to monist views of science, arguing that it is the role of pluralists to oppose these assumptions, replacing them with pluralist tenets. Moreover, in this chapter I argue that there is a limit to the extent of plurality in scientific practices. I argue that the boundaries of pluralism posed by these pragmatic values do not lead to monism.

Finally, in chapter 6, I define pragmatic values, proposing a pragmatic framework to understand the role of values in scientific practices. In this chapter I aim to show how the broader context of scientific inquiry shapes scientific practices and their aims. Using contemporary accounts of John Dewey's logic of inquiry, I argue that values play an important role in determining the aims of scientific inquiry and shaping scientific practices by determining the extent of plurality.

Chapter 2

2.1 Philosophy of science in practice approach

The Society for Philosophy of Science in Practice (SPSP) was established in 2005 in order to promote an approach in philosophy of science that is more engaged with scientific practices and uses of scientific knowledge (SPSP 2015, Ankeny et al. 2011). The new approach promoted by SPSP is in response to the traditional forms of philosophy of science (PoS) that focus on 'the relation between scientific theories and the world, oftentimes to the neglect of scientific practice' (Ankeny et al. 2011: 304). Ankeny et al. (2011) argue that the focus on the relationship between the theories and the world limits the philosophical accounts of science. Instead, Ankeny et al. (2011) argue that pursuit of PoS must 'consider theory, practice and the world simultaneously and never in isolation form one another' (Ankeny et al. 2011: 304).

I will argue that in order to have a better philosophical understanding of science it is essential to explore not only the theories (or other products such as models, explanations, etc.), but also the practices that produce them. That is, traditional questions in PoS (including metaphysical, epistemological and methodological) must be answered in such a way as to take all aspects of scientific inquiry into account: the world as its subject of study, scientific accounts of the world (including theories, models, explanations, etc.) and practices as organised activities with a distinct aim. Ankeny et al. (2011) further articulate the philosophy of scientific practice (PSP) approach as follows:

> Rather than asking abstract or theoretical questions about the appropriate scientific standards for evidence, recasting the questions of interest in terms of activities allows us to explore various (and often competing) approaches to the generation and weighing of evidence. Examining the goals underlying the activities associated with science also forces us to focus not

> only on epistemological considerations but also on the values, norms, and ideals inherent in the pursuit of scientific knowledge. Further, it encourages us to question the metaphysical and ontological assumptions underlying these practices rather than taking them as obvious or as unquestionable 'givens.' In short, focusing on practice allows philosophy of science to return to fundamental issues which have increasingly become neglected in favour of a relatively narrow preferred approach to the field which is largely epistemic, highly theoretical, and often overlooks the implications of the sciences as practiced. (Ankeny et al. 2011: 305)

The aim of this chapter is to defend the PSP approach in detail and set out the main philosophical questions I will address later in this dissertation. The two main questions I will address later are how to interpret the pluralities in science (chapters 4 and 5) and the role of values in science (chapter 6), and can only be answered by attending to the relevant scientific practices and their broader context. In the first half of this chapter (section 2.1), I will present an argument for adopting a PSP approach, focusing on the importance of broadening the subject matter of philosophy of science to include scientific practices. Moreover, I present a preliminary argument for both epistemic pluralism and a pragmatic framework for understanding the role of values in science. The argument I put forward in the second part of this chapter (section 2.2) is that scientific practices, particularly their aims, must be studied with respect to their broader socio-economic and political context. I further argue that it is essential to understand how the aims of different practices are shaped by their broader context. Thus, the main goal of this chapter is to outline the PSP approach and its benefits.

Section 2.1.1 describes the traditional view in philosophy of science, which is often used in philosophy of scientific practice literature, referring to a view shared by a diverse group of philosophers, characterised by their focus on the relationship between theories and

the natural world, while disregarding scientific practices. It is difficult to articulate a precise definition of the traditional view, since it is not clear which philosophers to include as exemplars, nor is it easy to define a time window in which the traditional view was prominent.[1] Thus, I will focus on the traditional view characterised in PSP literature, as the position to which the PSP approach responds.

In section 2.1.2, I will focus on Thomas Kuhn's 'normal science', where he argues that philosophy of science must go beyond study of theories and look at paradigms as a whole. Although there are many discussions on the precise meaning of a paradigm, here I focus on a paradigm as a disciplinary matrix. Kuhn argues that philosophy of science must study paradigms, which consists of theories, practices, values, assumptions etc. Kuhn's emphasis on the importance of the extra-theoretical aspects challenges the traditional view, underlining the importance of philosophical study of *everyday practices* in science.

In section 2.1.3 I move on to discuss the works of the so-called Stanford School, particularly those of Ian Hacking (1983) and Peter Galison (1987). I focus on Hacking and Galison given their close engagement with scientific practices, particularly experimentation, in order to address traditional questions in philosophy, including the realism and anti-realism debates. The Stanford School represents an approach in philosophy of science that productively engages with scientific practices in order to answer traditional philosophical question. In line with Kuhn, members of the Stanford School argued for the importance of studying scientific practices in order to address philosophical questions regarding scientific knowledge, the subject matter of science and the scientific method.

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[1] [1] Exemplars of the traditional view include the works of Nagel (1961) and Maxwell (1962). Both authors focus on theories as the main unit of analysis for philosophy of science. (Nagel's work on the reduction of theories is later discussed in section 4.4.1 in light of the contemporary debate on reductive explanations in life sciences).

I take the arguments put forward by Kuhn and the members of the Stanford School as (noteworthy) predecessors of the PSP approach, given that both positions argued for broadening the subject matter of philosophy of science to include scientific practices. That is, Kuhn and members of the Stanford School argue that the theory-centric view in PoS is inadequate for understanding science, and the subject matter of philosophy of science must be broadened by including extra-theoretical aspects of scientific inquiry, especially scientific practices.

In section 2.2, I introduce both the values debate and the pluralism debate. In section 2.2.1, I review the values debate, illustrating the role of values in scientific practices. In particular, I focus on how the aims of particular scientific practices are determined with respect to their broader socio-economic and political context. Here I provide a preliminary argument for a pragmatic framework, which I will discuss in detail in chapter 6. In section 2.2.2 I provide the preliminary argument for contextual pluralism, which I will further discuss and develop in chapters 4 and 5. The two questions I set out here are treated together, in the sense that I use the values literature to address problems that arise in the pluralist arguments I review.

2.1.1 Traditional View

The traditional form of Philosophy of Science (PoS), as referred to by Ankeny et al. (2011), is not a unified position that can be defined in a straight forward way.[2] It refers to a multifaceted body of work produced by a diverse group of philosophers. My aim here is not to provide a comprehensive history of philosophy, but to characterise the traditional forms of PoS, criticised in the PSP literature. In order to characterise the traditional view, I will follow Hacking (1983), who identifies the

[2] Ankeny et al. can be regarded as a manifesto for the PSP approach: it was written as an introduction to a special edition of the European Journal of Philosophy of Science on the PSP approach, defining it and listing the broad motivations and goals of the SPSP.

traditional view by comparing the works of Rudolf Carnap and Karl Popper. Hacking's characterisation is succinct and identifies the basic premises of the traditional form that PSP rejects (I will discuss Hacking's work in detail in section 2.1.3).[3]

Hacking (1983) identifies Carnap and Popper as two philosophers who shared the traditional view and compares their philosophies, attending particularly to their disagreements to build the same basic view of science that they share. Hacking argues that the disagreements between Carnap and Popper were only possible because they have the same fundamental view of science (Hacking 1983: 5). Herein, I will follow how Hacking constructs the traditional view by reviewing the disagreements between Carnap and Popper.

Hacking argues that both Carnap and Popper regard natural sciences (especially physics) as the best example of human rationality (Hacking 1983: 5). Thus, both Carnap and Popper aimed to develop criteria to demarcate science from 'ill speculation'. For Carnap the demarcation criterion is verifiability, where scientific statements must be empirically verifiable; otherwise, they are meaningless. However, Popper argues that scientific statements can never be verified because of their wide scope. For Popper, a statement is scientific if it is testable and thus might be shown to be false, i.e. falsifiable (this will be further discussed in section 2.1.2).

Carnap takes observation as the foundation of scientific knowledge, in which observation statements can be used to verify (or support) a hypotheses using inductive logic. Thus, Carnap argues that good reason relies upon howthe way in which empirical observation confirms a hypothesis. For Popper, there are no foundations of knowledge and all knowledge is fallible. Popper argues that the rationality of science is not due to how well scientific knowledge is supported by evidence, but

[3] Hacking is cited as one of the precursors of the PSP approach in the Mission Statement of (Brown 2013, p.837)

the method by which it is acquired. The Popperian method involves scientific theories being subjected to constant and rigorous testing. That is, if a theory fails a test, it is refuted; if it passes the test, it is only corroborated.

Hacking argues that Carnap and Popper disagree on so many points because they have a shared image of science:

> whenever we find two philosophers who line up exactly opposite on a series of half a dozen of points, we know that in fact they agree about almost everything. They share an image of science (Hacking 1983: 5).

For Hacking, Carnap and Popper share an image of science that constitutes the traditional view. That is to say, Carnap and Popper can have different opinions on so many aspects of science because they share common ground. Hacking summarises the main features of the traditional view as follows (Hacking 1983: 5):[4]

- there is a sharp distinction between theory and observation.
- there is a scientific method that must be employed by all sciences.
- scientific development is cumulative, approaching towards the truth (or approximation of the truth).
- there is a difference between the context of discovery and the context of justification.

In order to explain the theory-focused approach in the traditional view of PoS, Hacking attends to the distinction between the context of

[4] These features are characterised by Hacking, and must be regarded as analysts' categories. Therefore, it is not a definite list and can be interpreted in different ways.

discovery and the context of justification. This distinction was put forward by Reichenbach (1938), arguing that the role of philosophy is to reconstruct scientific reasoning in a way that can be subject to logical analysis. Reichenbach's work has been discussed in detail by Howard (2006) and Richardson (2006).

According to this distinction, the context of discovery includes intuitive or irrational processes (such as serendipity, inspiration, luck, etc.) that may lead to the conception of a new theory. However, the context of justification involves verification and testing of the new theory, in which theories are validated and knowledge is acquired as a result of logical reasoning. The distinction has been discussed widely in philosophy of science literature, particularly how this distinction must be drawn (c.f Kordig 1978, Gutting 1980, Hoyningen-Huene 1987, Schickore and Steinle 2006).

Hacking argues that the distinction between context of discovery and context of justification underlines the lack of attention to practice in philosophy of science. Specifically, Hacking argues that the traditional view holds that philosophy of science is about 'justification, logic, reason, soundness, methodology' (Hacking 1983: 6), and therefore philosophy of science is interested in the processes within the context of justification. The context of discovery needs to be studied by historians and sociologists, questioning the 'circumstances of discovery, psychological quirks, the social interactions, and economic milieu' (Hacking 1983: 6). That is to say this distinguishes philosophy of science from history of science and social studies of science. The distinction between context of discovery and context of justification can be seen as a reason for scientific practice being ignored by philosophy of science: the traditional view did not include everyday practices of science as a subject of study.

I will now shift my focus to how Kuhn differed from the traditional view and how his ideas made novel contributions to the history and philosophy of science, making a difference to the methodology of philosophy of science. It is worth underlining the importance of Kuhn's

break from the traditional view is significant for the PSP approach I am arguing for here, given that Kuhn argued that the everyday activities of scientists are as important for making philosophical sense of science as particular instances that are traditionally discussed.

2.1.2 Kuhn: Normal Science

Thomas Kuhn's body of work is distinct from the traditional forms of PoS described in section 2.1.1. Kuhn provides a different picture of science, making a clear distinction between two phases of science: normal science and revolutionary science. Kuhn's work has been scrutinised by both history and philosophy of science literature and social studies of science literature (c.f. Lakatos and Musgrave 1970, Barnes 1982, Longino 1994, Nickles 2003, Bird 2005). Here I argue that Kuhn's picture of science takes everyday activities in science and scientific theories as the subject matter. That is, Kuhn argues for the importance of studying scientific practices and theories:

> History, if viewed as a repository for more than anecdote or chronology, could produce a decisive transformation in the image of science by which we are now possessed. That image has previously been drawn, even by scientists themselves, mainly from the study of finished scientific achievements as these are recorded in the classics and, more recently, in the textbooks from which each new scientific generation learns to practice its trade […] This essay attempts to show that we have been misled by them in fundamental ways. Its aim is a sketch of the quite different concept of science that can emerge from the historical record of the research activity itself. (Kuhn 2012: 1)

Here Kuhn argues for a change in the subject matter of philosophy (and history), shifting from reconstruction of science that one finds in text books, to research activity itself. As Rouse (2002) asserts, 'Kuhn reorients the philosophy of science toward an account of scientific practices rather than scientific knowledge. In line with Rouse, I will underline Kuhn's emphasis on the need to broaden the subject matter

of philosophy of science to include extra-theoretical aspects of science. Here I focus on Kuhn (2012) and Kuhn (1970b), in which he argues for the need to study the everyday activities of scientist to have a better (philosophical and historical) understanding of scientific inquiry. Kuhn puts forward his view on how science progresses, as follows:

normal science – crisis – scientific revolution – normal science

Kuhn defines normal science as periods in which scientists adhere to a paradigm, which can be thought of as a disciplinary matrix consisting of accepted theories, models, methods and metaphysical assumptions. It is important to note that there is a rich literature on the precise definition of Kuhnian paradigms. Here I am using the definition of paradigm Kuhn provided in the postscript (Kuhn 2012: 181), in which he argues for the importance of extra-theoretical factors in understanding science. For Kuhn, paradigms provide necessary tools for scientists to explore certain aspects of phenomena allowed by the limitations of that particular paradigm.[5] Kuhn describes normal science as 'puzzle solving', arguing that periods of normal science correspond to periods in which scientists do not always aim to produce major conceptual changes or revolutionary breakthroughs (Kuhn 2012: 35).[6] Kuhn asserts that:

> Bringing a normal research problem to a conclusion is achieving the anticipated in a new way, and it requires the solution of all sorts of complex instrumental, conceptual, and mathematical puzzles. The man who succeeds proves himself an expert

[5] Kuhn argues that in a disciplinary matrix, scientists use multiple tools (theories, methods, values, metaphysical assumptions and so on) to answer the questions the paradigm poses.

[6] This point can be seen as a response to Popper's picture of science in which scientists are constantly testing their theories stringently, trying to falsify them. I return to this point later in this section.

> puzzle-solver, and the challenge of the puzzle is an important part of what usually drives him on. (Kuhn 2012: 36)

Furthermore, Kuhn argues that the failure to achieve anticipated results during normal science is regarded as the failure of scientists, not a failure of the theory or method (Kuhn 2012: 79). Kuhn repeatedly states that in case of failures in normal science, scientists do not blame their tools, but their ability.[7] However, in cases of persistent failure and anomalies, a crisis can emerge. Kuhn argues that in times of crisis, the paradigm comes under scrutiny, and new paradigms emerge and replace old ones. Kuhn calls this process scientific revolution that results in paradigm shift.

Kuhn's picture of science has been widely criticised, particularly for the way in which normal science is described. For instance, normal science is compared to religious dogma in the sense that scientists do not criticise paradigms until problems mount and the paradigm falls into crisis (Popper 1970, Watkins 1970). Stephen Toulmin (1970) asserts that the sharp distinction between normal science and scientific revolutions are not as clear as Kuhn argues.

Here, instead of focusing on Kuhn's argument on how science progresses, I focus on Kuhn's description of normal science, and particularly his argument (1970b) that philosophy of science should attend to normal science and the research activities as much as it does to scientific revolutions. The argument put forward by Kuhn is similar to that of Ankeny et al. (2011), in the sense that they both argue that philosophy of science must not be restricted to only studying theories (or rational reconstructions of science in textbooks), but also attend to scientific practices.

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[7] Kuhn likens scientist blaming the paradigm for failure during normal science to a bad carpenter blaming his/her tools (Kuhn, 2012: 79).

Kuhn argues for the importance of normal science in response to his critics, in particular Popper's criticism (1970).[8] Kuhn argues that he and Popper have many things in common, including their interest in the dynamic process in science:

> We are both concerned with the dynamic process by which scientific knowledge is acquired rather than with the logical structure of the products of scientific research. Given that concern, both of us emphasize, as legitimate data, the facts and also the spirit of actual scientific life, and both of us turn often to history to find them. (Kuhn 1970b: 1)

Kuhn also points out that he and Popper oppose the same classical positivist thesis:

> the intimate and inevitable entanglement of scientific observation with scientific theory; we are correspondingly sceptical of efforts to produce any neutral observation language; and we both insist that scientists may properly aim to invent theories that explain observed phenomena and that do so in

[8] Kuhn argues that his and Popper's argument have a common ground: both are interested in the dynamic processes involved in the development of scientific knowledge. The idea that Kuhn and Popper have a common ground might seem at odds with Hacking's analysis of Popper discussed in the previous section (2.1.1). It is important to note the origins of Kuhn's 1970 paper in the the 1965 International Colloquium in the Philosophy of Science (held at Bedford College, Regent's Park, London). At this colloquium, Kuhn was directly responding to Popper in person. Taking this fact into consideration, Kuhn's aim was to show the commonality between his and Popper's position in order to build his response which I discuss in the remainder of this section. On the other hand, Hacking's analysis aimed to show how Popper's theory centric view (taking theories as the sole subject matter for philosophy of science) is in line with the traditional view in philosophy of science. While they might share a common ground (interest in dynamic processes in science), Kuhn's analysis of scientific inquiry goes beyond theories and focused broadly on paradigms as subject matter in philosophy of science. Thus, Kuhn's and Hackings view of Popper's works are not at odds.

> terms of real objects, whatever the latter phrase may mean. (Kuhn 1970b: 2)

Moreover, Kuhn argues that they both emphasise the importance of understanding scientific life:

> Among the most fundamental issues on which Sir Karl and I agree is our insistence that an analysis of the development of scientific knowledge must take account of the way science has actually been practiced. (Kuhn 1970b: 8)

Despite these similarities, Kuhn argues that Popper arrives at different conclusions from his own:

> Sir Karl and I do appeal to the same data; to an uncommon extent we are seeing the same lines on the same paper; asked about those lines and those data, we often give virtually identical responses, or at least responses that inevitably seem identical in the isolation enforced by the question-and-answer mode. (Kuhn 1970b: 3)

As discussed in section 2.1.1, Popper argues that scientists must subject their theories to constant testing, in which each test is aimed at falsifying the theories. For Popper, no test can fully verify a theory, but can falsify it. Popper argues that theories that pass the tests are only corroborated, not validated. The examples Popper uses are Lavoisier's calcination experiments and the eclipse expedition of 1919 (Popper 1963). In summary, for Popper, scientific progress is possible through conjecture and refutation: scientist making bold conjectures and trying to falsify them. Kuhn points out that Popper's examples for supporting conjectures and refutations are rare and can only be seen during scientific revolutions in which established theory is overthrown. However, Kuhn argues that such revolutionary events are very rare in the history of science. That is to say, Kuhn does not completely disregard Popper's conjectures and refutations, but limits it to times of crisis.

In contrast to Poppers' conjecture and refutation model, Kuhn argues that testing in normal science aims to describe phenomena and match them with theory. The aim is not to test the limits of the theories, but to further articulate them. The key difference is their view of theory change. Kuhn points out that Popper's conjectures and refutations can only explain how some theories may be accepted or rejected in idealised scenarios that are rare in scientific practice. Kuhn argues that philosophers of science are not likely to understand the development of knowledge or science in general by focusing on special instances in the history of science:

> neither science nor development of knowledge is likely to be understood if research is viewed exclusively through the revolutions it occasionally produces. (Kuhn 1970a: 6)

Kuhn argues that periods of normal science are as important as times of revolution, and deserve the attention of philosophers of science. Kuhn further argues that the historical and philosophical accounts of science must go beyond theories and look at paradigms as a whole.[9] Kuhn asserts that theories or sets of theories are shared within the community of scientists. However, scientists conceptualise theories differently from philosophers of science:

> As currently used in philosophy of science, however, 'theory' connotes a structure far more limited in nature and scope than the one required here. Until the term can be freed from its current implications, it will avoid confusion to adopt another [term]. (Kuhn 2012: 181)

Instead of focusing on theories as the only subject matter, Kuhn argues that historians and philosophers of science must consider paradigms, which he describes paradigms as disciplinary matrices. A disciplinary

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[9] I would like to thank Yafeng Shan for his comments and discussion on this topic.

matrix is a collection of scientific groups that work on common problems and share similar goals (Kuhn 2012, p.182). Thinking about science and scientific knowledge in terms of paradigms (instead of theories) allows historians and philosophers to take extra-theoretical factors into account.

More broadly, Kuhn argues that his aim is to provide an account of science that emerges from the 'historical record of the research activity itself' (Kuhn 2012: 1). Thus, Kuhn argues that such a philosophical account cannot rely on logical analysis only, but must consider the disciplinary matrix. In contrast to Popper's rational model of testing and theory change, Kuhn explains theory changes using perceptual psychology experiments (such as Gestalt switches) in his account of scientific development. That is to say that the everyday practices of the scientist are not merely dictated by logic and experiment alone, but social values and psychological imperatives shared within the community. In summary, Kuhn argues that rather than understanding scientific practice as rational reconstructions (as they are often understood in the traditional forms of PoS, as discussed in section 2.1.1), philosophers of science must think about everyday activities within science as a disciplinary matrix in order to prove a more comprehensive picture of scientific inquiry.

Kuhn's ideas that challenged the theory-focused philosophy of science were taken up by groups of philosophers interested in scientific practices, particularly experimentation, values and pluralism. Moreover, he opened up avenues of discussion between philosophers of science and historians of science and social studies of science (see Barnes 1982; Nickes 2003). It is important to note the impact of Kuhn on philosophy of science: his challenges to the traditional view led to discussions of the subject matter of philosophy of science and how to interpret scientific practices as a whole (discussed in the second part of this chapter). Before moving onto these topics, I will discuss the Stanford School, consisting of philosophers who challenged the traditional view in a similar way to Kuhn.

The Stanford School challenged the theory-centric view in philosophy of science, as well as the unity of science thesis (in its various forms), arguing for a philosophical understanding of science that is built bottom-up, focusing on scientific practices as their subject matter.

2.1.3 Stanford School

The Stanford School consists of philosophers Nancy Cartwright, John Dupré, Peter Galison, Ian Hacking, and Patrick Suppes, all of whom worked at Stanford University at various times. Members of the Stanford School are known for the methodological, epistemic and metaphysical arguments they developed against the unity of science thesis. Broadly, members of Stanford School reject restrictive accounts of inquiry, opposing arguments that scientific method and knowledge is universal and the phenomena is uniform (Cat 2017). Arguments put forward by the members of the Stanford School are significant for the development of the PSP approach for engaging directly with scientific practices to address traditional philosophical questions. For instance, Patrick Suppes (1978) focuses on scientific practices and scientific journals to argue that different subject matters, methods and languages used in different scientific disciplines are not reducible to one unified subject matter, method and language. Using case studies from scientific practices (including neuroscience and quantum physics), Suppes argues that scientific activity is an act of perpetual problem-solving, in which scientists are confronted with new problems, which they approach with, ‘a potpourri of scientific methods, techniques, and concepts, which in many cases we have learned to use with great facility’” (Suppes 1978: 14).

John Dupré (1993) and Nancy Cartwright (1999) provide metaphysical arguments against the unity of science thesis, providing metaphysical foundations for the disunity thesis and pluralism (further discussed in section 4.1). Both Dupré and Cartwright have a bottom-up approach, starting from scientific practices to build their metaphysical arguments: promiscuous realism (Dupre 1993) and the dappled world (Cartwright 1999). While much can be said about both the promiscuous realism

and dappled word arguments, here I limit my discussion to methodological and epistemic questions. I am interested in building an account that addresses epistemic and methodological questions (plurality in scientific practices and the role of values in science) while remaining agnostic about metaphysical questions.

Ian Hacking (1983) and Peter Galison (1987) address methodological and epistemological questions, while underlining the importance of understanding scientific practices, in particular experiments. In this section I am going to focus on Hacking's *experimental realism* and Galison's work on *the experimental life*, given their emphasis on the everyday activities of scientists. Both philosophers argue for the importance of extending philosophical inquiry beyond scientific theories and look at scientific practices as a whole.[10] Here I focus on Hacking and Galison as two representatives of the Stanford School who approached methodological and epistemic questions by focusing on scientific practices.

2.1.3.1 Experimental Realism

Ian Hacking argues that philosophy of science has focused on theories and representations of reality and has disregarded experiments (Hacking 1983: 149). Moreover, Hacking argues that the history of natural sciences has become the history of theory. The consequence of this theory-focused approach is the dismissal of pre-theoretical activities and experimental observation by philosophers (Hacking 1983: 150). Hacking attends to experimental science, which according to Hacking, has a life of its own. He argues that 'the relationship between theory and experiment differ at different stages of development' (Hacking 1983: 154).

[10] It is important to make it clear that the need to expand the subject matter of philosophy to include everyday practices in science (as opposed to only focusing on theories and the rational reconstruction of scientific inquiry) is shared by all members of the Stanford School.

Hacking underlines that this may be an obvious statement, but it is often denied by the traditional view described above. Popper (2002), for instance, argues that theorists formulate a sharp, falsifiable question that acts as a guide for the experimenter, stating that, 'theory dominates the experimental work from its initial planning up to the finishing touches in the laboratory' (Quoted in Hacking 1983: 155)

For Popper, the aim of an experiment is to test and attempt to falsify a theory (discussed in section 2.1.1). The reason for recalling Popper here is to demonstrate how Hacking's argument diverges from the traditional view. Hacking rejects the notion that the aim of an experiment is to test a theory; instead, Hacking argues that the relationship between theories and experiments can differ (as quoted above). Moreover, Hacking argues that the relationship between experiments and theories must be examined case-by-case. For instance, Hacking uses David Brewster's experimental work in optics to illustrate the complex relationship between theory and experiment (Hacking 1983: 157). Hacking describes Brewster as a prolific experimenter who was a major figure in experimental optics in the first half of the nineteenth century. Brewster's work (including laws of reflection and refraction of polarised light), according to Hacking, produced the experimental results that were used in the development of the wave theory. Hacking argues that Brewster was not testing or comparing theories in his experiments. Brewster's experiments focusing on how light behaves contributed towards development of the wave theory of light, even though Brewster himself supported the Newtonian corpuscular theory of light. Hacking asserts that

> Brewster firmly held the 'wrong' theory while creating the experimental phenomena that we can understand with the 'right' theory, the very theory he vociferously rejected. (Hacking 1983: 157).

That is, Brewster's experimental work was not aiming to test the wave theory of light. In order to understand Brewster's contribution to the development of wave theory, one must study his experimental work.

Hacking's main question is the relationship between theory and experiment. Hacking argues that theory and experiment can develop independently from one another. Moreover, Hacking rejects the notion that theories precede experiment, where the goal of experimentation is to test or further theory. Hacking argues that the relationship between theories and experiment differs from case to case:

> Some profound experimental work is generated entirely by theory. Some great theories spring from pre-theoretical experiment. Some theories languish for lack of mesh with the real world, while some experimental phenomena sit idle for lack of theory. There are also happy families, in which theory and experiment coming from different directions meet. (Hacking 1983: 159)

This underlines Hacking's overall argument: experimental aspects of scientific inquiry are not subsidiary to scientific theories in our philosophical understanding of science. The relationship between theories and experiments are just two aspects discussed by Hacking; we might add other aspects such as values, assumptions etc. as important aspects that require scientific inquiry. Hacking's argument is informed by the history of science that focuses on scientific practice and experiment, rather than theories. Hacking later addresses the realism/anti-realism debate, building his experimental realism. In line with the PSP approach, Hacking argues that theory-centric approaches in philosophy of science neglect the essential aspects of scientific inquiry, namely experimentation. Hacking's argument is a prime example of how the traditional questions in philosophy of science can be adequately addressed by broadening the subject matter of philosophy. This broadening allows for the recasting of philosophical questions and building philosophical accounts that are closely engaged with scientific practices, making the philosophical account of scientific inquiry relevant to scientists, policy-makers etc.

2.1.3.2 The Life of Experiments

Similar to Hacking, Galison (1987) argues that philosophical and historical accounts of science are incomplete or inadequate due to this asymmetrical emphasis on theory. Galison (1987) tracks the lives of experiments, looking at intermediate states between first suspicion and the final argument. Galison's account focuses on the 'actual practices' in the lab including 'twisting of wire, the shielding of chambers, the hoisting of thousand-pound steel plates' (Galison 1987: 19)

Galison (1987) questions the scope of experimental autonomy, a question he addresses by focusing how different levels of theory influence experimental work. Galison argues that prioritising theory over experiment or *vice versa* is not definite since priorities change from case to case:

> it is necessary to avoid some of the pitfalls of a view that wants to put observation or theory 'first'. Both of these views […] reveal partial insights into the character of experimentation. (Galison 1987: 12)

Galison's work is significant from a PSP perspective due to the emphasis he puts on the daily activities of scientists, and how they prioritise different factors in establishing scientific facts. Galison's work focuses on three different periods of experimental physics in the twentieth century, demonstrating the different forms the relationship between experiments and theories take. Galison particularly studies the experiments on microphysics, focusing on the debates and assumptions that lie behind decisions made by experimenters. Concentrating on everyday practices, Galison demonstrates the influence of the social and psychological factors embedded in everyday scientific practice on knowledge production. Galison argues that the daily practices in the lab are heterogeneous processes that cannot be explained merely by logical reconstructions or psychological models.

Galison recalls Kuhn's (and to an extent Hanson's [1958]) use of perceptual psychology, namely Gestalt images as a way to understanding the everyday aspects of scientific practices. Galison

argues that while the use of psychological models encourages interesting questions regarding scientific practices, abstract models (such as Gestalt images) fail to adequately explain the mechanism in which psychological factors (such as theoretical presuppositions) influence experimental life. For Galison, psychological models alone are too simplistic to describe the relationship between theories and experiments, especially Kuhn's Gestalt switch that suggests scientists see different things based on theoretical presuppositions (Galison 1987: 68). Galison argues that:

> The task of understanding the relation of theory to experiment is contingent on grasping the different levels theory that are involved in the experimenter's work and on analysing the various mechanism that connect the experimental work with the elements of theory. (Galison 1987: 69)

The argument here is similar to one put forward by Hacking, in the sense that in order to understand the relationship between experiments and theories, it is necessary to study them case by case. Galison describes the task of unravelling theoretical and experimental factors shaping scientific practice as a historical enterprise that has no fixed rules:

> experimental physics cannot be re-written as a logical fantasy in which all theorising is forbidden until 'facts' clinch the argument. Nor can experimentation be parodied as if it were no more grounded in reason than negotiation over the price of a street fair antique. (Galison 1987: 277)

In summary, Galison argues that in order to have a better understanding of scientific inquiry, philosophy of science must study scientific theories and experiments. Moreover, he argues that scientific practices (and the knowledge they produce) are shaped by various intellectual and social factors. The way in which Galison engages with scientific practices is important to underline here. Galison engages in ethnographic study of the lab following the social and the intellectual

life in the laboratory in order to address the epistemic and methodological questions. Galison's work is in stark contrast with the traditional view in terms of the way that Galison follows the everyday activities of scientists in everyday lab work, as opposed to relying on the rational construction of theory testing. Moreover, Galison's audience is not only philosophers of science but also historians, sociologist and the scientists themselves. Galison (like Hacking) engages directly with scientists, following scientific practices, making philosophical accounts of scientific inquiry more pertinent and far-reaching.

2.1.4 What comes after the Practice Turn

The arguments I discussed in the first part of the chapter are to describe and support the PSP approach that I will adopt in this dissertation. Here, I argued that the theory-focused traditional view leads to the neglect of important aspects of scientific inquiry. Moreover, I now argue that scientific theories must not be regarded as special among other scientific accounts of phenomena, such as models, explanations etc. The PSP approach aims to study and understand scientific inquiry as a whole, in which scientific practices are as important as the accounts (including theories, models, explanations) as a subject of study for philosophers of science.

The broadening of the subject matter allows the reframing of traditional questions in philosophy of science (such as the realism/anti-realism debate), but also motivates new questions. In this dissertation, I focus on two: the role of values in science, and how to interpret the pluralities in scientific practices and accounts. In the second part of this chapter I provide provisional arguments for scientific pluralism and the role of values in science. I will explore both questions using a case study, looking at Neglected Tropical Disease (NTD) research. The aim of the second part of this chapter is to set out the two philosophical questions I will address later, as well as providing a background to the main case study I will use to further the philosophical discussion.

2.2 Contextual Pluralism

2.2.1 Context and the Uses of Knowledge

In section 2.1.1, I defined scientific practices as organised activities, working towards achieving certain aims. I will argue that scientific practices have multiple aims, and that particular aims must be understood in their broader context. These aims are not exclusively epistemic (i.e. the production of knowledge), but also the production of knowledge to serve a purpose. Here, I argue that the PSP approach must acknowledge the plurality of aims in scientific practices; moreover, particular aims must be understood in the broader context of scientific inquiry. This is in line with the PSP approach outlined by Ankeny et al. (2011):

> Practice, of course, happens in the real world, and SPSP is eager to encourage investigations not only of the acquisition and validation of knowledge, but also of the use of such knowledge in the material and social world. Our concern is not only about how pre-existing knowledge gets applied to practical ends, but also about how knowledge itself is fundamentally shaped by its intended uses. (Ankeny et al. 2011)

Herein, I argue that in order to understand how knowledge is shaped by its intended use, we need to pay closer attention to the socio-economic and political contexts of scientific inquiry. My argument is grounded in the values literature, initially challenging the notion that science is value-free, arguing that values play an important role in science (see McMullin 1982, Kuhn 1977, Longino 1990, Douglas 2000, Douglas 2009, Lacey 2005, Laudan 1984, Kitcher 2003). According to the traditional view (discussed in 2.1.1), the context of justification is free from values, meaning that the rational processes in science such as theory choice were also free from values. Contrary to the traditional view, Kuhn (1977) argued that scientists appeal to a set of epistemic

values in order to assess theories.[11] The epistemic values described by Kuhn (accuracy, simplicity, consistency, fruitfulness and a broad scope) are constitutive and internal to science, i.e. they characterise a good scientific theories, allowing scientists to choose (Kuhn 1977). Although Kuhn acknowledges that scientist use values in the way they assess theories, these values were thought to be particular to science, still maintaining the notion that non-epistemic (social, political etc.) values had no role to play in science. Longino (1990) argues that in addition to epistemic values, contextual values also play a role in scientific practices, and that the role of values in science arises from the underdetermination of scientific theories. Longino asserts that underdetermination is:

> the semantic gap between hypotheses and data that precludes the establishing of formal relations of derivability without employing additional assumptions […] I take the general lesson of underdetermination to be that any empirical reasoning takes place against a background of assumptions that are neither self-evident nor logically true. Such assumptions, or auxiliary hypotheses, are the vehicles by which social values can enter into scientific judgement. (Longino 2004: 132)

Longino argues that unless the background assumptions are eliminated from scientific practices, values (both constitutive and contextual) cannot be eliminated from science. Longino's contextual empiricism holds that the evidential relevance of data can only be secured by background assumptions, asserting that these assumptions can differ from context to context. Longino asks 'what controls background assumptions?' (Longino 1996 : 40). Longino argues that there is no justification to privilege a set of values (usually referred to

[11] Kuhn is not the first philosopher to argue that scientists appeal to sets of values to assess theories and hypotheses. Hempel, Churchman and Levi also argued similar points. Douglas (2009) provide a detailed overview of the values debate in the history of philosophy of science.

as epistemic) over others. Longino builds her argument using cases from feminist epistemology where different sets of values are used by feminist scientists to further their research (Longino 1996). I discuss Longino's argument further in section 6.2.

Douglas (2000) focuses on the concept of inductive risk to argue for values in science. Douglas defines inductive risk as the 'risk of error in accepting or rejecting hypotheses' (2000: 561). Douglas argues that values are necessary for scientific reasoning, in which scientists consider a range of values to assess the inductive risk. Moreover, Douglas argues that both epistemic and non-epistemic values are used by scientists, where values play an important and legitimate role in directing the scientific research efforts:

> To place the idea of inductive risk in context, it should be noted that there are three decision points in the scientific process where non-epistemic values are widely recognized as having a legitimate role (here, Douglas follows Longino 1990, 83-85). First, values (both epistemic and non-epistemic) play important roles in the selection of problems to pursue. Second, the direct use to which scientific knowledge is put in society requires the consideration of non-epistemic values. For example, if science enables the development of a new technology, values are (or should be) consulted to determine whether such a technology is desirable. Third, non-epistemic values place limitations on methodological options, such as limitations on how we can use humans in experimentation. (Douglas 2000: 563-564)

Douglas adds that although values have a direct role in decision-making, they do not directly dictate what should be taken as true. Instead, Douglas argues that values allow scientists to assess the consequences of the possible error in accepting or rejecting a hypothesis, following one method over another or framing the problems and questions to pursue. In summary, values are used by scientists to consider the consequences of errors in arguments concerning evidence (Douglas 2009). I will discuss this further in section 6.2.1.

Understanding the role of values in science requires close engagement with scientific practices, in which values are used by scientists to make decisions, define problems and questions and set aims. Here (and later in chapter 6) I focus only on Longino's and Douglas's argument for why values are required even in the 'internal' and supposedly value free part of scientific inquiry. However, it must be noted this is not the complete account of values in science presented by either author. In this thesis, I am interested in how different values determine the aims of scientific inquiry and shapes the scientific practices. In the following section (2.2.2), I provide an overview of the current efforts coordinated by WHO to combat Neglected Tropical Diseases (NTDs). My aim here is to show how the broader context of NTDs shapes and influences the scientific and medical practices in this field. Chapter 3 is reserved for a detailed discussion of the case study, focusing on a particular NTD: Human African Trypanosomiasis (HAT).

2.2.2 Neglected Tropical Diseases

NTDs are a medically diverse group of diseases that mainly affect the poorest populations. The term 'NTDs' was coined by the World Health Organisation (WHO) in the aftermath of the United Nations' Millennium Development Goals (MDGs), which is a framework to galvanise and direct international efforts to fight global poverty. NTDs feature in MDGs as 'other diseases': goal six is to 'combat HIV/AIDS, malaria and other diseases'. While this goal received a global response from policy-makers, they were mostly focused on HIV/AIDS, malaria and tuberculosis,[12] while 'other diseases' remained neglected. In response, Molyneux (2004) asserts that:

[12] It led to the establishment of the international organisation The Global Fund to Fight AIDS, Tuberculosis and Malaria. It also led to development of the policy document known as PEPFAR, the President's Emergency Plan For AIDS Relief.

> The Millennium Development Goals and a plethora of initiatives have focused on the control of HIV/AIDS, tuberculosis, and malaria (…) The focus of health policy-makers on HIV/AIDS, tuberculosis, and malaria, as well as emerging or re-emerging diseases causes funding for neglected diseases to be overlooked, with deleterious effects on the social and economic wellbeing of the poorest quintile of populations in the least developed and low-to-middle income countries. (Molyneux 2004: 380)

Although these 'other diseases' were neglected by policy circles, the first decade of the twenty-first century witnessed an increase in advocacy for these diseases by scientists working on tropical diseases, aiming to increase awareness on these diseases and the need for research. Hotez et al. (2007) list thirteen parasitic and bacterial infections that affect approximately 2.7 billion people who live on less than $2 per day. Diseases listed by Hotez et al. (2007), referred to as NTDs, are all prevalent in rural and poor urban settings of low-income countries in Sub-Saharan Africa, Asia and Latin America.

Deaths caused by NTDs are substantially fewer than deaths caused by HIV/AIDS, malaria and diarrheal diseases. However, when numbers of years lost to disability and premature deaths caused by NTDs are calculated, they constitute the most significant chunk of the global disease burden. Furthermore, in addition to being a major health problem, authors argue that lack of action against these diseases perpetuates the poverty in these regions by reducing worker productivity. Hotez et al. (2007) assert that:

> the poverty results from disfigurement or other sequelae of long-term illness, impaired childhood growth and development, adverse outcomes of pregnancy and reduced productive capacity (Hotez et al. 2007: 1019)

In 2010, the WHO published their first report on NTDs, identifying seventeen such diseases (adding four to the original list), caused by

different pathogens (viruses, bacteria, protozoa and helminths). In this report, NTDs are defined as follows:

> Neglected tropical diseases are a group of communicable diseases which thrive in impoverished settings and blight the lives of around one billion people worldwide, while threatening the health of millions more. Of the world's poorest 2.7 billion people (defined as those who live on less than US$ 2.00 a day), more than 1 billion are affected by one or more neglected tropical disease. These diseases not only survive and spread in conditions of poverty, they also exacerbate and perpetuate the poverty of affected communities. (WHO 2010: 1)

What these seventeen diseases have in common is not biological, but the socio-economic and political contexts in which they occur. The common features of these diseases are further articulated by the WHO (2010) as those that:

- are a proxy for poverty and disadvantage;
- affect populations with low visibility and little political voice;
- do not travel widely;
- cause stigma and discrimination, especially affecting girls and women;
- have an important impact on morbidity and mortality;
- are relatively neglected by *research;* and
- can be controlled, prevented and possibly eliminated using effective and feasible solutions.

Therefore, the term NTDs can be thought of as an advocacy term to draw attention to a diverse group of diseases that require urgent political attention as well as scientific and medical research. The term NTD brought together different efforts to eradicate these diseases, providing a united platform for further advocacy and galvanising

political and financial support. Commitment to unite different efforts to combat NTDs was expressed in the London Declaration on Neglected Tropical Diseases, a declaration endorsed by the WHO, the World Bank, the Bill & Melinda Gates Foundation, thirteen pharmaceutical companies and government representatives from multiple countries (WHO 2012a). The London Declaration sets out a collaborative effort to control, eliminate and eradicate NTDs by 2020:[13]

> we believe there is a tremendous opportunity to control or eliminate at least 10 of these devastating diseases by the end of the decade. But no one company, organization or government can do it alone. With the right commitment, coordination and collaboration, the public and private sectors will work together to enable the more than a billion people suffering from NTDs to lead healthier and more productive lives – helping the world's poorest build self-sufficiency. (London Declaration on Neglected Tropical Diseases 2012)

The important point here is that the socio-economic and political context of these diseases play an important role in framing scientific questions and the ways in which scientific practices are organised to address these questions. In this dissertation, I mainly focus on the pharmaceutical research developing new drugs to treat NTDs, in order to show how values play an important role in scientific practices.

Current drugs that treat parasitic diseases are not ideal due to their high toxicity and acquired drug resistance of the parasites (Nwaka and Ridley 2003). However, the need for new drugs for NTDs is not matched by the pharmaceutical industry: only 13 of 1,300 drugs developed between 1975 and 1999 were directed at tropical diseases

[13] Exact dates and goals vary for each disease, I will discuss particular dates and goals for Human African Trypanosomiasis later in section 3.1.

(Trouiller et al. 2001, Pink et al. 2005).[14] The lack of research and development in NTDs is explained through the lack of market potential for such treatments, due to the patients' (or healthcare systems') inability to pay for any new treatments, resulting in the disengagement of the pharmaceutical industry (Moran 2005). In order to reverse this trend, public-private partnerships (PPPs) were established by organisations including the WHO, Médecins Sans Frontières, the Bill and Melinda Gates Foundation, bringing academia, private industry, governmental and non-governmental organisations together (Pink et al. 2005).

Public private partnerships are non-profit organisations that bring together the different expertise required to develop new treatments for NTDs. PPPs are often described as virtual pharmaceutical companies, in which different stages of the drug discovery and development process are outsourced to different partners. This allows distribution of the economic burden of drug development among partners involved.

The Drugs for Neglected Diseases initiative (DNDi) is an example of a PPP (established in 2003 by Médecins Sans Frontières) working on an alternative research and development model. DNDi's collaborative model is described as follows:

> DNDi does not operate its own research facilities to develop new treatments. It functions based on a collaborative research model […] whereby research is outsourced but actively managed and directed by DNDi personnel, highly experienced in pharmaceutical R&D […] A team is set up for each project, under the leadership of a DNDi Head of Programme, to coordinate all relevant partners and expertise. Such collaboration is governed by various types of contractual

[14] These values were taken from (Pink et al. 2005) The list of tropical diseases referred to in their numbers include six NTDs plus malaria. This is used to show the general trend in market-driven pharmaceutical research.

> agreements, ranging from research funding collaborations, to technical service agreements, to long-term co-development partnerships with industrial partners. (DNDi 2011: 19)

Partners share different responsibilities at different stages of the process of developing a new drug. In the following section I will focus on the discovery and development process, aiming to develop anti-parasitic drugs, as it is a clear demonstration of how the socio-economic and the political context of diseases shape the way in which the scientific inquiry is organised. Moreover, this is a case in which it is clear to see how the range of values that guide scientists are constructed and selected. In the following subsection, I will give an overview of the drug discovery and development pipeline that entails development of a registered drug from scratch. I will return to this example multiple times, but here I would like to provide an overview to familiarise the reader with the overall process.

2.2.2.1 Drug Discovery and Development Pipeline

The anti-parasitic drug discovery process is a lengthy one that can take ten or twenty years, with the ultimate aim being the development of a new drug that has considerable benefits over existing treatments. This process entails development of a small molecule that is able to manipulate a specific target (often a macromolecule such as a specific nucleic acid) in a parasite that is necessary for its growth and survival.

The drug discovery process is described as a pipeline that is divided into different phases. In DNDi's case, it is divided into four phases: discovery, pre-clinical, clinical and implementation. The discovery phase can be divided further into three major tasks: (i) target validation, (ii) lead identification, (iii) lead optimisation.

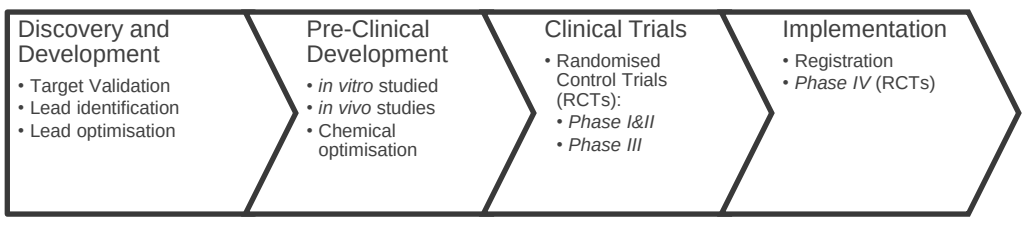

Figure 1. A typical drug discovery pipeline

During Target Validation, a macromolecule is identified in a parasite's metabolism necessary for its survival. The identified molecule is called the 'target'. Lead Identification is the phase in which a molecule that can interact with the target is identified. This step often yields a group of molecules, called 'lead', that can be developed into drugs that can be used on patients. Lead Optimisation is the phase in which lead molecules are modified to optimise and enhance their desired effects and minimise any potential adverse effects they may cause in humans. At the end of this stage the lead is called a 'drug-candidate'.

The following stage is the pre-clinical phase, in which the drug candidate is studied *in vivo* using cell cultures and animal models. Next is the clinical phase, in which clinical trials are conducted, and this is the first time the drug candidate is studied in humans. If the drug candidate is shown to be safe in humans and has the desired therapeutic effects, it is approved and considered as a drug. Finally, the implementation phase entails studies of the approved drug. The drug discovery process is long and complex.[15] I return to different stages of the drug discovery pipeline in my discussion in sections 2.2.3 and 4.2. However, in this section, I give an overview of the whole process, with a focus on the ways in which it is managed in order to minimise the risks of failure, in particular failure for a lead to match the properties of a desired drug. The drug discovery and development process I described here is a high-cost and high-risk process, in which the chance of leads making it to the final stage of approval is low. The reason for this is twofold. Firstly, the process of extrapolating molecules' behaviour *in vivo* from the drug discovery and development

[15] See Nwaka and Hudson (2006) for a detailed overview of the drug discovery pipeline. Frearson et al. (2007) provide a detailed description of the target assessment and validation (discussed in detail in section 4.2). Torlee et al. (2010) discuss the pre-clinical development and the clinical trial stages for the NCE Fexinidazole for HAT treatment in great detail.

phase where drug candidates are studied *in vitro* means that drug candidates that might show high potency for targets, but then might not be as potent when they are tested in animal models or humans. Secondly, and specific to NTDs, the research approach of DNDi is focused on developing drugs that meet specific patients' needs (see section 6.1.3 for a detailed discussion on patients' needs), and therefore making the conditions in which drug candidates can be approved more stringent. The specifications for a drug derived from patients' needs are listen in a Target Product Profile (TPP).[16] TPPs are defined at the beginning of the process to guide decision-making during the drug discovery process. For instance, a molecule is identified a 'lead' (and a lead is considered a drug candidate) only if it fulfils the criteria listed in the TPP . As stated in Wyatt et al.,

> The TPP can be used during the earlier phase of the drug discovery process to define the attributes required for drug development candidates or compound series to pass from one phase of the drug discovery process to the next. (Wyatt et al. 2011: 1276)

The usual components of TPPs are a drug's pharmacological properties (desired efficiency, tolerable toxicity, dosage), target patient population, cost, and modes of delivery (oral, intravenous, intravascular). All components of the TPP are determined using existing knowledge of the parasite; disease epidemiology; patient demographics and patient groups' perception of disease; social factors (such as stigma) that influence health-seeking behaviour; and broader institutional, political and economic structures that provide healthcare services. TPPs are not static and need to be reassessed throughout the process, based on the outcome of the different stages. I will discuss TPPs in detail in section 3.2.

[16] TPPs are also called therapeutic product profiles in some contexts.

The TPPs guide and influence scientific practices in the drug discovery and development process. Furthermore, the TPPs are formulated based on our knowledge of diseases from biological, pharmacological, epidemiological and socio-economical perspectives. TPPs can be thought of as tools for scientists to assess the inductive risk of a lead molecule to match TPP at the end of the process (discussed in detail in section 6.1.2). Moreover, TPPs promote plurality of approaches in order to increase the confidence that the drug candidates will match the TPP. Target validation is a step in which a plurality of approaches to explain and explore phenomena is beneficial, as different approaches provide complementary and confirmatory evidence as to whether a target is essential for parasite growth. For instance, potential targets can be identified either by looking at the parasite's genome (they are often analogous to known molecules that play essential roles in metabolic pathways that are well understood in similar organisms) or using biochemical information about the parasite's metabolism.

Assessment of a potential target entails the use of various methods to prove that it is essential for parasite growth and survival. Two different validation methods are defined by Wyatt et al. (2011): *Chemical* and *Genetic*. *Chemical* validation involves using known drugs or experimental compounds to show that specific inhibition of the potential target is detrimental to parasite growth and survival. If the potential target is an enzyme with a known activity, for instance a kinase,[17] known kinase inhibitors are used to see if inhibition of the target is detrimental to parasite growth and survival. *Genetic* validation employs a genetic engineering method called 'gene knock-out'. This technique disables a given gene from functioning, resulting in the elimination of its product from the cell mechanism. So if the potential target X is assessed by genetic validation, the gene coding for X, called GENEX, is disabled. Once GENEX is disabled its product X is no longer

[17] Kinases are common proteins in all organisms that catalyse phosphorylation reactions.

available in the parasite. If the parasite ceases to grow or survive in the absence of X, it is accepted as a valid target for drug development. Both chemical and genetic validation have distinct advantages; however neither is sufficiently robust to provide the *conclusive result* required at this stage. As a consequence, both methods are used when possible. I will discuss this further in section 4.2

In addition to chemical and genetic target validation methods, further tests are employed to assess the potential target. In the Drug Discovery Unit at the University of Dundee, five other criteria are used in addition to target validation. These criteria are described by (Frearson et al. 2007) as follows:

- *Durability* looks at the presence of features that favour interaction with known structures.

- *Assay feasibility* is concerned with the development of assays that can be used in the next step of the research (this will become more evident in the following paragraphs).

- *Toxicity* is concerned with selectivity, i.e. if a homologue of the parasite target is present in the human genome, it may mean that a drug for such a target may be toxic for humans. An ideal target is one that is unique to the parasite.

- *Resistance Potential* is a problem caused by the presence of possible mechanisms to surpass the effects of manipulation of the target. The presence of these mechanisms can be predicted to a degree in this stage.

- *Structural information* is necessary for structure-based drug discovery as described below. This criterion examines if any information about the target is available.

Based on information gathered on potential targets in the light of target validation (genetic and chemical) and the five criteria above, potential

targets are evaluated using the ‘traffic light’ system where each criterion is assessed individually. For instance, if we take target validation:

i) **Red**: no or weak evidence that the target is essential for parasite survival.

ii) **Amber**: evidence from either genetic or chemical validation methods suggests that the target is essential for survival.

iii) **Green**: evidence from both genetic and chemical validation methods suggests that the target is essential for survival.

The traffic light system is a management tool to prioritise potential targets and helps scientists to assess the feasibility of succeeding with a given target. Thus, this is an important step to maximise the possibility of success in later stages.

The drug discovery and development pipeline is a useful case study to investigate the role of values in scientific practices. Moreover, it is an interesting case to use to understand the pluralities in scientific practices. I will return to the details of the pipeline later. In particular, I will focus on one specific NTD: Human African Trypanosomiasis (HAT), a parasitic disease prevalent in Sub-Saharan Africa. However, before going any deep into my case study, I will shift my focus to the second philosophical question I seek to answer in this dissertation. The drug discovery and development pipeline involves a plurality of approaches focusing on different aspects of phenomena, each providing an account that explores and explains specific features of phenomena. The second, and the major question I aim to address in this dissertation is how to make sense of such multiplicity. The final section of this chapter is reserved to providing a preliminary argument for epistemic pluralism, which I will develop in chapter 4 and chapter 5.

2.2.3 Epistemic Pluralism

The shift from the theory-centred traditional view in philosophy of science to PSP also allowed for a better understating of the pluralities in scientific practices. The pluralist thesis I develop in this dissertation takes the pluralities in scientific practices as the starting point. I argue that plurality must be regarded as an important characteristic of scientific inquiry; moreover, I argue that the role of PSP is to make sense of these pluralities and further the way we understand scientific practices and knowledge in light of the pluralities.

The scientific pluralism I put forward is the philosophical thesis that claims no single system or practice can explore and explain all aspects of some phenomena of interest. My argument follows directly from three pluralist arguments: those of Kellert, Longino, and Waters (2006), Chang (2012) and Mitchell (2003). While these three are not the only pluralist arguments, they align well with the pluralist theses I aim to put forward in this dissertation. These three pluralist arguments are directly engaged with current and historical scientific practices; moreover, they take the pluralities in scientific practices as evidence to pursue their pluralist arguments. The common feature of the three pluralist arguments put forward by Kellert, Longino, and Waters (2006), Chang (2012) and (Mitchell 2003) is the rejection of monist assumptions about science that can be broadly characterised as arguing that the aim of science is to provide a single complete and coherent account of the world. Instead, three pluralist theses acknowledge the multiplicity of aims in scientific practices, in which different systems of practices produce a partial account of phenomena. Section 4.1 provides an overview of the broader pluralist literature, followed by three sections discussing each work in detail before outlining the pluralist theses I aim to further. In the remaining part of this section, I would like to provide the reader with a preliminary argument for pluralism, by demonstrating the pluralities in pharmaceutical research that I take as evidence supporting pluralist arguments.

The pluralism I develop is empirically motivated, arguing that both historical and current scientific practices point towards the natural

world as complex and inexhaustible with a single, complete and comprehensive account. I further develop my pluralist argument by dissecting pluralist arguments as descriptive and normative. Descriptive pluralism, a philosophical interpretation of the multiplicities in scientific inquiry, is best exemplified by Kellert, Longino, and Waters (2006). Kellert et al. identify their position as the Pluralist Stance (discussed in section 4.1.1), which they define as the commitment to avoid reliance on monist assumptions about science and openness to the ineliminability of pluralities in scientific inquiry (Kellert, Longino, and Waters 2006: xiii)

Normative pluralism, on the other hand, aims to go beyond describing pluralities and argue for the benefits of plurality. Chang (2012) puts forward Active Normative Epistemic Pluralism, arguing that pluralism is more beneficial to science, given the aims and values in science. I focus on how the pluralist argument can be made normative. By comparing the two, I argue for a form of pluralism that is bounded by the context of inquiry (section 5.4). That is, while I argue that plurality of systems is beneficial in allowing us to produce and proliferate knowledge by tapping into different aspects of phenomena, the extent of the plurality of systems is also bounded by the broader context. Using the HAT case, I argue that the aims set by the WHO to eliminate this disease by 2020 leads to the prioritisation of anti-parasitic drug development, which in itself is a pluralistic enterprise.

The pluralist thesis I develop here aims to understand pluralities within the broader context of scientific practices. While I argue that pluralism must be regarded as an important characteristic of scientific inquiry, the limits of plurality must be realised within the context of scientific practices (I will further develop this point in chapter 5).

2.2.4 Anti Parasitic Drug Discovery and the Boundaries of Pluralism

In this chapter, I argued that focusing exclusively on theories as the subject matter of philosophy leads to inadequate accounts of scientific

inquiry by ignoring important aspects such as scientific practices. Following Ankeny et al. (2011), I provided an overview of different arguments made by Kuhn and the members of the Stanford School, emphasising the importance of broadening the subject matter of philosophy of science. The philosophical approach I take here aims to understand scientific inquiry as a whole, where theories are among other accounts that scientific practices produce to explain and explore phenomena. I take scientific practices and the various types of accounts they produce as the subject matter. Moreover, I consider the broader context of scientific practices, arguing that scientific practices are influenced, and to a large extent shaped, by their broader context.

This chapter also identified two questions to address in this dissertation: (1) how to interpret pluralities in scientific practices; and (2) the role of values in scientific practices. The preliminary argument presented in this chapter is that scientific practices must be studied in their broader context in order to understand how the aims and values operating in scientific practices are constructed. In the following chapter, I will provide a detailed overview of Human African Trypanosomiasis, attending to the broader context of current efforts to combat it and how the broader context shapes relevant medical and scientific practices.

Chapter 3

3.1 Human African Trypanosomiasis

In chapter 2 (section 2.2.2) I provided a brief introduction to Neglected Tropical Diseases, a group of diseases associated with poverty and neglected by both scientific medical research and policy debates (for instance, they are referred to as 'other' diseases in the Millennium Development Goals). In this chapter, I further develop my argument that the scientific practices (and accounts of the world produced by scientific practices) are to a large extent shaped by their broader context. I aim to argue that the current efforts to combat NTDs, particularly drug discovery and development programmes, serve as a good example of how the socio-economic and political context of diseases influence the aims of scientific practices and how they are organised. In addition, I will argue that the drug discovery and development process requires plurality of approaches in order to achieve their particular aims.

In this chapter, I will focus on a specific NTD: Human African Trypanosomiasis (HAT), also known as the sleeping sickness, a disease prevalent in sub-Saharan Africa (MAP) and endemic in 36 countries. HAT is a parasitic disease, caused by the Trypanosoma brucei and it is transmitted through the bite of tsetse fly. HAT is a fatal disease unless it is treated. Current tools used to diagnose and treat HAT are less than ideal, requiring intrusive techniques such as lumber puncture and archaic drugs with high toxicity. I will provide a historical perspective on HAT (from a Western scientific and medical point of view), followed by description of the causal agent and disease mechanism (3.1.2). I will also provide an overview of the current diagnostic methods (3.1.3), drugs available to treat HAT (3.1.4), epidemiological details of HAT and control methods. The second part of this chapter focuses on current efforts to eliminate HAT, and challenges to achieving this. The final section discusses the Drugs for Neglected Disease Initiative (DNDi), a public-private partnership that

focuses on developing new drugs to treat HAT that match patients' needs.

The main aim of this chapter to provide a background to the main case study used in this thesis. I am to provide a foundation for the rest of my argument by demonstrating how current research is influenced by the broader socio-economic and political context of this disease. Here, I argue that scientific practices are shaped by the broader context of the scientific inquiry. In order to understand the current scientific practices and broader efforts to eliminate HAT it is necessary to look both at the historical and current context of HAT. Here I will argue that the current aim to eliminate HAT, and the way to achieve this aim is determined by the current scientific and medical knowledge on this disease as well as the socio-economic and political context of the disease endemic region. In other words, I want to argue that WHO (and DNDi) put forward a set of pragmatic aims and values (based on the broader context and the current medical and scientific knowledge on HAT) in order to justify the aim of eliminating this disease by employing screening campaigns, and therefore prioritising the anti-parasitic drug discovery. Here I present the justificatory narrative for prioritising one set of approaches in scientific practices based on particular aims and values.

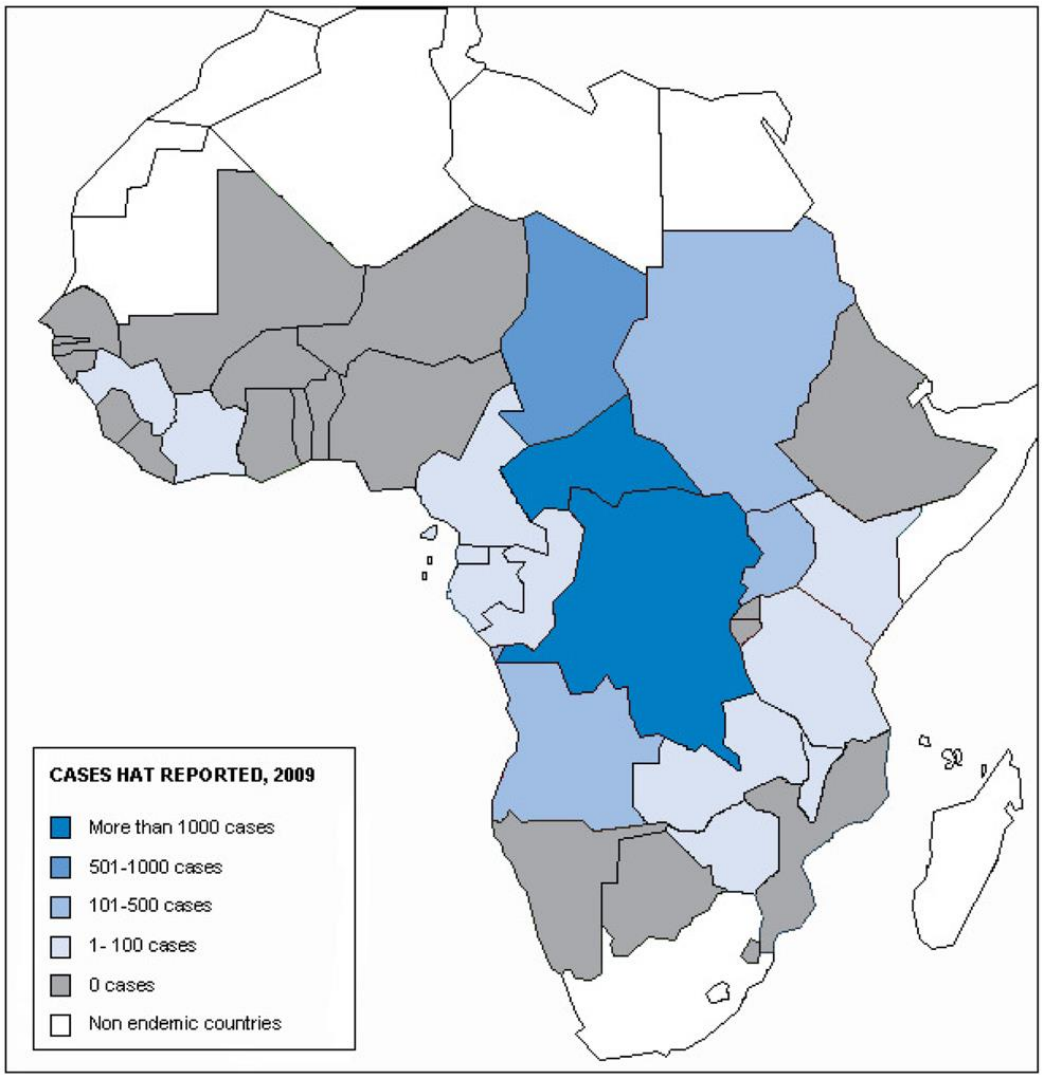

Figure 2. Map of HAT-endemic areas based on number of cases reported in 2009 (adapted from Simarro et al. 2011).

3.1.1 Historical Background of HAT

The early twentieth century witnessed several HAT epidemics in central and eastern parts of Africa, bringing HAT to the attention of the colonial administrations. Lyons (2002), Headrick (2014) and Raadt (2005) argue that these epidemics were caused by changes to social structures in the disease-endemic region due to colonisation. In particular, Headrick (2014) argues that the expansion of colonial rule in central and East Africa led to an increase in migration and trade across the continent, changing the social and economic structures in the regions. Changes in social and economic structures also brought about changes in the physical environment, providing conditions that allowed infection rates to increase to epidemic levels (see Ford, 1971; Iliffe, 1979; Giblin, 1990; Lyons, 2002; Headrick, 2014).

Here I argue that a close attention to the colonial history of HAT outbreaks shows that the disease aetiology is complex and the causes of HAT outbreaks can be conceptualised in multiple ways. As described above the biological cause of HAT in a person is *T. brucei* infection. However the conditions which people are exposed to the parasite depend on a range of factors. While disease was endemic in the area, changes in physical habitat and changes in social and political structures led to outbreaks at larger scales. Here I argue that the complexity of the aetiological picture leads to a plurality of approaches to control outbreaks and to the elimination of HAT. This is very clear in different ways in which colonial powers responded to outbreaks. In general, the colonial responses to epidemics had humanitarian, economic and scientific motivations (Lyons, 2002; Headrick, 2014). The colonial responses were *ad hoc*, depending on range of factors including political and economic interests of colonial powers, geographic features of disease endemic area, presence of other diseases (human diseases such as small pox or zoonic diseases such as rinderpest), etc. Treating this disease was seen as key to the development of Africa: HAT epidemics led to a shortage of manual labourer's necessary for colonial economic expansion, and made large

areas of land uninhabitable (Raadt, 2005; Headrick, 2014). One significant impact of colonialism was expansion of human habitat into tsetse areas for industries set up by colonial regimes such as rubber, farming, mining etc. (Lyons, 2002). Thus, HAT posed political and economic problems for colonial regimes in the region as much as a humanitarian problem. Different colonial regimes employed various control methods, depending on their relationship with the local populations, available resources and environmental factors (Headrick (2014) provides a detailed overview of the different colonial responses in central and eastern Africa). One significant approach is an environmental approach which involved destroying tsetse breeding grounds and removing people from tsetse infested areas. For instance, the British administration in Uganda employed environmental approaches including depopulating tsetse-infested areas (such as the islands and shores of Lake Victoria), destroying the tsetse breeding grounds and establishing camps in which patients could be treated (Headrick, 2014; Worboys, 1994; Soff, 1969).

The French and German administration on the other hand, employed a biomedical approach where the aim was to identify and treat HAT. For instance, in French Equatorial Africa, mobile teams of French military doctors and local nurses (along with several soldiers and porters for logistics) were employed to travel from village to village to examine and treat the local population (attending examinations was compulsory). The treatment used by the French was atoxyl, also known as arsanilic acid: the first drug used specifically to treat HAT. Atoxyl was developed by Robert Koch during his scientific mission to eastern Africa in 1906, during which he experimented on human subjects, testing different arsenic-based compounds. Atoxyl was found to be effective against HAT; however, it had severe side effects, such as leaving patients blind (Beck, 1971; Headrick, 2014). Discovery of atoxyl was part of the German medical efforts in Tanganyika, which relied on Robert Koch's recommendation to identify and treat with atoxyl. German administration used locals, named 'glad feelers' to identify patents and administer atoxyl. This programme had limited success owing to the

refusal of participation of the local population due to the high toxicity of atoxyl. The German approaches that focused on identification and treatment was cut short as German colonies were lost to Britain after the First World War. In keeping with this change in colonial administration following the First World War, the approach used in Uganda became largely environmental, including the widespread use of controlled burnings to clear wild bush.

To highlight the importance of finding a cure (or a solution) for HAT, it is useful to look at the rhetoric used to describe the drug Germanin (now known as Suramin), developed by the German company Bayerische Farbwerke in 1916 (Raadt, 2005). The discovery of this drug was announced in 1922 by the former District Governor in German East Africa in 1922, describing it as 'the key to tropical Africa, and consequently the key to all colonies' (Pope, 1924: 413). Germanin's formula was to be kept from other nations, unless Germany's former colonies in East Africa (lost after Germany's defeat in the First World War) were restored:

> its value is such that any privilege of a share in it granted to other nations must be made conditional upon the restoration to Germany of her colonial empire. (Pope, 1924: 413)[18]

In addition to environmental approach (such as bush-clearing in British Uganda), identify and treat approach (as in French Equatorial Africa), an integrated medial approach was developed by the Belgian administration in Congo Free State (CFS). The medical approach entailed opening specialised rural clinics and implementation of

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[18] Although its formula was kept secret, samples of this drug were provided for research purposes, and its formula was eventually revealed by Ernest Fourneau, working on HAT at the Institute Pasteur in France (see Raadt, 2005; Steverding, 2010).

compulsory screenings (Lyons 2002). Unlike the British, the Belgians did not attempt to separate the human habitat from tsetse, but instead aimed to eliminate *T.brucei* in human population by strict policing. This Belgian approach involved designation of a 'cordon sanitaire' around fly infested areas via the control of movements of people. Travellers were required to hold medical passports, and individuals suspected to have trypanosome were sent to medical camps, staffed by Catholic nuns, for treatment with atoxyl. These camps were unpopular due to their poor conditions, the side effects of atoxyl treatment, and the consequences of long-term removal from the community, and were thus guarded to preventpeople from escaping. This draconian approach was later replaced with medical corps which travelled to villages examining and treating people. Moreover, Belgian administration in CFS opened local clinics, hospitals and injection centres. This medical approach in CFS allowed screening of 70% of the population, leading to a significant reduction in the number of cases reported (Figure 3).

These approaches to control epidemics were regarded as successful, given that by the 1960s less than 5,000 new cases of HAT were reported in the disease-endemic region (WHO 2000). It is important to note that while the control measures were successful in overcoming epidemics, people living in the disease endemic areas had to live in a police state, forced to take part invasive medical checks and treatments with adverse side effects, displaced from their homes or witness destruction of the natural habitat where they live (Headrick 2014; Lyons 2002). In section 3.2.2 I will further discuss patients' perceptions of current control methods, underlining barriers and taboos associated with diagnostic and therapeutic measures.

With de-colonialisation of the disease endemic region and the establishment of new independent states, there has been a dramatic increase in the number of cases reported, reaching 37,000 in 1998 (WHO 2000). Ford (1971) argues that the control measures discussed above were not sustained in many cases (such as DRC) given that the

expertise in running the colonial control measures were confined to a ‘dwindling group of ex-colonial civil servants’. The problem was exasperated by the lack of interest in the disease by market driven pharmaceutical research (as discussed in section 2.2.2), and the lack of local expertise in the new generation of researched pursuing HAT research in the global north. The third factor that contributed to interruption of control measures was the competing health priorities (such as HIV/AIDS) as well as war and internal conflict in the region. Currently, HAT is endemic in 36 Sub-Saharan countries, and in 2013 87% of all HAT cases were reported in the Democratic Republic of Congo (DNDi 2014).

Here, I descried three main approaches employed by different colonial powers in disease endemic regions. Here I demonstrated the multiplicity of methods for controlling and eliminating HAT. However, I want to take my argument further to underline the plurality in the way in which we can understand the causal picture. While HAT is in endemic in central and eastern Africa (figure 2), the epidemics recorded in twentieth century (figure 3) are cause by the changes in natural habitat due to rapid colonisation and the subsequent changes in the socio-economic and political structure in the region. Different colonial responses were developed in particular socio-economic and political contexts. Moreover, these efforts were shaped by various environmental factors such as breeding grounds for tsetse fly, presence of other human (small pox) or zoonic diseases (rindpest). Each approach focused on the different part of the causal picture. For instance, the environmental approaches used by the British mainly focused on the entomological aspects of the disease targeting tsetse breeding grounds disrupting the parasite life cycle. Belgian biomedical approaches on the other hand focused on eliminating the parasite in human population through policing population movement and forced drug treatments.

The current challenge is to implement control measures to reverse the increasing trend of new patients. As discussed above there are

multiple ways in which disease aetiology can be conceptualised in current environmental conditions and socio-economic and political context. Thus, there are multiple ways in which HAT can be controlled and eliminated. Different approaches (environmental, biomedical, etc.) must be assessed in light of the boarder context of HAT outbreak . Here I will focus on the current efforts which focuses on screening campaigns aiming to diagnose and treat patients. However, it is also acknowledged that the screening methods cannot achieve control and elimination (as defined by WHO) without new diagnostic and therapeutic tools better suited to patients' needs. I will discuss current efforts to control and eliminate HAT in section 3.1.5. However, first I wish to provide a biological and clinical overview of HAT (3.1.2) and an overview existing diagnostic and therapeutic tools (3.1.3 and 3.1.4), underlining the shortcomings of such tools. With these overviews, I wish to provide my reader with the difficulties faced by the medical and scientific practices combating HAT, where these difficulties will explain the new efforts headed by WHO, which I will describe in section 3.2.

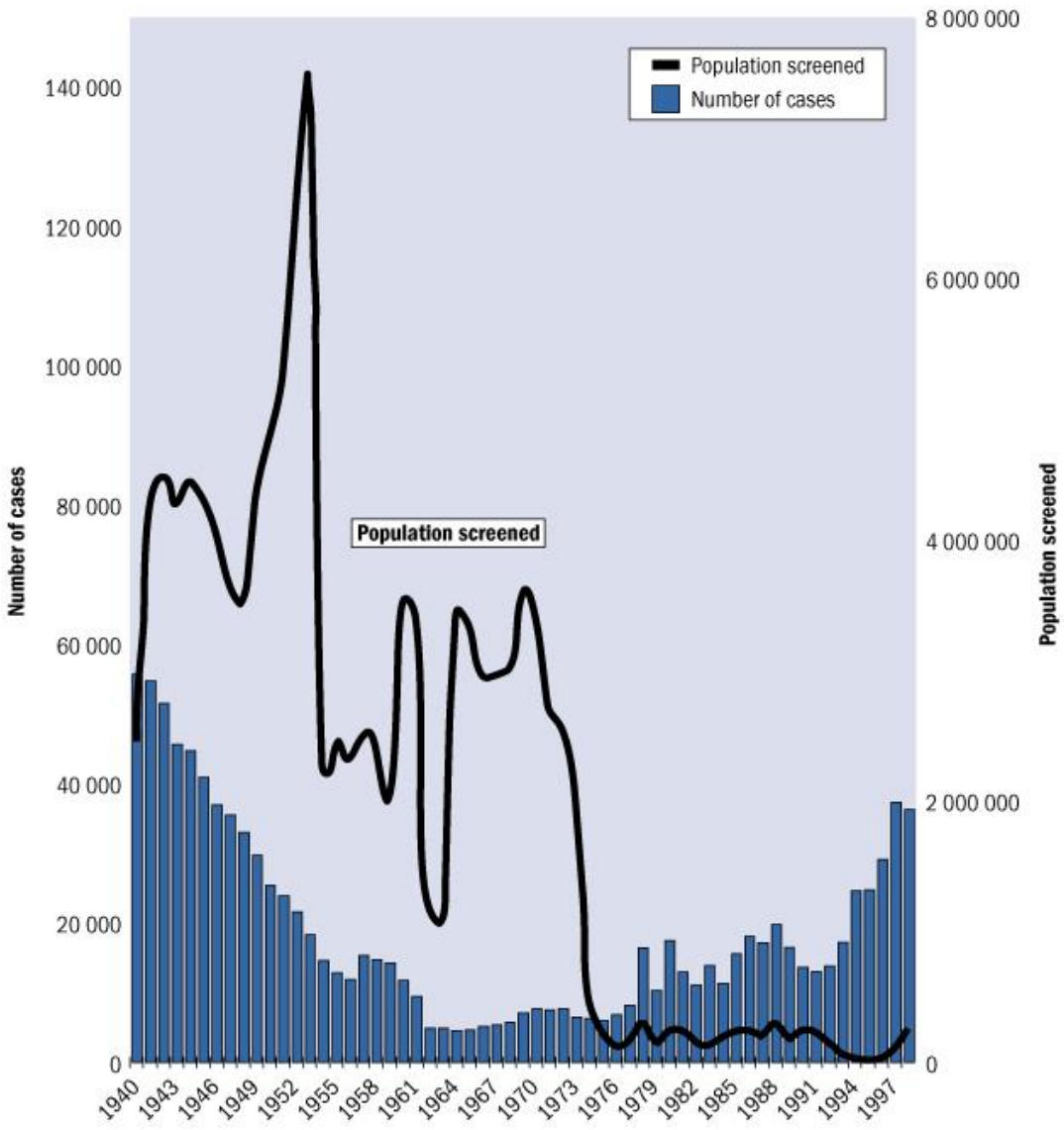

Figure 3 Number of cases reported versus population screened between 1940 and 1998. Data reported by the national African trypanosomiasis control programmes and published in WHO (2010)

3.1.2 Parasite and Disease

Human African Trypanosomiasis is a protozoan disease, caused by the unicellular organism *Trypanosome brucei.* This parasite belongs to the phylogenetic order Kinetoplatida, which also includes *Trypanosoma cruzi*, which causes Chagas Disease in South America, and *Leishmania* which causes leishmeniasis (Barrett et al. 2003; Stuart et al. 2008; Brun et al. 2010). In this section I underline that the *T. brucei* is a sophisticated organism, with complex cellular biology and defence mechanisms against the host immune system, and describe the clinical aspects of the disease to argue that HAT is clinically and epidemiologically complex, posing many challenges for current control and elimination efforts (discussed in section 3.2).

T. brucei has two sub-species*, T.b. gambiense* and *T.b. rhodesiense.* These sub-species are separated geographically, with *gambiense* prevalent in central and west Africa, and *rhodesiense* prevalent in south and east Africa (WHO 2000). The two subspecies are morphologically identical and cannot be differentiated under the microscope, but rather with *in vitro* methods using molecular markers (WHO 2013: 42), or via clinical observation: *T.b. gambiense* causes chronic illness, whereas *T.b. rhodesiense* causes acute illness. This difference can be linked to the difference in parasitaemia (presence of the parasite in blood stream, measured as parasite per ml of blood). In *T.b. gambiense* infections, there is often low parasitaemia, whereas *T.b. rhodesiense* has a rapid rate of infection and high parasitaemia (WHO 2013: 48).

Trypanosome parasites are extracellular and live freely in the bodily fluids, including the bloodstream, lymph and cerebrospinal fluid (Fenn and Matthews 2007). *T. brucei* has a unique cellular mechanism to evade the host immune system, whereby the parasite's cell surface is covered with variant surface glycoproteins (VSG), providing protection from both innate and acquired immune system (MacGregor et al. 2012). The VSG acts as a sieve, only allowing nutrients to reach the cell membrane while inhibiting larger molecules of the innate immune

system (such as antibodies). *T. brucei* can also adapt the VSG once the acquired immune system develops an antigenic response. *T. brucei* has over 2,000 individual VSG genes that code for glycoproteins, which have same overall structure but unique amino acid sequences, allowing the parasite to avoid the antigenic response of the acquired immune system (Engstler et al. 2007). The ability of *T. brucei* to neutralise the hosts' innate and acquired immune system makes it unfeasible to develop a vaccine, and untreated HAT is often fatal.

HAT is known as the sleeping sickness due to its most characteristic symptom. HAT infection has two stages: the haemo-lymphatic stage, and the meningo-encephatitivc stage. In the first stage, the parasite infects the blood and the lymphatic system causing clinically non-specific symptoms (WHO 2013: 103). In the second stage of the disease, parasites invades the central nervous system (CNS), leading to more specific symptoms, such as disturbances in the sleep pattern (Kennedy 2006a). The symptoms for HAT are the same in both *T.b. gambiense* and *T.b. rhodesiense* forms of the disease. As stated above, both forms of the disease are fatal, varying only in the frequency and the duration of illness. *Rhodesiense* is acute, leading to death within six months (reaching the second stage in a few weeks), whereas *gambiense* is chronic, leading to death within three years (roughly equally divided between the first and second stages) (Checchi et al. 2008). In the following sub-sections I will provide detailed descriptions of common symptoms in first and second stages of HAT infection.

Stage 1: In the first stage of HAT infection, patients experience non-specific symptoms such as fever and musculoskeletal pain (Blum et al. 2006). Another common symptom is headaches, which starts in stage one and gets progressively worse as the disease progresses into the second stage. Enlargement of spleen and liver are also observed in patients in the first stage of HAT infection; however, these symptoms

non-specific and are common in many other infections (WHO 2013: 103-105).

Stage 2: Disturbances in the sleeping patterns are observed in the second stage of HAT infection, characterised by frequent episodes of sleep, which can occur both day and night, lasting for short periods of time. The sleep episodes are described in the following way by L'Hermitte (1910) (as quoted in WHO 2013):

> Sleep overcomes the patient in a rapid and brutal way: the patient sleeps during a conversation without finishing the sentence or during a meal with a full mouth, the head sinks to the breast and the sleep is complete. During the first crisis it is possible to awake the patient, but in repeated crisis attempts to awake the patient are fruitless. (WHO 2013: 105)

HAT patients also develop neuropsychiatric disorders in the second stage. These include mood disorders, dementia, disturbance of consciousness, and epilepsy (Kennedy 2006a). Other common symptoms of the advanced disease are involuntary motor movement, tremor, weakness, slurred speech and difficulty walking (Blum et al. 2006). Patients will eventually go into a coma and die unless they receive treatment.

3.1.3 Diagnosis

As described above, the clinical symptoms of HAT (particularly in its earlier stages) are non-specific. Therefore, clinical diagnosis alone is not enough and further tests are required to confirm HAT (especially in earlier stages). There are three different diagnostic methods available currently: antibody detection, parasite detection and molecular detection (WHO 2013). Here I focus on three major methods currently used by control programmes, but there are many other methods available to confirm HAT (see Chappuis et al. 2005; WHO 2013). The important point here is that even though the diagnostic methods described below are widely used, they are not ideal for use in the disease endemic areas due to lack of resources and qualified staff. For

instance, the only available test to confirm the second stage of HAT is lumber puncture, which is a painful and invasive process. Given that HAT occurs in rural areas in sub-Saharan Africa it is important that the diagnostic methods are cost effective, simple (does not require sophisticated equipment and process) and rapid. The current diagnostic methods are less than ideal for use in the disease endemic region (see 3.2 for detailed discussion).

Antibody detection entails serological laboratory tests seeking the presence antibodies (IgG and IgM in particular) produced in high concentration in the presence of trypanosome in patients' blood stream. The most common format is the card agglutination test for trypanosomiasis (CATT), which is used widely by control programmes due to its simplicity, low cost and reliability (WHO 2013: 119). Currently, antibody detection is available for diagnosis of *T.b. gambiense,* but not for *T.b. rhodesiense.* This is due to the high antigenic variation of *T.b. rhodesiense* infections, meaning there are no specific antibodies to indicate the presence of trypanosome (WHO 2013: 128).

Parasitological tests entail direct confirmation of parasites in body fluids using a microscope. This is labour intensive and requires specialised equipment, including the microscope and the equipment to prepare samples for microscopic investigation (e.g. a centrifuge). Parasitological tests are the main method of diagnosis for *T.b. rhodesiense,* and used as a confirmation for *T.b. gambiense* (WHO 2013: 125). Therefore it is only used in *T.b. gambiense* cases when CATT test results are positive as a confirmation test.

Molecular detection techniques are also available, which confirm the presence of trypanosome DNA and RNA; however, these methods cannot be used in the field as they require specialised laboratory practices that cannot be employed by mobile teams. However, these tests can be used on stored samples for further study.

After the initial diagnosis confirming the presence of parasite in patients' bloodstream, it is necessary to see if the parasite invaded the central nervous system and determine the stage of the illness. Determining the stage of infection by investigating both vascular and central nervous system is necessary given the current treatments are different for first and second stages (discussed in detail in section 3.1.4). The second stage is confirmed by examination of cerebrospinal fluid (CSF) for both forms of *T. brucei* (Lejon and Bücher 2005). CSF is acquired by lumbar puncture. The stage of disease is determined by looking at the count of white blood cells (WBC) and presence of parasite in CSF:

Patients with ≤ 5 WBC/µl and no trypanosomes in the CSF are considered to be in the first-stage of the disease; those with > 5 WBC/µl or trypanosomes in the CSF are defined as in the second-stage. (WHO 2013: 131)

The three diagnostic methods listed here are the most commonly used. The important point here is that the currently available diagnostic methods are not suitable for use across most of disease endemic region due to a shortage of qualified staff and limited resources (I will further discuss the inadequacies of diagnostic methods in section 3.1.5)

3.1.4 Treatment

There are currently four drugs available for HAT treatment (Table 1). All four have severe side effects and only one can be used to treat both forms of *T. brucei*. All the currently available drugs are administered via injections over a period of time, which is undesirable in remote rural areas with limited access to clinical provisions. In this section, I provide an overview of all four drugs, with particular focus on their limitations.

Drug Name"	Used During:	Used Against:	Route of Administration:
Suramin	First Stage	*T.b. rhodesiense*	Intravenous
Pentamidine	First Stage	*T.b. gambiense*	Intramuscular
Melarsoprol	Second Stage	*T.b. rhodesiense* *T.b gambiense*	Intravenous
Eflornithine	Second Stage	*T.b. gambiense*	Intravenous

Table 1. List of currently available drugs for HAT treatment.

Suramin was developed in the early twentieth century (initially called Germanin as discussed in section 3.1.1) by the German dyestuff company Bayerische Farbwerke (Sneader 2005: 378). It is effective against both *T.b. gambiense* and *T.b. rhodesiense*; however, it is only used in the first stage of *T.b. rhodesiense* as it cannot pass the blood-brain barrier, and Surmin's use against *T.b. gambiense* is not recommended since it can lead to a severe allergic reaction in case of co-infection with onchocerciasis, a parasitic roundworm endemic to the East and Central Africa (WHO 2013: 163).

Suramin's action is slow, and treatment requires six injections, administered every seven days. Due to Suramin's low stability, it must be administered quickly once it is prepared (diluted in water) (WHO 2013: 155). Adverse side-effects of Suramin involve renal failure, bone-marrow toxicity, anaphylactic shock, skin lesions and neurological complications. However, it must be noted that this depends on the nutritional status of patients and concomitant diseases.

Pentamidine is used to treat the first stage of HAT *T.b. gambiense*. The treatment regimen entails daily injections for seven days (WHO 2013: 162). Pentamidine is delivered with an intramuscular injection,

since intravenous injections often cause hypotension. Pentamidine is well tolerated in general, with possible side effects including hypoglycaemia, gastrointestinal complications (nausea and diarrhoea) and pain and swelling at the site of injection. In addition, rare cases of leukopenia (raised liver function enzymes), hypoglycaemia and hyperglycaemia are reported (Sand et al. 1985). The range of side effects is due to high levels of pentamidine observed to be deposited in liver and renal cells.

Melarsoprol was developed in the 1940s and was used as a treatment for the second stage of HAT from 1949 (WHO 2013: 150). Melarsoprol is an arsenic-based drug treatment for second-stage HAT (WHO 2013: 157). Current Melarsoprol treatment for both *T.b. gambiense* and *T.b. rhodesiense* is 2.2mg/kg per day for ten days, administered intravenously. However, due to its low solubility in water it is administered with propylene glycol, which can cause irritation and pain, and therefore must be administered slowly via a drip.

Melarsoprol is highly toxic and has severe side effects that are life threatening: 10% of the patients develop encephalopathy, and half of the patients who develop encephalopathy die as a result of it (WHO 2013: 166). Melarsoprol also causes pyrexia, headache, gastrointestinal problems and cardiac failure (which leads to increases in the death toll).

Eflornithine was initially developed as an anti-cancer drug and is currently used for the treatment of second stage *T.b. gambiense* infection (and hirsutism). Eflornithine's efficacy against *T.b. gambiense* in animals was demonstrated in 1981 and its efficacy in humans in 1985 (Burri and Brun 2003). It was approved by the FDA as a treatment for *T.b. gambiense* in 1990, but production of Eflornithine ceased in 1995 due to low profits. Re-supply of Eflornithine was not until 2001, due to the efforts of WHO and MSF (WHO 2013: 150-152). Eflornithine has considerable side-effects, including bone-marrow toxicity, alopecia and seizures.

Eflornithine is administered intravenously every six hours for fourteen days. Although it is free to access this drug (due to donations by Sanofi) the administration of this drug is difficult in resource-poor settings due to the period of hospitalisation required. In order to reduce the treatment time, Eflornithine is co-administered with Nifurtimox, a drug used for the treatment of Chagas disease caused by *Trypanosoma cruzi*. The combination treatment is called NECT, which reduces the number of eflornithine infusions from 56 to 14, shortens the hospitalisation time and decreases the toxicity due to eflornithine exposure (DNDi 2014). Development of the NECT treatment is a result of the DNDi strategy and will be discussed in section 3.4.1.1.

Besides the severe side-effects, existing drugs have other limitations, including delivery methods, lengthy treatment periods and cost (see section 3.2). There is a need for new drugs that have tolerable side effects, shorter treatment periods and that can be delivered with no need for specialist equipment or staff.

3.1.5 Epidemiology and Control

So far, this chapter has focused on the disease mechanism and tools to diagnose and treat HAT. In this section, I concentrate on the control and surveillance methods employed to combat HAT. As discussed above (3.1.1), the control mechanism employed by the colonial administrations were effective in eliminating HAT; however, the interruption of control and surveillance activities after the advent of independence led to the re-emergence of HAT at an alarming level in the disease endemic regions (see WHO 2000, Brun et al. 2010). This re-emergence has led the WHO to enhance its role as a coordinator and promote networking among different partners (Including the governments of disease-endemic countries, pharmaceutical companies and NGOs). The WHO's efforts led to an increase in control and surveillance in the disease endemic regions, leading to a 69% reduction in cases reported, from 36,585 new cases to 11,382 new cases between 1997 and 2006 (Brun et al. 2010: 148). These figures must be regarded with caution, as there is a problem of under-

reporting, and lack of patient participation in the control and surveillance programmes (see section 3.2.2). Moreover, the success of the control measures is not sustainable in the long term, given that interruption of the control and surveillance programmes can lead to the resurgence of HAT. Overall, the current control methods rely on inadequate tools (both diagnostic and therapeutic) and also are not favoured by people living in disease endemic areas due to high cost and other social factors (see section 3.2.2) Before I discuss efforts to improve the control methods, I provide a detailed overview of the methods themselves.

The control methods used for *T.b. rhodesiense* and *T.b. gambiense* are different due to epidemiological differences between the two forms of the disease. The differences in the epidemiological characteristics are due to the known reservoirs of infection i.e. a species (or group of species) that permanently maintains the parasite population and from which the pathogen can be transmitted to the target population (WHO 2013: 8). For *T.b. gambiense,* the main reservoir is humans.[19] For *T.b. rhodesiense*, livestock and wild game animals act as additional reservoirs of infection. The existence or absence of an animal reservoir leads to significant differences in transmission patterns. The main purpose of control is to stop the transmission of parasites from reservoir to vector and from vector to host and other reservoirs. Therefore, the epidemiological differences between *T.b. gambiense* and *T.b. rhodesiense* lead to differences in how they can be controlled and eliminated.

There are no vaccines available for HAT (see section 3.1.2) and due to high toxicity of the current drugs, prophylaxis is not possible (see section 3.1.4). Strategies to control and eliminate HAT rely on detecting and treating infected humans (hosts), control of animal reservoirs, and vector control. Control of both forms of HAT requires

[19] There is no conclusive study to rule out the presence of other unknown reservoirs in the disease-endemic region.

understanding of the habitat of the tsetse fly, the main reservoirs of infection in a specific region and the human interaction with the environment.

Case Detection

Case detection can be achieved through active or passive case detection methods. Active case detection relies on mobile teams to travel disease-endemic regions in order to screen a population at risk of infection using the aforementioned diagnostic tools (CATT for *T.b. gambiense* and parasitological tests for *T.b. rhodesiense*, followed by a lumber puncture to determine the stage) and treat patients who tested positive. Passive case detection relies on health centres and hospitals where patients can be tested and treated. It is important that health centres and hospitals have necessary resources and infrastructure to provide adequate services (refrigeration and sterilisation are just two things difficult to maintain in disease-endemic areas). Furthermore, because the clinical symptoms of HAT are non-specific, especially in the first stage (see sections 3.1.2.1 and 3.1.2.2), patients who seek medical help often do so in the later stages of the disease, by which time the disease has had permanent effects on the neurological system.

Active screening is put forward by the WHO as the main control method for *T.b. gambiense.* In the absence of animal reservoirs, population screening and treatment in humans can be very effective in reducing the rate of infection without any other environmental or vector controls. For example, a recent resurgence of *gambiense* HAT in Luba, Equatorial Guinea, was quelled, eliminating *gambiense* HAT from this region via a major screening campaign (Simarro et al. 2006).[20] On the other hand, control programmes for *rhodesiense* HAT infections rely on passive case detection. Active case detection is not preferable in this

[20] Elimination of *T.b. gambiense* with current control methods is only plausible if these control programmes are well resourced and implemented frequently; see section 3.2.1

case due to the rarity of *T.b. rhodesiense* infection. Moreover, due to the acute progression of *T.b. rhodesiense*, infected patients develop specific symptoms much quicker, and thus seek medical help sooner.

Control of Animal Reservoir

For control of *T.b. rhodesiense*, the animal reservoir must also be targeted. The WHO state that in areas where there is a high prevalence of HAT in livestock, it is essential to prevent transmission from the animal reservoir to humans (WHO 2013: 195). For control of livestock and the domestic reservoir, chemotherapy or prophylaxis is used to complement passive case detection campaigns among the human population. Although wild animals act as a reservoir for HAT, it is not acceptable to intervene in their natural habitat, nor are such interventions are economically feasible to maintain on a large scale (WHO 2013: 196)

Vector Control

In addition to control in humans and animals, vector control is utilised in both forms of HAT. There are multiple ways to control the vector. Section 3.1.1 discussed clearance of vegetation and treatment of tsetse breeding sites with insecticide as the main methods of vector control methods in the first half of the twentieth century (WHO 2013: 196). Although this proved effective, these methods are no longer used due to environmental concerns (Jordan 1986). Current methods include the use of tsetse traps and screens (Lindh et al. 2012) and insecticide-treated cattle as bait (Holmes 1997).

Elimination of both forms of HAT requires interruption of transmission from reservoir to host. Due to the presence of animal reservoirs (both domestic and wild) in the case of *rhodesiense* HAT, the interruption of transmission is complex and deemed unfeasible by the WHO (WHO

2013).[21] Humans constitute the major (and only known) reservoir of infection for *gambiense* HAT, which makes elimination of this form of HAT feasible. Elimination in this context has a precise definition provided by the WHO. In the following section I will focus on this definition of elimination, and sketch out the rationale put forward to eliminate *gambiense* HAT. Focusing on WHO rationale to eliminate HAT (in a particular way) will allow me to show the way the context of HAT shapes the scientific and medical practices employed to eliminate HAT.

3.2 Elimination of HAT

In this section I aim to provide a definition of elimination set out by the WHO for *gambiense* HAT, which they deem to be feasible. I will also sketch arguments outlining the current challenges to achieving elimination determined by WHO.

The WHO's current aim is to eliminate HAT by 2030. Elimination is defined as:

> reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, as a result of deliberate efforts; continued action to prevent re-establishment may be required. (WHO 2012b: 3)

In addition, the WHO has an interim aim: elimination as a public health problem by 2020:

> detection of less than 1 new case per 10 000 inhabitants in at least 90% of endemic foci reporting less than 2000 new cases annually at continental level by 2020. (WHO 2012b: 3)

[21] *Rhodesiense* HAT is currently rare and does not pose a significant risk in disease endemic regions.

Elimination of *gambiense* HAT is deemed feasible by the WHO based on the fact that:

> *T.b. gambiense* is epidemiologically vulnerable. Humans are the significant reservoir, and the control strategies in use are effective. In an adequately resourced programme, a single round of active case detection and treatment through mass screening will result in identification of 50–80% of prevalent infections. Annual screening with or without supplementary vector control can reduce the prevalence to very low levels within a few years. (WHO 2013: 199)

Moreover, elimination was almost achieved by colonial administrations (see section 3.1.1):

> Proof of principle exists for gambiense HAT. In the 1960s, near-elimination was achieved with tools inferior to those currently in use, when the annual incidence in Africa dropped below 5000. Evidence that elimination is possible in some settings emerged more recently from Equatorial Guinea. (WHO 2013: 199)

The geographical distribution of *gambiense* HAT is well-known, wherein disease foci remains stable unless there are significant environmental changes in disease-endemic regions (WHO 2000). Detailed geographic knowledge is extremely useful for active case detection campaigns. Moreover, the scope and distribution of HAT in the disease-endemic area is limited:

> Less than 10% of the land area of endemic countries is estimated to be at risk, and 97% of reported cases are in only five countries: Angola, the Central African Republic, Chad, the Democratic Republic of the Congo and South Sudan (*94*), with a substantial majority in the Democratic Republic of the Congo. (WHO 2013: 200)

In order to achieve elimination as described above, active case detection and screening are crucial. Active screening campaigns are necessary given that population under risk live in remote areas with

limited access to healthcare facilities, and patients only self-refer in later stages of the HAT (as discussed in section 3.1.5). Therefore, active screening teams are necessary to reach these populations in order to detect and treat patients. However, as mentioned above, the current control methods are limited due to deficiencies in diagnostic and therapeutic tools, posing challenges to the WHO elimination goal. In the following sections I will focus on these challenges, first from a public health perspective (i.e. the practitioners' perspective), followed by challenges arising from public perceptions of screening programmes, particular diagnostic and treatment tools. These two issues are linked; however, here I discus them separately in order to highlight the variety of values from broader context taken into account in eliminating these challenges. This point is particularly important for my thesis, given that the main challenge is lack of drugs suitable for use in the disease-endemic regions. Thus, drug discovery and development projects aimed at developing drugs that overcome these challenges are guided by a broad range of values that I will discuss in sections 3.2.1 and 3.2.2.

3.2.1 Structural Challenges to Elimination

Controlling and eliminating HAT relies on sustained political support from disease-endemic countries and requires funding to implement surveillance activities.[22] One major challenge to implementing the surveillance and control measures necessary for elimination is the cost and availability of staff:

> The cost of intervention varies according to the accessibility of the foci but remains high due to the complexity of diagnosing, treating and following up patients. Intervention requires well trained staff and that mobile teams of specially trained health-

[22] Detailed discussion of control and surveillance programmes between 2000 and 2009 can be found in Simarro et al. (2011).

> care workers and specialized treatment services be available. (WHO 2010: 87)

It is important to note that the importance of sustaining the current control and screening methods, given that lapses in implementation of control and screening in the past has led to re-emergence of disease. However, implementation of the control methods is expensive and often compromised due to competing health priorities (see Simarro et al. 2015; Berrang-Ford et al. 2011).

Another challenge (directly linked to cost and availability of staff) is lack of access to populations under risk, given that HAT is most prevalent in remote areas (Simarro et al. 2014). It is expensive and time-consuming for mobile teams to reach remote areas carrying equipment. Furthermore, it is also a challenge to treat patients, as this requires hospitalisation (Mpnaya et al. 2015).

In summary, current control and screening methods are only effective if they are implemented without interruptions. Sustained implementation is expensive and relies on funding from partners (such as the initiative Programme National de Lutte contre la Trypanosomiase Humaine Africaine, [PNLTHA], funded by the Belgian government) and donations (from pharmaceutical companies Sanofi and Aventis). Therefore, WHO's aim to eliminate HAT requires expansion of the control and screening, as well as research developing new tools to overcome the inadequacies of current methods:

> The most immediate challenge is to expand and sustain control and surveillance activities using the best tools available. Research into new tools should be accelerated. Awareness about the disease should be raised, control of the disease should be prioritized and fundraising should be advocated. WHO should continue to support countries and to coordinate the work of all parties concerned with the control of, and research into, human African trypanosomiasis. (WHO 2010: 89)

In section 3.3 I will focus on research efforts to develop new drugs that will help with the cost of treatment, the need to carry out lumber punctures (by treating both stage one and two) and so forth. However, first, I will focus on another important challenge: making sure that patients participate in the control and screening campaigns. In the following section I focus on factors that determine patients' participation in the current control and screening programmes, focusing on social barriers and taboos that stop patients from taking part in both active and passive case detection campaigns. In the following section, I aim to demonstrate patients' perception of current control and screening methods, underlining the importance of patients' needs in the research and development efforts discussed in section 3.3.

3.2.2 Social Barriers and Taboos

Determining patients' perception of current control measures is a difficult task given that *gambiense* HAT is currently considered endemic in 24 countries, affecting a diverse group of communities. In order to keep my argument focused I will concentrate on patients' perception of HAT and the current control measures in the Democratic Republic of Congo (DRC), given that 83% of all reported HAT cases in 2013 were in the DRC (DNDi 2014). In this section I will focus on community participation in current HAT control. In chapter 6 (section 6.1) I provide a detailed discussion of the socio-economic and political context of current HAT control, extending my analysis to communities in Uganda and Angola.

As discussed above, in both active and passive control methods, the stage of disease influences the healthcare-seeking behaviour of patients. That is to say, patients with specific symptoms are more likely to seek and participate in control measures, in comparison to patients with non-specific symptoms (often seen in the first stage of HAT).

Hasker et al. (2011) study the healthcare-seeking behaviour in DRC, reporting that 50% of all HAT cases were detected through passive screening. Moreover, Hasker et al. (2011) report that participation in

active screening campaigns is very low, even when communities were visited by mobile teams. Hasker et al. interviewed a group of patients (diagnosed by passive screening) from two endemic areas in DRC, revealing that the 80% of patients lived in villages visited by mobile teams. However, only 4% of the patients interviewed by Hasker, et al. participated in the active screening campaigns when their village was visited by a mobile team. The negative trend in participation in active screening campaigns, reported by Hasker et al. (2011) is not an exception (see Robays et al. 2004, Robays et al. 2007).

Robays et al. (2007) present findings drawn from 33 focus group discussion in the province of Bandundu in DRC, covering twelve villages, eight in a savannah setting and four in the fluvial setting. In this province, thirteen mobile teams are active, visiting each village with two days' notice. Robays et al. (2007) argue that HAT is well known by the local communities and recognised as a major problem, but that there are major barriers to participation in screening. Robays et al. assert that toxicity and cost of treatment are two major barriers to participation in active case detection programmes. In addition, Robays, et al. argue that lack of confidentiality is an issue during screening due to the stigma attached to this disease.

Robays et al.'s interviews show that the cost of treatment hinders people from participating in screenings:[23] given that they cannot afford the treatment, why should they participate in screening? People refusing to participate in screening is thought to create a group of 'core transmitters' who remain infectious and act as a reservoir. In addition to the cost, people refuse to participate due to the stigma attached to mental health problems linked to HAT infection. Robays et al. argue that after the course of treatment patients are not taken seriously in the

[23] Patients are required to pay for a screening card during mobile teams' visits. The costs of screening (which can be as high as 1.5 US$ per family) and treatment were both identified as major barriers to participation within communities interviewed by Robays et al.

community. In particular, the lack of confidentiality during screening was quoted as problematic, since infection leads to exclusion from society but patients are vulnerable to social pressure or state sanctions if they fail to comply with the procedure.

Robays et al. argue that the toxicity of treatment (in particular, death and encephalopathy caused by Melarsoprol) constitute a major setback to patient participation. The death of seemingly healthy patients causes non-participation in screening programmes. The unpredictability of the outcome causes a lot of concern among patients and leads to conspiracy theories about the intentions of the mobile teams and medical staff. Another setback is the rest period after treatment. Participants claimed that a six month rest period where they are asked to refrain from labour and sexual activity creates social problems for the community, as the main income for participants is subsistence farming (and fishing in fluvial areas) and female participants also described marital problems caused by abstaining from sexual activity for six months.

Robays et al. (2007) argue that lack of participation in the current control and screening programmes is caused by the inadequacies of the current control measures (cost, lack of confidentiality) and treatment (toxicity, cost, recovery period), and not a lack of knowledge on the part of local communities affected by HAT. Thus, to improve patient participation in HAT control, changes must be made to the healthcare system. These can be short-term measures such as lowering the cost, using less toxic treatments (NECT), improving confidentiality, and long-term, such as developing new drugs and diagnostics that cater to patients' needs and are suitable for use in the field. In section 3.3 I will discuss the short-term and long-term in detail. However, first I will fist discuss the details of the socio-economic and political context HAT, where the current tools to eliminate HAT are inadequate. I argue that the current tools to diagnose and treat HAT are inadequate given the broader context oh HAT.

As argued above, the active screening campaigns play a significant role in the control of HAT in terms of reaching out to the majority of population that has no access to healthcare. However, to progress it is necessary to increase community participation in active screening programmes. It is important to stress again that these barriers are not due to lack of knowledge about the disease and treatments: as Robays et al. (2007) argue, the barriers are due to inadequacies of the current control and screening methods, particularly the cost and toxicity (among others mentioned above). For the WHO's aim to eliminate HAT by 2030 to be fulfilled, continued research to overcome the aforementioned inadequacies is crucial:

> The control tools currently available are not the most appropriate to design fine-tuned strategies for each epidemiological setting identified. Continuous research is needed to improve these weaknesses, mainly to allow the involvement of health services in eliminating Gambiense trypanosomiasis. (WHO 2012b: 25)

As discussed above the currently available drugs have unacceptable levels of toxicity and atrocious side effects. New tools must be designed to match the patients' needs: for instance, new drugs need to be orally bioavailable, have low toxicity, be effective against both stage one and two, and require a shorter treatment period. In the following section I shift my focus to research efforts to develop new treatments. In particular, I will focus on the public-private partnership Drugs for Neglected Disease Initiative (DNDi) that focuses on developing drugs that match patients' need. DNDi's patient needs-driven approach is a prime example of values arising from the socio-economic and political context influencing scientific practices.

3.3 Drugs for Neglected Diseases Initiative - DNDi

The Drugs for Neglected Disease Initiative (DNDi) is a public private partnership established in 2003 by Médecins Sans Frontières and the WHO to address specific research development needs of patients

suffering from Neglected Tropical Diseases. DNDi's work is patient-centred using target product profiles (TPPs, first discussed in 2.2.2) to guide and influence scientific practices. In this section I will focus on DNDi's approach to research and development for NTDs, underlining how a set of values is constructed based on the broad context of HAT that guides scientific practice. In the previous section I argued that the current tools are inadequate, underlining the need for new diagnostic and therapeutic tools. Herein, I focus on anti-parasitic drug discovery and development programme directed by DNDi to argue that broad range of values from the socio-economic and political context of HAT shapes the scientific inquiry conducted by DNDi. Here I focus on TPP as overarching set of values that describe the succinct properties of drug that matches patients' needs. The anti-parasitic drug discovery and development is a case where multiple approaches and accounts are employed to explore and explain different aspects of the phenomena (discussed in chapter 4 and 5). Moreover, it is a case where the influence of values on scientific inquiry is very clear (discussed in chapter 6) in the way that the broader socio-economic and political context of HAT determines particular aims of scientific practices and provides set of values to guide scientist along the way.

DNDi was established to address an existing imbalance in the impact NTDs have on the global disease burden and the lack of research that went into developing new drugs to treat these diseases. Trouiller et al. (2001) assert that only 1.1% of all new drugs approved between 1974 and 1999 were for NTDs, despite NTD's contributing to 12% of the global disease burden. DNDi's main aim is to develop new chemical entities (NCE) for the treatment of NTDs using an alternative approach to profit-driven pharmaceutical industry.

DNDi operates as a 'virtual pharmaceutical' company in which all the R&D activities are outsourced to different partners, while the organisation and management of each project is undertaken by DNDi. Within its first ten years DNDi formed over 350 collaborations globally in 43 countries, with partners including pharmaceutical and biotech

companies, universities, research institutes, governmental and non-governmental organisations (DNDi 2011) and delivered six new treatments and twelve NCE in preclinical and clinical development since 2003 (DNDi 2014).[24]

DNDi's alternative R&D model has four principles: keeping patients' needs at the centre of the R&D process; open access to knowledge and access to treatments; maintaining financial and scientific independence; building and sustaining solid alliances (DNDi 2014). The first principle, *keeping patients' needs at the centre of the R&D process*, is argued to be the most fundamental and distinct of all practices that take place in the organisation (DNDi 2014). Patients' needs are taken into consideration during the selection of target diseases, definition of aims, particularly during key decision and policy-making platforms:

Beginning with the end in mind, and keeping it in mind until patient needs are addressed appropriately, is ingrained in the way the organizational model is designed. (DNDi 2014: 3)

Target product profiles (TPP) play an important role in making sure that the patients' needs are considered at every stage of research. DNDi's definition of a TPP is a 'succinct description of the ideal specifications needed for a treatment, considering the needs of the patients and the main characteristics of [the] related health system'. (DNDi 2014: 3).

TPPs are disease-specific, and are determined by multiple actors including researchers, clinicians, patient representatives and disease

[24] Pharmaceutical companies (including AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Roche and Sanofi-Aventis) had the average overall output around ~7 NCE per year between 2005 and 2010 (Bunnage, 2011). During this period, total R&D spending increased, reaching $60 billion per annum 2010. Taking these numbers into account, the DNDi model can be seen as a success, however further work is required for a healthier comparison.

control programme managers. The purpose of a TPP is to outline the properties of a desired product via the following questions:[25]

- Indications: Which disease(s)?
- Population: What type of patients and where?
- Clinical Efficacy: Does it treat the infection effectively?
- Safety and Tolerability: What level of acceptability for adverse events?
- Stability: How long is the shelf-life of the drug(s) and what are the storage conditions?
- Route of Administration: What is an acceptable way to administer the treatment to the patient population?
- Frequency and Treatment Duration: How often and for how long must it be given?
- Cost: Will it be affordable to the target population or health system?

TPPs links the scientific practices and broader context of HAT. Here I argue that TPPs are overarching values guiding scientific practices, most notably allowing scientist to assess the likelihood of a given project to yielding a drug candidate that matches patients' needs (see section 6.1). For instance, in early stages of the drug discovery pipeline, scientists must make judgements when validating drug targets (see Frearson et al. 2007; Torrie et al 2009).

[25] In chapter 4, I describe how Wyatt et al. (2011) demonstrate different criteria that link the molecular properties of drug targets with the requirements listed in TPP.

In summary, DNDi can be understood as a virtual drug company that brings together partners with different capabilities to contribute to the R&D process and manages the whole process. DNDi's initial step can be seen as developing the TPP followed by forming a partnership that can deliver the target drug. In the following section I want to shift my focus to DNDi's 'two-pronged approach to R&D' in order to demonstrate different strategies in developing treatments that best suit patients' needs. Here I argue that the TPP consists of overarching values that direct and guide scientific practices involved in the R&D process.

3.3.1 'Two-pronged' approach to R&D

DNDi adopts two different strategies to address both urgent needs in the field in a short space of time and long-term goals to develop new chemical entities capable of changing how diseases are managed clinically, supporting sustainable control and elimination according to the WHO's definitions. The short-term approaches focus on re-appropriation of existing drugs and chemical entities for NTD treatment or optimisation of NTD treatments already in use. DNDi's short-term approach addresses very urgent needs, for instance in the case of the approval of Nifurtimox–Eflornithine Combination Therapy (NECT), which addressed the urgent need to replace Melarsoprol and its severe side effects. The long-term approach entails developing new medicines according to the TPP.

Short-Term Approach: NECT

Nifurtimox–Eflornithine combination therapy consists of co-administration of two registered drugs. NECT is the first new treatment to be registered for HAT in 25 years. Nifurtimox is a medication used widely for the treatment of Chagas disease, also known as American Trypanosomiasis. Chagas disease is caused by the parasite *Trypanosoma cruzi* (in the same genus as *T. brucei*), which is completely curable with nifurtimox if the treatment is administered swiftly. Eflornithine was initially developed as a cancer drug, which

later received attention for its effect on *T. brucei.* As discussed in section 3.1.4, eflornithine was proven effective against *T.b. gambiense* in the 1980s and approved by the FDA in 1990, but was only available for patients in 2001 through the efforts of MSF (Priotto et al. 2006). The combination of these treatments was facilitated by DNDi, starting in 2003 with a phase III clinical trial in Brazzaville in the Republic of Congo. This trial was continued and extended to various areas in the DRC. This study was a multi-centre clinical study with 287 patients enrolled and completed in 2008. NECT combination therapy was approved and added to WHO's essential medicines list. (Opigo and Woodrow 2009) The benefits of combination therapy in comparison to the Eflornitine mono therapy are significant: the total number of intravenous infusion of eflornithine is reduced from 56 to 14 and the number of days of hospitalisation is reduced from 14 to 10. The combination therapy requires two doses during day time instead of four times day and night, making NECT more suitable for the resource-poor local healthcare system and patients.

The short-term approach is to deliver rapid solutions to urgent situations. However, as discussed above, this requires new drugs to be available, to achieve the WHO's aim of elimination by 2030. Therefore DNDi's second approach is to focus on developing new chemical entities that can be used for HAT treatment.

Long-term approach: New Chemical Entities

The long-term approach entails development of 'break-through' therapies that can transform the way patients are treated:

Such 'breakthrough therapies' – ideally implemented at the primary healthcare and/or community level in combination with a simple diagnostic tool – have the potential to fundamentally transform how patients are treated for their disease, supporting optimal individual case management and, potentially, large-scale disease elimination strategies. In addition, such treatments would relieve the burden placed on healthcare workers and lower the cost to health systems. (DNDi 2014: 13)

Unlike the short-term approach where the focus is on the clinical research (modifying the registered treatment), a long-term approach starts with pre-clinical drug discovery and development research. The long-term approach is crucial for HAT, given that current tools (both diagnostic and therapeutic) have major limitations (discussed in section 3.2) in achieving elimination. That is, in order to achieve elimination by 2030 there is a need for new drugs that are better suited for use by active case detection campaigns i.e. orally bioavailable, with has short treatment and recovery times, tolerable toxicity and manufactured and supplied to patients at low cost.

DNDi's virtual R&D model faces several challenges. The most prominent is access to knowledge, compound libraries and data from second parties. The specific contracts with partners use financial and economic incentives to build partnerships with second parties such as private pharmaceutical companies and academic research institutions with in-house expertise on drug discovery and development.

Two distinct methods are employed in the long-term approach. The first is intensive compound library screening, where the first step is the validation of a drug target and screening compound libraries in order to find small molecules that can interact and modulate the target activity. In the following chapter, I am going to focus in the initial stage target validation, paying close attention to Wyatt et al.'s paper that provides an account of how TPPs are used in scientific practices. In my argument I underline how TPP is used to justify plurality of practices employed to fulfil the aims of research.

An example of a compound developed by DNDi is Oxaborole SCYX-7158, a NCEs developed by DNDi, managed to advance from early drug discovery and development phase to, pre-clinical research phase where it was tested *in vivo* models was approved for phase I clinical trials in humans in 2012 (DNDi 2014).

The second method is compound mining where past drug discovery and development efforts that never reached a conclusion (for

commercial or strategic reasons) are revisited. For HAT, assessment of anti-invectives called nitroimidazoles led to the re-discovery of the compound Fexinidazole. This compound is currently in phase III clinical studies, with the aim of registering it as a 10-day oral treatment for second phase of *T.b. gambiense* in adults and the first phase in children aged between 6 and 14 years old.

In this chapter I argued that the scientific practices involved in developing new drugs for Human African trypanosomiasis must be understood within the broad socio-economic and political context of this disease. I demonstrated that the current scientific inquiry and research aims are guided by TPP's, constructed by asking particular questions about the disease and its broader context. Elimination of *gambiense* HAT is possible, but current efforts to control and eliminate HAT have considerable limitations. This chapter follows from chapter 2, further developing the idea that scientific practices must be understood in their broader socio-economic and political contexts. In the following chapters I will refer back to the current research into developing new drugs to eliminate HAT. Here, I presented a preliminary argument that the scientific practices are guided by particular aims (elimination of HAT) and set of values (TPP's). In this thesis, I argue that the scientific practices must be understood in their broader context. In this chapter I demonstrated the links between the broader context of HAT and the scientific practices aiming to develop new anti-parasitic drugs to address patients' needs. In the following chapters I will refer back to the HAT case study to argue that plurality of accounts and approaches in scientific practices is an important characteristic of the scientific inquiry. Furthermore, I will argue that the extent of plurality and the benefits of having multiple approaches in any field of science must be understood with respect to the particular aims and values in that field.

Chapter 4

4.1 Epistemic Pluralism

In this chapter I aim to provide an argument for epistemic pluralism. In chapter 2, I argued that broadening the subject matter of philosophy of science to include scientific practices leads to the question of how to make sense of multiplicities in scientific practices and accounts. Here, I argue that these multiplicities are an important feature of scientific inquiry. In this chapter I provide detailed analysis of three pluralist theses: Kellert, Longino, and Waters (2006), Chang (2012) and Mitchell (2002). I use these three theses as a starting point for my pluralism, since all three are concerned with scientific practices and the use of scientific knowledge produced. Moreover, all three theses are empirically motivated, taking pluralities in scientific practices as justification for pursuing a pluralist line of argument.

Pluralist debate has a rich and multifaceted history. In section 2.1.3, I presented Suppes (1978) assertion that close examination of scientific practices reveals a plurality in science, in methods, language and subject matter. Suppes further argues that neither languages nor the subject matter of different scientific disciplines can be reduced to a single language or subject matter. Suppes calls for acceptance and further philosophical study of pluralities in science. Although the roots of the pluralist argument can be traced before Suppes (1978), as I argued in chapter 2, the pluralist argument I put forward in this thesis is motivated by the shift in philosophy of science from the traditional view to philosophy of science in practice. Following Suppes, members of the Stanford School, Dupre (1993) and Cartwright (1999), provide metaphysical arguments supporting the pluralist account of the world. Many pluralist arguments that preceded the three pluralist arguments I will focus on here (Kellert, Longino, and Waters 2006, Chang 2012, Mitchell 2002) responded to the unity of science thesis, arguing against reductive accounts of science (see Galison and Stump 1996). Further, proponents of the disunity of science and pluralism also provided

alternative readings of the origins of the unity of science thesis set out by the logical positivists (see Cartwright et al. 1996, Uebel 1991). As stated, I focus on the pluralist argument, following the shift from the traditional view in philosophy of science to philosophy of science in practice (see section 2.1).

The outline of the pluralist argument I wish to develop here is as follows: both historical and current scientific practices point out that the natural world is complex and cannot be captured with a single, complete and comprehensive account. Motivated by the state of affairs in scientific practices, I argue that there are multiple approaches in scientific practices, each focusing on different aspects of phenomena and producing partial accounts. An important characteristic of the pluralist argument I pursue here is the rejection of the notion that the aim of science is to come up with a single and complete account. Instead, I argue that plurality of approaches and accounts result from plurality of aims in science. While I acknowledge that the broad aim of science can be thought of as producing and proliferating knowledge about the world, in order to have a better sense of the state of affairs in scientific practices it is necessary to understand particular aims in science, which in turn allows me to investigate the role of values in science from a pluralist perspective (discussed in section 4.5 and further developed in chapters 5 and 6).

This chapter is divided into five main sections. In the first, I develop the pluralist argument I aim to advance in this thesis. The pluralist thesis I develop here is built on the pluralist arguments put forward by Kellert, et al. (2006), Chang (2012) and Mitchel (2002) where all three arguments are motivated by the apparent pluralities in scientific practices, each aiming to provide a philosophical account of the multiplicities of accounts and approaches in scientific inquiry. In section 4.1, I provide an overview of all three arguments, while developing the pluralist thesis I will defend. In section 4.2, I return to my case study, focusing on the pluralities in drug discovery and development for HAT, demonstrating the plurality of approaches in scientific practices and

further articulating my pluralist thesis. In section 4.3, I focus on the units of analysis, underlining the terms I use in understanding and analysing the pluralities in sciences. That is, I introduce the terms I wish to use in defining and describing pluralities in scientific practices in building my own argument for pluralism (which I will further develop in chapter 5). In section 4.4, I provide a defence against possible reductionist arguments against the pluralist thesis I develop here. I argue that reductionism can be recast in such a way that it seen as part of scientific practices and not a way to get rid of plurality. Herein I use Kaiser (2012) and Waters (1990) to support my pluralist argument against possible reductionist objections. In the final section (4.5), I provide a summary of the pluralist thesis developed in chapter 4, where I argue that pluralities in scientific practices are an important characteristic of scientific inquiry. Furthermore, I argue that scientific inquiry is ought to be pluralistic in order to explain and explore different aspects of phenomena (I will further develop the normative aspects of my argument in chapter 5). In this chapter I use several case studies (mainly from life sciences) to support my argument that multiple approaches produce partial accounts in order to explain and explore different aspects of phenomena. Moreover, I will use these case studies to argue for the plurality of aims in science.

4.1.1 The Pluralist Stance

The pluralist stance, as defined by Kellert, Longino, and Waters (2006), is the philosophical interpretation of multiplicities of approaches and accounts in scientific practices. Kellert et al. assert that the multiplicities in current and past scientific practices serve as empirical evidence for the pluralist stance. Instead of ignoring these pluralities or considering them to be a problem, Kellert et al. argue that such plurality must be accepted as a feature of scientific inquiry. Thus, given that the plurality of approaches is the character of scientific practice and scientific knowledge produced by different approaches, Kellert et al.'s pluralist stance is the philosophical interpretation of this state of

affairs. Kellert et al. argue that each approach in science provides different and partial accounts of phenomena.

The pluralist stance can be framed as negative and a positive theses: the negative thesis is the denial of monism and the positive thesis is the argument for a pluralist approach to understand and explain scientific practices and their products. Kellert et al. mainly focus on *approaches* and *accounts* as their main subject of study in scientific practices: approaches can be thought of as distinct sets of scientific practices focusing on particular aspects of phenomena, while accounts are the *products* of approaches such as theories, representations, models, explanations, etc. (I will further discuss units of analysis in section in 4.3, comparing units of analysis used in pluralist arguments).

Negative thesis: pluralism as rejection of monism

Kellert et al. start by defining the pluralist stance as a rejection of monism, which is a thesis characterised in terms of the aims of science:

> the ultimate aim of science [is] to establish a single, complete, and comprehensive account of the natural world (or the part of the world investigated by the science) based on a single set of fundamental principles. (Kellert, Longino, and Waters 2006: x)

Following Kellert et al.'s characterisation, I wish to further analyse monism on three different levels: metaphysical, epistemic and methodological. Here I argue that monism is a complex concept and can be understood in different ways (in sections 4.5 and 5.1 I will argue that the form of pluralism I develop in this thesis rejects epistemic monism). Kellert et al., (and other pluralists discussed here) react against monism, rejecting it as the traditional dominant view of science. Here I will argue that monism is complex and comes in different forms.

The *metaphysical* argument for monism can be thought of as follows: the world is such that it can be explained with a universal, complete and coherent account. That is, metaphysical monism is the commitment to the notion that world is structured in a way that it can be

captured by one complete universal account (a theory, model, etc.). *Epistemic* monism is the philosophical commitment that one complete and universal account is knowable by us. That is to say epistemic monism is the notion that world can be described and explained by a single, complete, comprehensive and *universal* account based on fundamental principles. Thus the aim of science is to produce this universal account. Thirdly, the methodological argument that there is one (best) method that can provide the monist account; moreover current methods can be judged based on whether they can yield such account (or closest to that account in that particular time).[26] As described by Kellert et al.,

> whether they provide (or come close to providing) a comprehensive and complete account based on fundamental principles." (Kellert, Longino, and Waters 2006: x)

Kellert et al. argue that in the monist interpretation, the multiplicities in science are regarded as a temporary state, caused by immature or incomplete science. They suggest that there is no definitive argument for monism; rather it is based on *a priori* assumptions about the natural world and the aims of science. Kellert et al.'s rejection of monism is therefore the rejection of such assumptions. Instead, Kellert et al. take the state of current scientific practices as the starting point for their argument for the pluralist stance, a position they summarise as follows:

> *Scientific pluralism,* in contrast, holds that there are no definitive arguments for monism and that the multiplicity of approaches

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[26] A fourth category, axiological monism can be added to the list. Axiological monism can be thought as the view that scientific practices have a single aim: universal accounts of phenomenon. In other words axiological monism takes science to have a single set of values and aims that define what scientific practices ought to be and what scientific accounts ought to contain. Axiological monism is not further developed in this thesis as it is not discussed by Kellert et al., Chang and Mitchel, whose work forms the basis of my pluralist account.

> that presently characterizes many areas of scientific investigation does not necessarily constitute a deficiency. As pluralists, we do not assume that the natural world cannot, in principle, be completely explained by a single tidy account; rather, we believe that whether it can be so explained is an open, empirical question. (Kellert, Longino, and Waters 2006: x)

It is important to note here that Kellert et al.'s rejection of monism is not the rejection of the possibility of the natural world being such that it can be explained with a single account. However, treating the metaphysical commitment that the world is such that it can be explained by a single complete and comprehensive account as an open question undermines the epistemic argument for monism:

> if we don't know whether the world can be fully accounted for by a single comprehensive account, then it seems unreasonable to assume that the ultimate aim of science is to achieve such [an] account. (Kellert, Longino, and Waters 2006: x-xi)

Thus, Kellert et al. reject the notion that there is a single overarching aim in science that can be used to assess different accounts and approaches. Moreover, they argue that it is unreasonable to accept or reject approaches based on whether they can produce an account that can be used to understand and explain all phenomena. Kellert et al. summarise their position as follows:

> if the nature of the world is such that important phenomena cannot be completely and comprehensively explained on the basis of a single set of fundamental principles, then the aims, methods, and results of the sciences should not be understood or evaluated in reference to the monist quest for the fundamental grail. (Kellert, Longino, and Waters 2006: xi)

Kellert et al.'s rejection of monism is supported by case studies presented in the collected volume, including the works of Fehr (2006) on the evolution of sex, Sent (2006)'s account of the plurality on economics and Dickson (2006)'s account of quantum dynamics. Kellert

et al. assert that the pluralist stance is empirical in the sense that it takes current state of affairs to support the pluralist argument. While Kellert et al. assert that they regard metaphysical monism as an open question, they argue against epistemic monism. For Kellert et al., metaphysical assumptions about the natural world remain an open question. However, epistemic and methodological assumptions about the aims of science are not supported by either the historical or current state of scientific practice.

In summary, Kellert et al. take scientific practices as the starting point for their argument for scientific pluralism. Kellert et al.'s position regards the metaphysical assumptions of the state of the world as an open question. Moreover, Kellert et al. reject any *a priori* assumptions about the aims of science. Instead they provide a pluralist framework as a way to understand scientific practices and their products, replacing the monist commitments with:

> the commitment to avoid reliance on the monist assumptions in interpretation or evaluation coupled with an openness to the ineliminability of multiplicity in some scientific contexts. (Stephen Kellert, Helen Longino, and Waters 2006: xiii)

In the following section I provide a detailed analysis of the empirical argument Kellert et al. provide as the basis of the pluralist stance.

Positive thesis: Empirical Argument

Kellert et al. argue that the pluralist stance is a philosophical approach to interpret the content and practices of scientific inquiry. The pluralist stance Kellert et al. take is empirical in the sense that the starting point of philosophical inquiry is scientific practices:

> According to the pluralist stance, the plurality in contemporary science provides evidence that there are kinds of situations produced by the interaction of factors each of which may be representable in a model or theory, but not all of which are representable in the same model or theory. Each factor is necessary for the phenomenon to have the various characters it

> has, but a complete account is not possible in the same representational idiom and is not forthcoming from any single investigative approach (as far as we know). (Kellert, Longino, and Waters 2006: xiv)

Kellert et al. point out that all factors relevant to a given phenomenon cannot be represented or explained in a single complete and coherent account. Instead, different approaches can produce representations of phenomena that focus on different aspects, producing partial representations of specific phenomena.

> all representations are partial in that any representation must select a limited number of aspects of a phenomenon (else it would not represent, but duplicate). This selective and partial character of representation means that alternative representations of a phenomenon can be equally correct. Hence, it should be obvious that different accounts, employing different representations, might be generated by answering different questions framed by those different representations. (Stephen Kellert, Helen Longino, and Waters 2006: xv)

Kellert et al. argue that different accounts of phenomena focus on different aspects of phenomena. Thus, different accounts of a given phenomenon can be equally valid:

> [the] pluralist stance keeps in the forefront the fact that scientific inquiry typically represents some aspects of the world well at the cost of obscuring or perhaps even distorting other aspects. (Stephen Kellert, Helen Longino, and Waters 2006: xv)

Kellert et al. suggest that in order to understand and explain different aspects of phenomena it is necessary to have multiple approaches. Instead of recognising such multiplicity as a problem, Kellert et al. argue that plurality is an ineliminable characteristic of scientific inquiry, and that our understanding of science should be free of the assumption that pluralities will be resolved through convergence and integration. However, they also take an empirical approach here, suggesting that

convergence of different approaches and accounts must be studied case by case, rather than judged on the basis of a blanket assumption, stating that:

> scientists sometimes must make decisions about whether to pursue or to defer the quest for comprehensive or convergent accounts. A pluralist approach advocates that such decisions be made on empirical case-by-case, pragmatic grounds rather than on the basis of blanket assumption. We expect that decisions made on those grounds will yield more fruitful and effective results. (Stephen Kellert, Helen Longino, and Waters 2006: xxi)

Kellert et al.'s argument can be thought of in simpler terms, as follows: our gut instinct should not be how we can combine multiple accounts and different approaches working on the same phenomena. Equally, one must not impose pluralism in cases where convergence occurs as part of scientific practice; the pluralist stance does not rule out integration or convergence among accounts as part of scientific practice. Thus, the pluralist approach to questions of convergence or integration must be empirical and pragmatic in the sense that we must consider the particular aims of a given practice and assess the question of convergence or integration according to these aims.

In summary, the pluralist stance is a meta-philosophical argument, outlining how to make sense of scientific practices and knowledge in light of the plurality of approaches and accounts in science. The pluralist stance, described by Kellert et al., rejects the notion that scientific practices aim to provide a complete and concrete account of the natural world. Kellert et al. argue that scientific inquiry must not be assessed on the monist assumptions about the world and the aim of science, but rather that the plurality in scientific practices and the practical success in achieving pragmatic aims serve as empirical evidence for the need for multiplicity in scientific inquiry. This pragmatic way of thinking is prominent in Kellert et al.'s pluralist stance, which I will further develop in chapter 5 (section 5.4) and in chapter 6 (section 6.2). Before I further develop a pragmatic argument for pluralism, I will

shift my focus to Chang (2012), who argues for a normative form of pluralism, which I will use to advance a pragmatic form of pluralism in section 5.1.3.

4.1.2 Active Normative Epistemic Pluralism

Similar to Kellert et al. (2006), Chang (2012) calls for a re-examination of fundamental assumptions about scientific practices and their accounts of the world. Chang asserts that the main motivation for his account is plurality in scientific practices. Chang (2012) focuses on three different periods in the history of chemistry to argue for the benefits of multiple approaches operating simultaneously to produce accounts of phenomena, stating that:

> we are limited beings trying to understand and engage with an external reality that seems vastly complex, apparently inexhaustible, and ultimately unpredictable. If we are not likely to find the perfect system of science, it makes sense to foster multiple ones, each of which will have its own unique strengths. (Chang 2012: 255)

There are two underlying assumptions in Chang's argument: abundance and complexity. Chang argues that there is an unending abundance of inquiry, claiming that,

> nature holds an indefinitely large number and diverse types of facts there to revealed, and this makes it likely that each different system of practice could tap into a different part of that inexhaustible reservoir, and continue to tap into it. (Chang 2012: 256-257)

Chang argues that losing sight of this abundant potential restricts what we can learn about the world. Thus, it is necessary to preserve and promote the plurality of systems in order to maximise how we acquire knowledge. Furthermore, Chang argues that given the complexity of nature there is a need to produce simple schemes that pick out specific aspects.

> It seems that any domain of nature we choose to study reveals an indefinite degree of complexity, while human minds can only handle relatively simple schemes, no matter how much help we have from increasing computing power. (Chang, 2012: 257)

Chang's argument for pluralism is similar to that of Kellert, Longino, and Waters (2006) in the sense that they both oppose monism. Chang argues that monism is the notion that the aim of science is the search for the truth about the natural world. In other words, Chang argues that monism relies on the assumption that there is one natural word, and therefore there must be one truth about it. Chang offers pluralism as way of understanding scientific inquiry, defining it as 'the doctrine advocating the cultivation of multiple systems of practice' (2012: 260), in which a system of practice is a 'coherent and interacting set of epistemic activities performed with a view to achieving certain aims' (2012: 260).

Chang presents two objections to monism. Similar to Kellert et al., the first objection is to do with the aims of science. For Chang, monism should not be regarded as the ultimate aim. Building on his empirical work on the history of chemistry, Chang argues that the aims of science vary, just as the questions scientists have about phenomena vary. Thus, Chang argues that it is more likely that these aims are better served by multiple interacting accounts of phenomena. In order to understand this, we need to look at Chang's historical work on developments in chemistry from the mid-eighteenth century to the late nineteenth century. In particular, Chang focuses on the common narratives of the chemical revolution, in which the phlogiston theory was replaced by Lavoisier's theory of oxygen. The traditional narrative is that the phlogiston theory was wrong about the nature of elements and was replaced by the theory of oxygen put forward by Lavoisier (see, Thagard 1990; Pyle 2000; McEvoy 2010). This kind of narrative assumes that the two theories were aiming to do the same thing and that they were compared against the same evidence and assessed accordingly. However, Chang argues that phlogistonists and oxygenists were focusing on different sets of questions and had

different aims. Therefore, the success of the two systems cannot be compared with one another, as each system was producing a valid account of phenomena peculiar to their particular aim. In other words, phlogistonists and oxygenists were interested in different questions about phenomena, therefore producing different but valid accounts of phenomena. Chang demonstrates how both theories were telling us something useful and insightful about phenomena that was particular to the given approach. Each theory has merits according to either system's aims. Thus, each theory must be assessed according to the questions it attempts to answer, not according to a universal aim as monism suggests.

The usual narrative of winners and losers is addressed in Chang's work on triumphalism. Triumphalism can be understood as an approach in history and philosophy written from the perspective of the 'winners and losers'. According to Chang, triumphalism is entrenched in both the history and philosophy of science and is perpetuated by monist assumptions. That is to say, if we consider the aim of science as to provide a single, complete and coherent account, it is expected that only one of these accounts (phlogiston or oxygen) will provide the right answer. However, the pluralist interpretation of the chemical revolution reveals a different picture, in which Lavoisier's oxygen theory is as incorrect as phlogiston, if we are looking for winners or losers. However, Chang encourages us to move away from thinking about winners and losers and focus on different systems of practice that provide partial knowledge of phenomena that others cannot.

Going beyond monist assumptions about science, Chang argues that the plurality of systems of practices is beneficial for science.[27] Chang discusses the benefits of plurality under two different categories:

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[27] Chang brands his pluralism as active normative epistemic pluralism, which I will discuss in detail in chapter 5. However in order to draw parallels between Chang work and other pluralist arguments presented in this chapter, it is necessary to discuss his positive thesis.

toleration and interaction. The benefits of toleration can be summed up as allowing different systems of practices to pursue different aims in their own way. The benefits of interaction on the other hand can be further divided depending on the type of interaction between systems. Chang identifies the first form of interaction as integration, which occurs when

> none of the available systems by itself, not even all of them additively, can achieve a certain aim. In such cases, we may attempt to reach a better result by definition ad hoc integration of different systems. (Chang, 2012: 279).

Chang's definition of integration is very similar to integration as described by Kellert et al. The question of integration will be discussed in detail using Mitchell's account (section 4.1.3)

The second form of interaction is co-optation. This subcategory refers to cases in which a given system of practice co-opts an element from another system of practice. In order to better understand this, we must look into how Chang conceptualises system of practice. As mentioned above, a system of practice is a 'coherent and interacting set of epistemic activities performed with a view to achieving certain aims' (Chang 2012: 260). A system of practice is composed of different epistemic activities which Chang defines as 'a more-or-less coherent set of mental or physical operations that are intended to contribute to the production or improvement of knowledge in a particular way, in accordance with some discernible rules (though the rules may be unarticulated)' (Chang, 2012:15). Thus, the co-optation here refers to co-optation of different epistemic activities and different elements (such as theories, models, questions, methods etc.) from one system of practice to another.

The final form of interaction defined by Chang is competition. The competition should not be understood to have an end goal; instead, it is the interaction among systems in which different accounts are provided to explain phenomena. The competition is not to be the

‘winner’ of the debate, but to get more funding, resources etc. I will discuss this in detail in the following section with respect to case studies. Chang sums up his position as follows:

> An important part of my proposal is to keep in mind the aims that scientists are trying to achieve in each situation. The presence of an identifiable aim (even if not articulated explicitly by the actors themselves) is what distinguishes activities from mere physical happenings involving human bodies, and the coherence of an activity is defined by how well the activity succeeds in achieving its aim. (Chang, 2012: 16)

Chang’s pluralism is ‘an ideology of science aimed at promoting plurality in order to reap its benefits’ (Chang, 2012: 268). Chang aims to make normative claims about scientific practice and engage with scientific practice and cultivating plurality directly. In contrast, Kellert et al.’s pluralist stance sets out a research programme for philosophers, where the main aim is to have a new direction for the philosophical study of scientific practice.

In chapter 5 I will further discuss the main differences between the pluralist stance and Chang’s pluralism, to develop the pluralist thesis I present in this dissertation. The rest of this chapter is reserved to illustrate pluralist points I presented so far using case studies.

4.1.3 Integrative Pluralism

Following Kellert et al. (2006) and Chang (2012), in this section I will focus on integrative pluralism as argued by Mitchell (2002). Integrative pluralism is similar to pluralist arguments put forward by Kellert et al. and Chang in the sense that Mitchell takes scientific practices as the starting point for her argument. In particular, Mitchell focuses on the plurality of models in current scientific practices.

Mitchell and Gronenborn (forthcoming) start with a quotation from John Kendrew's Nobel lecture in 1963[28] in which Kendrew predicts that experimental methods to determine the functional protein structure, namely X-ray crystallography, will be redundant with the further development of *ab initio* methods. Kendrew suggests that a protein's three-dimensional structure can be determined from knowledge of their amino acid sequence alone i.e. a protein's structure can be elucidated by analysis of its building units. Mitchell and Gronenborn argue that, contrary to the expectation of Kendrew, current practices in protein structure determination mainly rely on experimental methods such as X-ray crystallography and Nuclear Magnetic Resonance (NMR), while *ab initio* methods are only confined to small proteins with relatively simple structures. Mitchell and Gronenborn argue that understanding protein structure and function relies on the plurality of models that are derived from different approaches (including experimental and *ab initio*):

> the complexity of phenomena investigated [functional protein structure] conspires with the inherent partiality of scientific representation to generate pluralities of explanatory and predictive models. (Mitchell and Gronenborn forthcoming: 4)

Similar to pluralist theses put forward by Kellert et al. and Chang, Mitchell and Gronenborn argue that plurality is ineliminable, where each approach produces partial accounts of the phenomena. They suggest that the determination of a protein structure, as an aim, is best achieved by multiple accounts. Here, I explore Mitchell and Gronenborn's argument for the ineliminability of plurality under two titles: partiality of representations and complexity of phenomena. Moreover, I wish to emphasise the pragmatic aspects of the argument put forward by Mitchell and Gronenborn, in which the benefits of

[28] John Cowdery Kendrew won (jointly with Max Ferdinand Perutz) the Noble Prize for chemistry for their studies of the structures of globular proteins.

pluralism are realised through the interaction of multiple models in order to explore and explain phenomena with regards to particular aims. Mitchell and Gronenborn explore a particular form of interaction, which is integration. Here I will argue that this form of integration is *ad hoc* integration in order to achieve pragmatic aims, as opposed to integration as a way of eliminating plurality.

In order to understand the Mitchell and Gronenborn's argument it is necessary to attend to their case study, the modelling of protein structure and function. Proteins are a diverse group of molecules, functioning in various ways in different biological systems. Mitchell and Gronenborn argue that such variety and complexity cannot be captured in a single representational system. Instead, different features of phenomena require different models to capture them. Mitchell and Gronenborn argue that current research in protein structure and function does not support Kendrew's idea that the function and structure of a protein can be determined by its amino acid sequence. That is, Mitchel and Gronenborn argue that the hope that functional protein structure can be determined by the amino acid sequence is not possible in light of current scientific practices, nor have we any empirical reason to expect to be able to predict functional protein structure from amino acid sequences in the future.

Determining functional protein structure requires knowledge of different aspects of phenomena that can only be attained through various methods. Different approaches provide knowledge on distinct aspects of proteins, such as cellular interactions with other molecules (such as co-enzymes), or looking at thermodynamic properties of the protein in different structural formations, or the atomic configuration of side chains in a different chemical environment that stabilises the functional structure. The point I make here is that each question about protein structure requires a different approach to answering it, and there is no reason to think that one approach is the most important, as different aspects have different importance in different contexts.

Mitchell and Gronenborn describe scientific models as abstractions or idealisations of phenomena.[29] They argue that models are scientific representations, produced by agents to fulfil particular aims, highlighting certain features while leaving others out. That is to say, scientific representations do not map one-to-one onto the natural world: they are partial with regards to the aim of different scientific practices. Thus, Mitchell and Gronenborn argue that scientific models should not be judged merely on how complete they are or how well they map onto the world, but rather on their ability to serve agents' goals:

> Scientific models are judged for their ability to help us explain and predict what goes on in nature. To be successful they need to capture (by similarity, isomorphism, structural or causal mirroring etc.) features that are relevant to the process and events we want to understand and on which we might be able to intervene in order to produce or prevent effects of interest. (Mitchell and Gronenborn, forthcoming: 6)

Mitchell and Gronenborn further develop their position on scientific representations:

> What is true for all these accounts is that not every describable feature of a system in every possible degree of precision is required for identifying that which permits prediction, explanation, and intervention on that system. We do not need to have a complete representation, in that sense, for successful science […] What is represented and what is left out are usually tailored to meet some explanatory or pragmatic goal. (Mitchell and Gronenborn, forthcoming: 6)

[29] Founded on existing accounts of scientific representation by Ronald Giere (2004, 2006, 2010) and Bas Van Fraassen (2010).

The important point in Mitchell and Gronenborn's argument on scientific representation is similar to Kellert et al.'s and Chang's arguments in the sense that the aim of scientific representations is not to be a single and complete model of the world. All three pluralist theses recognise the plurality of aims and goals in scientific practice. Moreover, the three pluralist theses accept the existing plurality of accounts (including representations, theories, models etc.) as an important characteristic of scientific inquiry. In particular, Mitchell focuses on the interaction of different accounts, in particular the integration of different accounts to explain a particular phenomenon. In her previous work, Mitchell (2002) focuses on social insect colonies as a case study, identifying different explanatory models for social behaviour, including the genetic diversity model, the foraging for work model and the learning model. Mitchell argues that each model has merit in explaining an aspect of insect behaviour, but none of these models alone are sufficient in explaining the behaviour of particular insect colonies (i.e. bees, ants etc.). Therefore, Mitchell argues that in order to explain the social behaviour of each colony we integrate different models, asserting:

> At the concrete explanatory level, on the other hand, integration is required. However complex, and however many contributing causes participated, there is only one causal history that, in fact, has generated a phenomenon to be explained. (Mitchell 2002: 66)

In order to explain social behaviour in bees for instance, Mitchel argues that there is one explanatory model that is the product of integrating three different models (genetic diversity, foraging for work and learning) derived from idealised situations, and hence Mitchell argues that they do not directly apply to complex phenomena. Thus, Mitchell concludes:

> The complexity of nature and the idealized character of our causal models to explain that complexity conspire to entail an integrated pluralistic picture of scientific practice. Complexity in

> the sense of the diversity of the contingent, evolved properties of biological phenomena has important implications for how we understand the relationships among the plurality of theories and explanations found in contemporary biology. (Mitchell 2002: 67)

For Mitchell, the complexity of phenomena requires multiple accounts that focus on different aspects. Furthermore, Mitchel argues that in order to explain particular phenomena we need to integrate different explanatory accounts.

Mitchell's integrative pluralism was criticised by Kellert et al., describing it as modest. Kellert et al. characterise Mitchell's argument as follows:

> nature varies in its strategies, using different strategies to achieve the same end, but for each situation in the natural world there is a single complete and comprehensive account that can be given. (Stephen Kellert, Helen Longino, and Waters 2006: xii)

Kellert et al. argue that integrative pluralism is modest because it does not recognise the possibility that for some phenomena there may not be a single, best account. As discussed in section 4.1.1, Kellert et al. are open to the ineliminability of plurality, accepting the possibility that for some phenomena there can be equally valid but irreconcilable (or non-mutually consistent) accounts. In her later work, Longino (Longino 2013) expands her criticism, arguing that Mitchell's pluralism is guided by the idea that multiplicity can be overcome though integration to produce a complete model. Longino argues that:

> Epistemologically, we may learn more about a system by utilizing multiple partial representations, each of which enables us to go further in our study than would the attempt to obtain a complete representation of all causal interactions. Our understanding of the system may require not the integration of the different models but acknowledgement that each represents one aspect of the system (Longino 2013: 147)

Here, I provide a different reading of Mitchell's integrative pluralism to that of Kellert et al. (2006) and Longino (2013). I argue that integration as described by Mitchell is *ad hoc*, to fulfil a particular aim (e.g. explain a particular behaviour in bee colonies), in which the result of integration is a new partial account that allows scientists to learn about phenomena. That is to say, Mitchel does not argue for integration for sake of a universal, complete and coherent account, but a local account that is complete and coherent with regards to the specific aims of a particular inquiry. As discussed above in 4.1.1, here I argue that aiming at single universal and complete account is necessary for epistemic monism. In Mitchel's account discussed so far, she only focuses on local integration of different causal accounts to answer a particular question regarding the behaviour of different insect colonies. However, Mitchell does not assert that there is a knowable, single, universal account or a single best method to yield such account.[30] In order to further my argument I will return to protein structure and function research.

Mitchell and Gronenborn argue that all models are partial to different goals of inquiry. Moreover, functional protein structure requires plurality of models; different methods target different features of protein structure. Mitchell and Gronenborn study a few approaches, including X-ray crystallography, nuclear magnetic resonance (NMR), and *ab initio* methods. X-ray crystallography and NMR provide information on the location of atoms in three-dimensional space. X-ray crystallography entails exposing crystallised protein samples to an X-ray beam and looking at the diffraction pattern of X-rays after hitting the protein crystals. The diffraction caused by each atom allows crystallographers to locate each atom (depending on the quality of data) and build a

[30] Although it must be noted that Mitchell suggest that there is only one causal structure which alludes to metaphysical monism, however Mitchell does not argue that a single causal structure can be represented or understood by inquirer through one, universal complete account.

static model of the protein. NMR, on the other hand, does not require crystallised protein, but uses purified protein samples in solution. NMR experiments require exposing protein in solution to electromagnetic radiation, which is absorbed by distinct atoms (either hydrogen or carbon, depending on the type of experiment), emitted at different times and intensity based on their chemical environment. Structural chemists exploit this to map the reaction between atoms in three-dimensional space. Because proteins are in solution, it is possible to make time-based experiments to study protein movement (not possible using crystallography). However, X-ray crystallography models provide high-resolution models if high-quality crystals are obtained.

Both X-ray crystallography and NMR provide structural information. These structures, however, are not sufficient to understand the functional structure of these proteins. Proteins undergo a series of modifications and are structurally mobile *in vivo*. Protein models at the cellular level (studying the cellular location of proteins and their interactions with other molecules) provide further information that cannot be captured by models at the atomic level. Enzyme kinetics, for instance, looks at the reaction rates catalysed by proteins, which entails the study of interactions between a protein, its substrates and any other molecule involved in the reaction.

These examples demonstrate how different approaches focus on distinct features of a given phenomenon (protein structure and function in this case), thereby producing different models. Furthermore, each approach has a distinct aim: produce a kinetic model of protein substrate interaction, or a three-dimensional model of atomic interaction between protein and substrate, etc. In order to fulfil these aims each approach is constituted by different cognitive elements (methods, theories, assumptions, models etc.). Integration is not the unification of aims, but rather the use of different cognitive elements or existing approaches to create a new approach that seeks to fulfil different aims. Thus, integration here must be understood as part of scientific practice, referring to a process in which a new approach is synthesised by using elements of different approaches. It is important

to note that integration does not lead to the elimination of existing approaches, but the generation of a new approach that addresses particular questions that existing approaches cannot address.

An example of integration is homology modelling. Homology modelling entails deducing the structure of a molecule using the experimental model of its homologous protein. Two proteins are thought to be homologous if their amino acid sequences, (i.e. their primary structures) are similar. Homology modelling relies on the assumption that proteins with similar amino acid sequence will fold in the same way, i.e. have very similar tertiary structure. Based on these assumptions, the structure of a protein can be deduced by using the known structure of its homologous protein. Homology modelling is an approach in which *ab initio* and experimental models are used in combination in order to deduce protein structure using computational methods. For instance,

- the amino acid sequence of both protein X and Protein Y is known;
- protein X is homologous to protein Y;
- the three-dimensional structure of protein X is available; thus
- by aligning the sequences of protein X and Y, the three-dimensional structure of Y can be deduced based on the three-dimensional structure of X.

Homology modelling as an approach is the product of integrating *ab initio* and experimental approaches. It employs elements from both in order to answer a particular question. Homology modelling is often used in cases where it is difficult to get protein to crystallise, or if a protein is not stable alone in a solution (for example, surface proteins). In these cases, the homology modelling is used in order to construct a three-dimensional model. Homology modelling does not replace other experimental methods, nor is it an *ab initio* approach as described above: it is the result of integrating different elements of different approaches. The new approach, homology modelling, produces representation of phenomena that is also limited and relies on the assumption that homologous proteins have similar three-dimensional

structures, producing limited accounts of phenomena that serve a practical aim of producing a computer model of a particular protein.

Mitchell's integrative pluralism thus must be seen as a way to understand the interaction among different approaches in scientific practices. In the case, for instance, homology modelling is a new approach that is the result of integrating cognitive elements from different approaches (experimental, *ab initio*, etc.), without replacing them. It is important to note that integration is not the only mode of interaction between different approaches. Here I provide a different interpretation of Mitchell's integrative pluralism where the aim of integration is not motivated by epistemic (or methodological) monism given that the aim of integration is not to produce a universal, complete and coherent account of the world. This alternative reading of Mitchell is important for my argument given Mitchell provides a way to think about how different accounts and approaches can be brought together without epistemic and methodological monism. In the following section I will discuss the different ways in which approaches interact with one another in order to answer different questions and fulfil particular aims. In particular, I will focus on interaction among different approaches in early drug discovery research for HAT.

4.2 Plurality in Pharmaceutical Research

Section 2.2.4 described the early stages of drug discovery and development in anti-parasitic drugs. Here I will focus on scientific practices involved in identifying metabolic pathways specific to the parasite and essential for its survival and growth. The aim is to pick out a macromolecule (e.g. a protein) in the metabolic pathway, whose action can be manipulated and disrupted with a synthetic compound (which can be developed into a drug). This stage is referred to as target identification and validation.

Wyatt et al. (2011) give an overview of different approaches used in target identification and validation. Although the main concern is to

identify a target essential for parasite growth and survival, there are other properties such as assay feasibility, toxicity etc. Here, I will mainly focus on essentiality for parasite growth and survival (I will discuss anti-parasitic discoveries further in chapter 5 in order to underline the importance of socio-economic and political context in defining other properties such as toxicity and delivery method)

Wyatt et al. argue that multiple approaches are used in order to establish if a given target is necessary for parasite growth. The two main approaches the authors present are *chemical* and *genetic,* complementary approaches that use small molecule inhibitors or genetic methods respectively to modulate the functional activity of the potential target. Wyatt et al. argue that:

> neither method on its own is sufficiently robust to provide absolute proof of essentiality and, whenever feasible, complementary and confirmatory evidence should be sought using both approaches. (Wyatt et al. 2011: 1277)

Chemical validation entails the use of experimental compounds or existing drugs to address questions around ‘druggability’ of the target molecule. Druggability can be best described as the likelihood of the target molecule responding to small molecules *in vivo*. Druggability is discussed in detail in Frearson et al. (2007), Hunter (2009), and Chatelain and Ioset (2011),- each describing the importance of assessing druggability in the early stages to ensure success in the clinical phases of drug development.

Chemical approaches as described by Wyatt et al. (2011) determine whether specific inhibition of any given target molecule with a small molecule will result in impaired growth or death of the parasite. Moreover, chemical approaches can address several key issues including cell permeability, selective toxicity, drug metabolism and pharmacokinetic properties both *in vitro* and *in vivo*. In addition, chemical approaches allow identification of both protein and non-protein targets.

The genetic approach, on the other hand, uses several techniques such as gene knockout or RNA interference (RNAi) to inhibit the expression of the gene coding for the target molecule. The genetic approach is regarded as the most definitive method for target validation since it provides knowledge of the cell metabolism in the absence of a target. It shows if there are alternative metabolic pathways that can compensate for the absence of a given target, but cannot identify non-protein targets. Moreover, genetic approaches cannot show if a given target can be modulated by a drug to achieve the desired effect.

Since both approaches have limitations, both are employed to increase confidence that a putative target is both essential and *druggable*. Herein, I want to clarify my point by looking at the case of chemical and genetic validation of trypanothione synthetase.

Trypanothione synthetase is an enzyme involved in thiol metabolism in *T. brucei*. Uniquely, trypanosomes depend on trypanothione as their primary thiol, while other organisms use glutathione. Trypanothione is responsible for trypanosome thiol-redox homeostasis mechanism including cellular processes involved in defence against oxidative stress and xenobiotics (Wyllie et al. 2009). Trypanothione synthesis is a two-step reaction in which both stages of the reaction are catalysed by the enzyme trypanothione synthetase.

Genetic approaches have shown that trypanothione synthetase is essential for parasite survival both *in vitro* and *in vivo*. Comini et al. (2004) report that the genetic inhibition of trypanothione synthetase (TryS) expression in *T. brucei* established that TryS is essential for the entire synthesis of trypanothione (T(SH)2), demonstrating that a 15% drop in T(SH)2 levels led to proliferation arrest[31], and if sustained for days impaired the viability of parasite due to increased sensitivity to hydrogen peroxide and other hyper-oxides. Inhibition of TryS

[31] Proliferation arrest here refers to an arrest in parasite reproduction. Proliferation arrest is an indicator of druggability, indicating that the target is necessary for the parasite's life cycle.

expression shows the metabolic importance of this target molecule, and that there are no alternative pathways to overcome oxidative stress. In general, genetic approaches allow investigation at the cellular level, providing knowledge on the metabolic pathways both *in vitro* and *in vivo*. It is important to note that similar experiments were done in animals in order to see if oxidative stress in the mammal bloodstream had the same results. Studying the same phenomena in animal models allow medical scientist to assess potential side effects of TryS inhibition in mammalian systems. The plurality of methods allows for strengthening the claim that a given metabolic pathway is druggable but also allows to assess potential side effects of inhibiting a given pathway in humans. Given the complexity of the biological system both epistemic and methodological plurality is beneficial for achieving the aims of drug discovery and development.

Although genetic approaches showed that trypanothione synthetase is essential for parasite survival, genetic approaches failed to provide knowledge on the druggability of this target. Torrie et al. (2009) managed to develop the enzyme assay suitable for high throughput screening, which is an automated process that detects a specific interaction between the target protein and a large number of small compounds. Torrie et al.'s *in vitro* study allowed identification of small molecules that interact specifically with the target, where these interactions demonstrated desirable potency and selectivity. Moreover, it was shown that the interactions are allosteric, meaning that the small compounds interact with trypanothione synthetase at an alternative site to the site at which it catalyses trypanothione synthesis. The significance of this study is that it provides further evidence that trypanothione synthetase is essential for parasite survival and is druggable. The case of trypanothione synthetase shows how single phenomena (role of trypanothione synthetase in parasite metabolism) can be studies using two different approaches, genetic and chemical. Where two different approaches focus on different aspects of phenomena.

This section demonstrated the epistemic and methodological plurality in pharmaceutical practices, using examples drawn directly from scientific practice and emphasising how different approaches are supported by different cognitive elements that allow the study of different aspects of phenomena. In the following section, I will shift my focus to philosophical literature in order to discuss how we can start analysing the pluralities in scientific practice from a pluralist point of view. So far I have discussed the pluralist theses put forward by Keller, et al. (2006), Chang (2012) and Mitchell (2002). I highlighted important aspects of the three pluralist theses I wish to use in developing contextual pluralism. In the following section I will focus on units of analysis.

4.3 Units of analysis

Hasok Chang initially defines systems of practice and epistemic activities in his book *Is water H_2O?* (2012). He develops these concepts in Chang (2014) as follows:

> An epistemic activity is a more-or-less coherent set of mental or physical operations that are intended to contribute to the production or improvement of knowledge in a particular way […] The presence of an identifiable aim (even if not articulated explicitly by the actors themselves) is what distinguishes activities from mere physical happenings involving human bodies, and the coherence of an activity is defined by how well the activity succeeds in achieving its aim. (Chang 2014: 72)

Gene knockout or high throughput screening (discussed above) are two different epistemic activities, each consisting of physical and mental operations with an identifiable aim, to inhibit gene expression and screen large compound libraries respectively. These epistemic activities exist in accord with each other, forming systems of practice to achieve certain aims. Chang differentiates the aims of an epistemic activity from the aims of systems of practice: the former has an inherent purpose and the latter has an external function. The inherent

purpose of epistemic activities exists independently of external factors. The inherent purpose of genetic knockout is independent of the genetic validation of a drug target; the purpose there is to inhibit the expression of a certain gene. This inherent purpose, however, serves an external purpose in a given system of practice. In Chang's words,

> The inherent purpose of an activity exists regardless of any external functions that the activity may or may not serve. Both inherent purpose and external function fall under the rubric of aims, so the talk of aims needs to be disambiguated accordingly. (Chang 2014: 73)

Although they fall under the rubric of aims, as stated by Chang, it is possible to differentiate the inherent purpose of epistemic activities that may be used in different systems of practice. This is best demonstrated in the homology modelling example: epistemic activities from different systems of practices are brought together to form the new system of practice. Chang argues that one must look at the external factors to understand why different epistemic activities come together. I will further this in the following chapters (sections 5.1, and 6.2), but for now, we can accept that external factors determine the broad aims, and thus determine the composition of each system of practice. That is to say, what makes the system of practice different is the combination of epistemic activities brought together to serve larger or more complex aims. In Chang's words, 'systems of practice are crafted in order to achieve certain aims which go beyond the inherent purposes of the activities that are pulled together to constitute the system.' (Chang 2014: 74)

However, it must be noted that both systems of practice and epistemic activities are analysts categories; therefore these categories can change based on analysts' aims. For instance, Chang recognizes that, 'a system of practice, if it has a clear inherent purpose, can be taken as a single activity that may form part of a larger system.' (Chang 2014: 74)

The purpose of including Chang's units of analysis is to further the pluralist discourse. Each system of practice provides a partial account of phenomena. Accounts are products of different epistemic activities, working together to achieve a particular aim. Thus, each system of practice is limited since they only contain a certain amount of epistemic activity. This analysis serves as the epistemic justification for the plurality of approaches in scientific practice. That is, we need plurality of systems to learn as much as we can about the world. I will further discuss the normative aspects of Chang's pluralism in chapter 5. However, first it is important to underline that analysts' categories are not stable and change from analyst to analyst.

Helen Longino uses approaches as her unit of analysis. An approach is defined as,

> [a] set of questions, experimental and observational strategies for answering these questions, patterns of argument and a specification of phenomena about which the questions are asked and the strategies are applied. (Longino 2013: 390)

Longino makes a clear distinction between theories and approaches. Theories are thought to be set of laws or principles that explain a given phenomenon expressed in a formal way. Longino states that an approach is not a theory in the sense that it does not require an explicit set of principles. However, an approach entails an implicit theory or a model of the phenomena in question. Longino argues that approaches are not empirical competitors, meaning they ask different questions to phenomena. Each approach employs a method that discriminates alternative hypotheses from each other. Moreover, Longino argues that integration of approaches is not without loss of content. Finally she argues that each approach provides partial knowledge of phenomena.

Longino (2013) argues that different approaches to studying human behaviour can only provide partial accounts. Each account looks at a specific area of causal space while obscuring the others. Longino's argument is based on the claim that human behaviour is a multi-causal

phenomenon. For instance, genetic approaches will be able to provide an account of the genetic causes (genes, inheritance patterns etc.) for homosexual behaviour. While genetic factors are causally relevant and important in determining human sexual behaviour, they are not the only causally relevant factors. Looking at human behaviour, Longino argues that causal space can be divided into seven areas. She states that,

> The specificity of assumptions informing and shaping the individual research approaches and the methods of observation and measurement they employ means that this range or space of potential causes, all members of which are implicitly agreed to play some role, is only partially activated in any given research approach. (Longino 2011: 29)

Longino demonstrates this using a horizontal grid, where different approaches can only explore a few sections of the causal space. Figure 1 is taken from Longino (2011), where the first grid (A) shows the undifferentiated causal space and the second grid (B) shows the causal space (gray boxes) studied by genetic approaches to explain certain behaviour patterns (aggression in this case). Longino uses her case studies to argue that genetic approaches can only investigate genetic aspects with regards to the socio-economic status of the subjects.

Each approach or system of practice is partial due to its composition, which is determined by each approach aim. Here I propose the use of the term ‘approach’ to describe plurality in scientific practice, where different approaches are constituted by cognitive elements (i.e. different methods, theories, models or anything that contributes to production of knowledge). Herein, I keep the definitions of each unit of analysis broad since it is very difficult to give a precise definition due to the diversity of approaches in different disciplines in science. Here, I take an approach to be a way of answering a question (or set of questions) within science that serves an aim. Within each approach, different cognitive elements are used in order to achieve the aim and answer distinct questions. The aims and the ways in which an aim can

be fulfilled determine the cognitive elements that are involved in making the approach. I will further discuss this matter in the following chapter when I discuss how the broader socio-economic and political context plays a role in determining the aims of scientific research.

A	Genotype (allele pairs)	Genotype (whole genome)	Intrauterine environment	Physiology & Anatomy	Non-shared environment	Shared environment	Socio-economic status
B	Genotype (allele pairs)	Genotype (whole genome)					Socio-economic status

Figure 4. Representation of causal space parsed by different approaches in behavioral studies (adapted from, Longino 2011: 29). Row A represent the undifferentiated causal space, where row B represents active causal spaces (in grey) and inactive casual spaces in black in case of genetic approaches in studying role of genetic variation in aggression among different socio-economic groups in society

4.4 A Question of Reduction?

So far I have provided three main philosophical positions arguing for pluralism that is empirically motivated by the multiplicity of accounts, producing partial accounts of phenomena. I also argue that the plurality in scientific practices is an important characteristic of scientific inquiry. The three pluralist theses by Kellert et al., Chang and Mitchell each provide a philosophical account of multiplicities, arguing for the benefits of multiple approaches to explain and understand phenomena. In the following chapters I will further explore the normative aspects of pluralism, while I develop contextual pluralism. However, first I wish to address a possible challenge to pluralism: reduction. In this section I provide a brief overview of the reduction/anti-reduction debate, followed by an alternative account provided by Kaiser (2012) to argue that reductive explanations are common in scientific practices (just like integration, discussed in 4.1.3), where reduction is a way of explaining phenomena, rather than eliminating the plurality of approaches and accounts.

The reductive explanation I will defend here is different to monist notion of reduction, which relies on the tenet that everything we know can be derived from our understanding of the fundamental components of the universe. Therefore, the aforementioned pluralities in scientific practices can be eliminated through reduction (where a given account of phenomena can be derived from the account of its constituent parts). It is necessary to approach this issue with caution since the reduction debate is multi-faceted, including issues in epistemology and metaphysics.[32] Sarkar argues that:

> There has often been a failure to keep epistemological and ontological questions separate. For instance, the questions, whether reduction is being attempted in order to explain some

[32] Reduction: explanation of theories through theories van Riel (2011);
Practice based epistemic issues focusing on education Brigandt (2013)

> theories, laws or facts by others, or whether reduction is intended to show what entities are composed of other, perhaps more 'fundamental', entities, have often been routinely confused. The former is an epistemological question, the latter is an ontological one – they are obviously not the same. (Sarkar 1992: 169)

Therefore, in addressing the reduction debate there is an important distinction to make: while metaphysical reduction is concerned with the relation between things in the world, epistemic reduction focuses on the interaction between knowledge about things in the world. While I remain agnostic about the metaphysical side of the discussion about the structure of the world (see Dupré 1993; Cartwright 1999 for a metaphysical argument for pluralism), I hold that there is no reason to think that any of our scientific practices has a privileged status in exploring and explaining the phenomena. In line with the pluralist thesis I aim to develop, I argue that plurality of approaches cannot be eliminated (nor that it should be eliminated) through the reduction of different accounts of phenomena to a single account without loss of knowledge or ways of attaining more knowledge about different aspects of phenomena. However, following Kaiser (2012), I argue that reductive explanations are used in scientific practices and my aim is to provide a pluralist explanation for these.

In this section, I will use Marie Kaiser's account to argue that epistemic reduction can be seen as part of scientific practice as opposed to a remedy for the plurality of approaches. The type of reduction I will describe here is in line with pluralism as described above in the sense that reduction is part of scientific practices as a opposed to a way of eliminating plurality. First, it is important to address the reductionism debate to dispel any doubts or confusion in the readers' mind, given the rich literature on reductionism. Starting from Nagel, 'reduction' is taken to be the deductive relation between different theories. Herein, I start with a brief description of Nagelian model of reduction, followed by an exegesis of the reduction debate following the Nagelian model. I conclude this section with Marie Kaiser's account (2011 & 2012) to

argue that one must go beyond the Nagelian model of reduction in order to make sense of reduction that is prevalent in current scientific practices.

4.4.1 The Nagelian model of reduction

In his paper 'Issues in the Logic of Reductive Explanations', Ernst Nagel takes reductions to be the deductive relation between different theories, where theories are taken to be sets of law statements. Nagel states that:

> every reduction can be construed as a series of statements, one of which is the conclusion (or the statements which are being reduced), while the others are the premises or reducing statements. (Nagel 1998: 907)

Nagelian reduction must be understood as a certain kind of explanation, in which the laws of a given science are the logical consequence of the theoretical assumptions of another. Nagel's account is based on cases from physics, in particular the reduction of classical thermodynamics that deal with macro-scale objects to statistical mechanics that deals with micro-level objects. On this point, Nagel states that:

> The claim that a theory T (e.g., the corpus of rules known as thermodynamics) is reduced to another theory T' (e.g., the kinetic theory of gases) would therefore be interpreted as saying that all the observation statements which can be derived from given data with the help of T can also be derived with the help of T', but not conversely. (Nagel 1998: 911)

In simpler terms Nagel argues that the behaviour of macro-scale objects are explained in terms of micro-scale processes. Nagelian reduction relies on two principles. The first principle is the *condition of derivability* under which a reduced theory needs to be derived from reducing theory. The second principle is the *condition of connectability*, under whic reduced and reducing theories either contain the same terms (in the case of homogenous reductions) or can be connected

with bridge laws (in the case of heterogeneous reductions). Bridge laws are used in cases where concepts and terms of reduced laws are not present in the reducing laws: bridge laws in most general terms link the vocabulary of two theories.

Although in his paper Nagel is focused on examples from physics, his model of reduction is meant to apply to scientific explanations in general. However, this claim is much contested, especially by philosophy of biology. In order to assess the Nagelian model of reduction, I will briefly look at this model's proponents and opponents before I move on to Kaiser's post-Nagelian reduction.

4.4.2 Proponents of Nagelian reduction

Dizadji-Bahmani et al. (2010) examine Nagelian reduction, defending it as a regulative ideal. Nagelian reduction received considerable attention in philosophy, including the work of Schafner (1993 & 2012), Butterfield (2011), van Riel (2011). Although, most of these papers cited may be regarded as departures from Nagel's model of reduction, their starting point is the model discussed in 4.4.2. Thus, I take them to be Nagelian in the sense that they do not reject the Nagelian model (or at least not completely) but depart from it in a sense that they take Nagelian model as an approximate model for reduction in thermodynamics, but they do not make any claims that Nagelian model can must be regarded as the universal model of reduction in science.[33] Here I focus on Dizadji-Bahmani et al.'s account using Nagel's initial example (the reduction of thermodynamics to statistical mechanics), allowing me to highlight how current accounts can defend Nagel's argument clearly without needing to go into detail. The reason for choosing Dizadji-Bahmani et al. is that their approach is close to the Philosophy of Science in Practice approach, given that they regard the

[33] This distinction will become clear in the following sub-section where I move on to discuss the Anti-Reductionist debate, where the main premise is the complete rejection of the Nagelian model.

question of whether a theory can be reduced to another as a practical (rather than philosophical) question, asserting:

> Whether any given theory can actually be reduced to another theory, or even whether theoretical reduction can be achieved across the board, is, in our view, a factual and not a philosophical question. (Dizadji-Bahmani, Frigg, and Hartmann 2010: 410)

The important point in Dizadji-Bahmani et al.'s account for Nagelian reduction is concerned with how reduction takes place in statistical mechanics in practical terms. Following their engagement with the practices, Dizadji-Bahmani et al.'s version of reductionism recognises that reduction is approximate in the case of reducing thermodynamics (TD) to statistical mechanics (SM). The modified model of reduction is described in the following way:

> a theory TP (here TD) reduces to another theory TF (here SM) iff the laws of TP can be deduced from the laws of TF and some auxiliary assumptions. The auxiliary assumptions are typically idealisations and boundary conditions […] reduction is the deductive subsumption of a corrected version of TP under TF, where the deduction involves first deriving a restricted version, T*F, of the reducing theory by introducing boundary conditions and auxiliary assumptions and then using bridge laws to obtain T*P from T*F. (Dizadji-Bahmani, Frigg, and Hartmann 2010: 398)

Dizadji-Bahmani et al.'s argument is notable, given that they are not supporting reductionism as way for all sciences to converge into one fundamental account. Instead, they argue that Nagelian reduction can be modified in the way described above in order to explain part of scientific practice in statistical mechanics. That is, while Dizadji-Bahmani et al. further the Nagelian model by looking at the question of reduction ion thermodynamics, they do not make generalizable claims about reduction in all science based on the Nagelian model. Hence,

their main claim is for reduction as a factual and not a philosophical question.

However, it must be noted that using the same example as Nagel to defend Nagelian reduction does not address the anti-reductionist arguments. The main anti-reductionist arguments come from philosophy of biology, mostly on the topic of the reduction of Mendelian genetics to molecular biology (Ruse 1971, Hull 1972, Maull 1977) and more recently arguments on the limits of reductionism in medicine and life sciences (Ahn et al. 2006, Mazzocchi 2008).

4.4.3 Anti-reductionism

Kenneth Waters (1990) summarises the anti-reductionist position, which I will use here to exemplify the rich literature on this topic. Waters's account of anti-reductionism focuses on the literature that objects to the possibility of reducing classical mendelian genetics to molecular biology. [34] Although there are differences among anti-reductionist thesis, Waters presents general tenets of anti-reductionist arguments as follows:

> according to the general anti-reductionist thrust, the relations between the levels of the organisation represented by the classical and molecular theories are too complex to be connected in the systematic way essential for a successful theoretical reduction. Antireductionists support this view by arguing that the gene concepts of the respective theories cannot be linked in an appropriate way. If the concepts cannot be linked, the reasoning goes, neither can the theoretical claims couched in terms of them. Hence, reduction will never be achieved. (Waters 1990: 125-126)

[34] See Ruse (1971) Hull (1972) Maull (1977) Rosenberg (1985) Kitcher (1984)

Anti-reductionist objections are summed up by Waters under two heading: (1) the unconnectability objection; and (2) the explanatory incompleteness objection.

(1)The main premise of the unconnectability objection is the conceptual gap between Mendelian genetics and molecular genetics. The concepts of the gene in both theories are far too complicated to be connected using Nagelian reduction. The main proponent of unconnectability, Rosenberg (1985), argues that connectability cannot be achieved in a Nagelian sense since the relationship between Mendelian phenotypes and molecular genes is very complex. Thus, forming bridge laws that can connect two sets of laws and theories are exceedingly complex. Rosenberg sums up his position as follows:

> In the end, the thesis that we can in fact deductively reduce Mendelian genetics to molecular genetics founders on the impossibility of meeting the criterion of connection between the terms of the two theories. Such vast, unwieldy, general statements as we might construct – In which a Mendelian gene is equated with the molecular one – will be full of disjunctions, conjunctions, denials, exceptions, qualifications. It will make so many appeals to stages in the pathway between the DNA and the phenotypic end-point of the pathway that it will be without any independent scientific standing. (Rosenberg 1985: 107)

(2) The second objection is explanatory incompleteness, which is based on the claim that molecular biology will never explain or enhance knowledge of Mendelian genetics. In other words, anti-reductionists argue that the 'gory details' of molecular biology do not enhance understanding of key processes underlying classical Mendelian genetics. For instance, Philip Kitcher argues that molecular genetics is more successful in explaining the process of DNA replication and characterisation of genetic mutations than classical Mendelian genetics (Kitcher 1984: 359). However, Kitcher further argues that,

> in the current practice of biology, nature is divided into levels which form the proper provinces of areas of biological study: molecular biology, cytology, histology, physiology, and so forth. Each of these sciences can be thought of as using certain language to formulate the questions it deems important and as supplying patterns of reasoning for resolving those questions. (Kitcher 1984: 370)

Kitcher later adds that meiosis should not be explained through the 'gory details' of reshuffling genes at a molecular level, but through observation of chromosome movements in cells at a cytological level. Thus, Kitcher argues that,

> anti-reductionism emerges as the thesis that there are autonomous levels of biological explanation. Anti-reductionism construes the current division of biology not simply as a temporary feature of our science stemming from our cognitive imperfections but as the reflection of levels of organization in nature. Explanatory patterns that deploy the concepts of cytology will endure in our science because we would foreswear significant unification (or fail to employ the relevant laws, or fail to identify the causally relevant properties) by attempting to derive the conclusions to which they are applied using the vocabulary and reasoning patterns of molecular biology. (Kitcher 1984: 371)

However, this criticism is not supported well, nor is it explained exactly why we cannot expect molecular biology to explain classical Mendelian genetics. That is, Waters argues that trying to apply the 'gory details' argument to Mendelian genetics makes it less plausible. Waters demonstrates this using the Holiday Model for genetic recombination (Waters 1990: 132-133). Moreover, Waters asserts that that the anti-reductionist argument is unreasonably pessimistic:

> The claim that the gory details of molecular biology do not enhance our under- standing of key processes underlying CMG

> is quickly becoming outdated. There is no question that molecular theory has greatly improved our understanding of gene replication, expression, mutation, and recombination. Furthermore, it is just a matter of time before it accounts for the pair-wise coupling and separation of chromosomes during meiosis. Anti-reductionists need to justify their pessimism and explain why we should not expect molecular biology to continue on its path towards explaining CMG in accordance with the spirit of post positivist reduction. (Waters 1990: 134)

Waters argues that two major objections to the reduction of Mendelian genetics to molecular genetics cannot stand 'rigorous' scrutiny. Waters show that neither reductionist nor anti-reductionist accounts can explain the connection between classical Mendelian genetics and molecular genetics. Waters states that:

> the anti-reductionist arguments were based on admittedly brilliant philosophical analyses that appeared plausible in the abstract. But, when scrutinised with respect to the details of the actual science, the arguments were found to rest on undue pessimism, on implausible judgments of comparative explanatory value, and on highly questionable assumptions about the structure of CMG and molecular biology. Practicing geneticists believe that the classical theory can be systematically explained at the molecular level, I suggest, because they have a firm grasp of the explanatory power and structure of molecular biology. (Waters 1990: 135)

For Waters, the response should not be that Nagelian reduction does not apply in biology and therefore reductive explanations have no place in the philosophy of biology. Instead, the main task for the philosophy of biology is to find a way to reformulate a conception of reduction that goes beyond the Nagelian model and theories. The key point to take away from Waters's account is that he takes a critical stance towards the reduction/anti-reduction debate in light of what is happening in scientific practice, stating that,

> The question of whether CMG is being reduced deserves to be reconsidered, not just because we have good reason to suspect that the anti-reductionist consensus is wrong, but also because it provides the opportunity to advance philosophical debates about the structure of theories and the nature of scientific explanation and theoretical reduction. (Waters 1990: 136)

The point here is that reductive explanations are present in life sciences and neither the Nagelian model nor the anti-reductionist critiques can explain. Kaiser argues that the opponents of Nagelian reduction do not offer a new version of reduction, but rather abandon the concept of a reductive explanation altogether. Kaiser argues that we must go past the Nagelian reduction as the main model for reductive explanations in science and elaborate on a new form of reductionism in order to account for reductive explanation in life sciences. For a pluralist taking a PSP approach it is necessary to provide a philosophical account of reductive explanations, given that the common objection to pluralism comes in some form of reductive explanation. In the following section I focus on Kaiser's account of reduction motivated by scientific practices in the field of biology as an alternative philosophical account of reductive explanations that is compatible with the pluralist argument I wish to develop in this thesis.

4.4.4 Kaiserian Reduction

Kaiser formulates a reductive account that moves away from Nagelian reduction in the sense that it ceases to look only at theories and the logical connections between them. The new account of epistemic reductionism Kaiser proposes 'captures the diversity of reductive reasoning strategies present in current biological research practice' (Kaiser, 2012: 251). Kaiser's criticism of Nagelian reduction centres on the general way of thinking about reduction, which can be summed up as a relation of logical derivation of theories from one another. Kaiser argues that Nagelian reduction is abstract, only focusing on theories. Kaiser further argues that Nagelian reduction is still flawed when it comes to thinking about reduction in biology:

> [a] formal model of theory reduction does neither capture the most important cases of epistemic reduction in biology nor does it account for the diversity of reductive reasoning strategies present in current biological research practice. (Kaiser, 2012: 252)

Kaiser argues that a philosophical account of epistemic reduction in the philosophy of biology should satisfy two criteria (criteria which Nagelian reduction fails to meet):

> [it should] capture and help understand the case of epistemic reduction that actually occur in current biology research practice, rather than focusing on epistemic reduction that can only be achieved in principle. In addition, it should account for diversity for the complexity of the cases of epistemic reduction that are present in contemporary biology. (Kaiser, 2012: 254)

Kaiser concludes that Nagelian reduction is deeply flawed when applied to life sciences, arguing that the formal model of reduction does not capture how reductive explanations are used in this field, nor does it reflect the diversity of such explanations. Kaiser moves on to provide an account of reductive explanations in life sciences. Similar points are made by Steel (2004) and Brigandt (2013), for whom the common premise is the need to provide a positive thesis for reductive explanations in science.

Kaiser (2011) demonstrates three different forms of reductive explanations used in life sciences: (i) decomposition and part-whole explanations; (ii) parts in isolation; and (iii) focusing on internal factors. Here I will focus on the two that are used in chemical and genetic approaches discussed above (see section 4.2)

Decomposition and part-whole explanations refer to entities located at a lower level being used to explain phenomena under investigation. Kaiser argues that decomposition and part-whole explanations must not be linked with fundamental level explanations, a metaphysical thesis which assumes that lower level explanations are more

fundamental. As mentioned above, epistemic reductions are concerned with the relations among different knowledge claims. Therefore part-whole explanations must be understood in terms of scale, as opposed to one being fundamental to another:

> What is crucial for the reductive character of an explanation is that it includes only lower-level factors, not that it refers only to fundamental-level factors. (Kaiser, 2011: 464)

Decomposition and part-whole explanation are used across life science. One example is sickle-cell anaemia, a condition that manifests itself physiologically where it is explained through mutation in a particular gene coding for haemoglobin. The mutation in this gene leads to mis-folding of haemoglobin, altering the shape of red blood cells. The change in the shape of red blood cells leads to the physiological traits of sickle-cell anaemia: low red blood cell count, increased risk of infection and recurring pain. The physiological traits of this disease are explained through haemoglobin mis-folding at molecular level due to a specific mutation on the HBB gene (coding for the beta globulin, one of four polypeptide chains that forms the haemoglobin molecule).

Population ecology is another case in which part-whole explanations are used. Population ecology is a case where a lower level does not have to be the molecular level. Individual-based models in population ecology explain the behaviour of a given population in terms of individual organisms and interactions among them. Here, the whole is the population and parts are individuals. It is important to underline this point, since part-whole reduction here is local and does not make any metaphysical claims about objects at lower levels being more fundamental. Kaiser's part-whole explanation focuses on two explanations at two different levels, say atomic and cellular, while a lower-level explanation is used to account for the higher-level phenomena.

The decomposition and part-whole explanations as described by Kaiser can be found in early drug discovery processes. In the case of trypanothione synthetase, kinetic assays have shown that higher concentrations of the natural substrate has no effect on the rate of inhibition. This phenomenon was explained by structural information at the atomic level: the atomic interaction between the trypanothione synthetase and an inhibitor molecule happens on a different site than the natural substrate, thus making the inhibition allosteric.

In summary, part-whole explanations are used in scientific practice where phenomena can be explained referring to phenomena that take place at a lower level, without holding any assumption that one level is more fundamental than the other.

Explanation of parts in isolation involves the explanation of a part of a system isolated from their native state in the organism. Explanation of parts in isolation (in a practical sense) requires purification of a compound of interest and studying its behaviour under controlled conditions. For instance, *in vitro* assays used for target validation entail isolation of trypanothione synthetase to its interaction with potential inhibitors. *In vitro* study plays a significant role in life sciences, particularly in biochemistry, to determine the tasks of each molecule in metabolic pathways.

Explanation of parts in isolation can also be seen in experimental methods used to determine functional protein structure. As described above, the three-dimensional structure of proteins is determined by x-ray crystallography or nuclear magnetic resonance, where both methods study proteins, not in their natural environment but rather isolated in a solution or in crystallised form. Although they are studied in isolation, I previously argued that such methods are necessary to generate three-dimensional models of proteins in order to explain atomic interactions involved in their functional activities.

These three types of reductive explanations can be discussed in depth, and each can be backed up by different case studies from current practices. It is important to note that each one of these three different

types of reductive explanations are also analytical categories and can be challenged in different terms.

In this section I argued that reductive explanations are used in scientific practices, particularly in life sciences. Following Kaiser's account, I argued that the Nagelian model of reduction (or the anti-reductionist arguments) does not give a successful account of the reductive explanations used in life sciences. Moreover, I argued that Kaiser's account of reductive explanations is compatible with the pluralist argument I present in this thesis. Kaiser's account allows understanding of reductive explanations as part of scientific practice. Reductive explanations must be understood as partial accounts of phenomena that explain certain aspects of phenomena. Both reductionist and holist approaches provide partial accounts, focusing on different aspects of phenomena.

4.5 The aims of pluralism: who are we trying to convince?

Section 4.1 provided an overview of three philosophical theses that aim to provide a philosophical interpretation of the pluralities in scientific practices. Following these accounts, I argued that multiplicities in scientific practices must be regarded as an important characteristic of scientific inquiry that allows scientist to explain and explore different aspects of phenomena. Moreover, I argued that each account provided by particular approaches aims to answer a different set of questions. That is to say, each approach has different aims, producing accounts to satisfy these aims. Section 4.2 demonstrated how the pluralities in HAT research, particularly in early drug discovery and development, can serve as a case study in which the plurality of approaches and accounts are beneficial to satisfy a particular aim (in this case, to validate a dug target). Following my discussion of pluralities in scientific practices and various pluralist arguments, I shifted my focus to ways in which pluralists analyse scientific practices focusing on units of analysis. I argued that the way in which pluralists parse scientific

practices to argue for the benefits of pluralism must be understood as analyst categories, which are contingent on analysts' projects. Recognising the partiality of analysts' categories will become important in chapters 5 and 6, in particular developing a normative argument for pluralism.

Section 4.4 provided an argument against possible reductionist objections to the pluralist argument I develop in this thesis. Following Kaiser (2012), I argued that the reductionist/anti-reductionist debate does not help explain the reductionist explanations used in scientific practices. I argued that the reductive explanations are not used in scientific practices to eliminate plurality of accounts or approaches. Instead, they are ways of explaining certain aspects of phenomena, discussing three types of reductive explanations outlined in Kaiser (2011).

In the following chapter, I will focus on active normative epistemic pluralism, first discussed in section 4.1.2, defined by Chang (2012). Chang asserts that pluralism as he means it is unapologetically normative. Moreover, Chang argues that pluralism must be active in the sense that pluralism must be promoted in all parts of scientific inquiry. In the following chapter, I address different questions that arise from Chang's active normative epistemic pluralism. The motivating question of the chapter 5 is this: who are we trying to convince to be pluralist?

Chapter 5

5.1 Active Normative Epistemic Pluralism

In the previous chapter I discussed three distinct pluralist arguments put forward by Kellert et al (2006), Chang (2012) and Mitchell (2002). Following these three accounts, my argument for pluralism in the previous chapter focused on building a philosophical account for the pluralities in scientific practices. I argued that the pluralities in current and historical sciences serve as evidence that the aim of scientific inquiry is not to come up with a single complete and coherent account of the world. Moreover, I argued that the multiplicities of accounts and approaches must be understood as an important characteristic of scientific inquiry. I also argued that different approaches have distinct aims, asking different questions about phenomena. In section 4.2, I argued that different approaches (genetic and chemical) in target validation during drug discovery processes focus on different aspects of phenomena. Both approaches have related aims, each producing partial accounts used by scientist to determine whether a given macromolecule can be used as a drug target. I argue that the different accounts reveal interesting information about the phenomena, and are the result of asking different questions and employing different sets of tools (both physical and cognitive). In previous chapters I discussed several case studies to argue that the plurality of approaches must be regarded as an important characteristic of scientific practices, and that the accounts of the world produced by each approach are partial to the particular aims of the approaches that produced them, in the sense that each account answers a distinct set of questions according to the aims of the given approach. I also argued that approaches and accounts interact with each other in different ways, including competition and co-option (4.1.2), ad-hoc integration (4.1.3), and reductive explanations (4.4).

The pluralist argument presented so far has focused on rejecting the monist interpretation of scientific inquiry. I argued for a pluralist

interpretation of the multiplicity of accounts in science and the way these accounts interact with each other in scientific practices. Moreover, I argued that the plurality of approaches and accounts in scientific practices are an important characteristic of scientific inquiry. I also argued that scientific inquiry is ought to be pluralistic to explain and explore different aspects of phenomena. In this chapter I wish to further this normative argument. Herein, I shift my focus to the benefits of plurality, building a normative pluralist argument. In this chapter, I will first argue that, in order to assess the benefits of pluralism, it is necessary to focus on particular aims in science. As I argued in the previous chapter, there are multiple aims in scientific practices and the benefits of multiple approaches must be understood in terms of a multiplicity of aims in science. In order to develop my argument for normative pluralism, I will focus on Chang's active normative epistemic pluralism, providing a critical reading of Chang's normative argument. In particular I will focus on the normative and active aspects of Chang's argument, in which he provides an argument for the benefits of multiple systems in science and argues that the pluralism he proposes aims at actively promoting a multiplicity of systems of practices by challenging monist assumptions in both science and the philosophy and history of science.

In section 5.1.1, I will examine Chang's normative and active claims, where he argues that plurality is more beneficial to science and goes on to define his form of pluralism as an ideology committed to promote plurality in scientific practices. In section 5.1.2, I will focus on the distinction between descriptive and normative forms of pluralism. Chang argues that Kellert et al. merely describe the states of affairs in scientific practices, where he argues to move beyond mere description and assert that scientific practices ought to be pluralistic. In section 5.1.3, I move on to focus on Chang's argument for active pluralism, where his form of pluralism is committed to challenging monism and proliferating multiple systems of practices.

In section 5.2, I argue that in order to understand the normative and active aspects of Chang's pluralism, it is necessary to further articulate the position Chang is reacting against. Thus, I ask the question 'what does it mean to be a monist?'. Here I identify three monist assumptions metaphysical, epistemic and methodological.[35] I argue that these assumptions lead to unnecessary limitations to the potential of scientific inquiry to explain and explore different aspects of phenomena. Herein, I argue that it is the role of pluralist to challenge and remove these assumptions. In section 5.2.1, I will further this argument using case studies from current debates in epidemiology, in which proponents of the potential outcomes approach (POA) argue that the only causally relevant factors are those that can be described as well-defined interventions, thus arguing that other approaches in epidemiology must be disregarded. I will argue that POA is a system based on an epistemic assumption of what can be counted as a causal factor, thus limiting the plurality of systems in epidemiology, which does not have the same concept of causality. In section 5.2.2, I will focus on gene-centric biology, in particular current systems of practices (such as the genetic validation approach discussed) using gene-centric methods (such as gene knockout or RNA interference) to investigate metabolic processes. I argue that the focus on gene-centric approaches is based on the assumption that the manipulation of genes is a useful way to investigate cellular processes, without any epistemic assumptions about genes being more important or causally fundamental in cellular processes.

In section 5.4, I summarise the active normative aspects of the pluralist argument I put forward in this thesis. Herein, I argue that scientific practices ought to be pluralistic in order to explain and explore different aspects of phenomena. Following Chang's call for action, I argue that it

[35] Herein I mainly focus on epistemic and methodological given that I remain agnostic to metaphysical argument. The main focus of my thesis is scientific practices and the accounts they produce to explain and represent the world.

is the role of pluralist to identify and challenge any assumptions that lead to unnecessary limitations to the potential of scientific inquiry. In the final section I presented a preliminary argument for pragmatic values. I argue that pragmatic values, different to the monist assumptions identified here, limit the extent of plurality in any given field of science with regards to the particular aims of scientific practices. I will further develop this argument in chapter 6.

5.1.1 Active Normative Epistemic Pluralism

Section 4.1.2 presented Chang's argument for pluralism, who argues that the aim of science is not to come up with a monist account of phenomena, but to fulfil different scientific aims:

> What we want science to do is to give us an account of the natural that serves whatever ultimate aim we may have (…) The monistic character of the account is itself not our ultimate aim. Aims of science can be served better in general by cultivating multiple interacting accounts. (Chang 2012: 260)

Chang argues that there are multiple systems of practices in science, which are sets of epistemic activities working together to achieve different aims. Moreover, Chang lists three main benefits of having multiple systems of practice (toleration, co-option, and competition, all discussed in 4.1.2), arguing that,

> pluralism is more beneficial to science than monism, given any reasonable position regarding the aims of science and the fundamental values operating in science. (Chang 2012: 269)

Chang describes his pluralism as an ideology of science, promoting the plurality of systems of practice to reap the benefits of having multiple systems of practice. Chang's argument is focused on improving knowledge acquisition by promoting the presence of multiple systems. Thus, Chang argues that that any field of science that is monistic must be reformed:

> proper ‘ism’ should be an ideology, which implies a commitment to action. So, pluralism about science is a commitment to promote the presence of multiple systems of scientific knowledge. (Chang 2012: 260)

> if we should find a field of science that is quite monistic, then that is quite likely not healthy, and we should consider reforming it. (Chang 2012: 269)

As discussed above, Chang’s argument is concerned with improving knowledge acquisition and opposing monist assumptions about the aims of science. Chang argues that accounts of phenomena produced by each system of practice are partial to the aims of a given system of practice. Chang asserts that each system of practice has a distinct aim, asking different sets of questions. In my example above (section 4.2), I demonstrated how chemists and geneticists ask different questions regarding target validation, each focusing on different aspects of phenomena: while chemists are interested in the question of whether manipulating a given macromolecule will lead to the death of parasite, geneticists are interested in understanding whether the presence or absence of a given macromolecule is essential for parasite survival. Both chemists and geneticists in this case are interested in establishing if a macromolecule can be a drug target, but the specific questions they ask are different, allowing them to learn about different aspects of the role of macromolecules in the cell (see section 4.2; more technical information can be found in Wyatt et al. 2011).

It is important to note that Chang uses an example in which two systems of practices are significantly different from one in terms of the questions they ask and how they conceptualise the phenomena, such as oxygen and phlogiston. Chang argues that as long as we regard the aims of a given system as worthy of pursuit, we should keep them alive. In summary, Chang argues that there are multiple systems of practice aiming to answer different questions about phenomena. Each system of practice produces an account of phenomena that serves whatever aim that system has. For instance, Chang argues that while

both oxygenists and phlogistonists were interested in understanding chemical processes such as combustion and constitution of substances, oxygenists were interested in theories of heat and changes of state, while phlogistonists were interested in explaining the properties of compounds in terms of the properties of their ingredients (Chang 2012: 20). For Chang, both oxygenists and phlogistonists asked different questions about phenomena according to their aims. Chang rejects the assumption that the aim of science is to provide a monist account of phenomena and acknowledges that different systems have individual aims, allowing these systems to study different aspects of phenomena. However, what is implicit in Chang's argument is the notion that the broad aim of science is to produce and proliferate knowledge about the world, and thus pluralism is more beneficial to science. Moreover, Chang argues that pluralists must be committed to promoting plurality of systems of practices:

> Pluralism as I intend is not a descriptive statement about what science is, or not even an armchair-normative statement about what science should be […] Pluralism about science is a commitment to promote the presence of multiple systems of scientific knowledge. (Chang 2012: 260)

Chang's strong emphasis on normativity (underlining the benefits of multiplicity of systems of knowledge) and his commitment to action underlines the main difference between Chang's active normative epistemic pluralism, Kellert et al.'s pluralist stance and Mitchell's integrative pluralism (see sections 4.1.1 and 4.1.3). Chang's argument goes beyond describing pluralities as the state of affairs in scientific practices, asserting that multiple systems of practice are more beneficial for scientific inquiry and plurality must be promoted. Chang develops his normative argument in comparison to Kellert et al.'s pluralist stance. For Chang, the pluralist stance is merely descriptive of pluralities in science. In the following section, I will focus on the normative aspects of Chang's pluralism.

5.1.2 Normative vs Descriptive Pluralism

Chang asserts that his argument for pluralism is unapologetically normative, which he further articulates by comparing active normative epistemic pluralism to the pluralist stance defined by Kellert et al. (2006). Chang uses this comparison to underline the normative aspects of his argument. As discussed in 4.1.1, Kellert et al. define the pluralist stance as:

> A commitment to avoid reliance on the monist assumptions in interpretation and evaluation coupled with an openness to the ineliminability of multiplicity in some scientific contexts. (Kellert, Longino, and Waters 2006: xiii)

Chang criticises Kellert et al. for being merely descriptive and passive, in the sense that the pluralist stance fails to promote a plurality of systems directly in scientific practices. Chang argues that the Pluralist Stance merely aims to interpret the content and practices of scientific inquiry. Chang asserts that interpreting science this way makes little difference. Instead, Chang argues that philosophers of science must demonstrate the benefits of plurality using current and historical case studies in order to challenge monist assumptions in our understanding of scientific practice. Moreover, Chang argues that, for every field in science, multiple systems of practices and account is more beneficial epistemically, as different systems will allow scientist to explore and explain different aspects of phenomena, thus producing more knowledge about the world.

Both Kellert et al. and Chang challenge monist assumptions regarding the aims of science and the nature of knowledge that science produces. Moreover, both Kellert et al. and Chang underline the partiality of different systems and approaches. However, Kellert et al. argue that the benefits of multiple accounts of phenomena is an open question that must be addressed case by case:

> we do not hold that for every phenomenon there will inevitably be multiple irreducible models and explanations. We hold that the task of identifying which situation require multiple

> approaches requires empirical investigation. (Kellert, Longino, and Waters 2006: xiv)

Chang argues that the benefits of plurality of systems of practices is not an open question, but a commitment. For Chang, an empirical investigation to choose between monism and pluralism is futile and requires an experiment where both monist and pluralist approaches are tried. Chang argues that only people who are committed to the benefits of pluralism will subscribe to an experiment to answer whether pluralism or monism is beneficial, thus making the question futile. In Chang's words:

> for that experiment, we have to make a genuine effort to create and cultivate a set of systems, and observe how they develop, each of them in itself and also through mutual interaction. We have to keep this going long enough to see whether any trends in successfulness that we detect are stable; if it turns out that the particular combination of systems that we try out really doesn't deliver goods, we have to try some other combinations of systems before we give up on pluralism in general. By that point we are up to our necks in pluralism with no clear end of experiment in sight, so we might as well be pluralists! The empirical question can only really be answered post-commitment, and it is pointless to insist on treating question as empirical if we are not going to try to answer it through real experience. (Chang 2012: 291)

Chang argues that individuals willing to try the experiment will commit to pluralist assumptions before the experiment concludes. That is, Chang's argument for pluralism is based on the commitment that plurality of systems is more beneficial to the broad aims of science, which he takes to be the production and proliferation of knowledge. Therefore, the open question to determine which situation requires a multiplicity of accounts and approaches (in Kellert et al.'s terms) is futile for Chang, given that Chang is committed that in every situation, a multiplicity of systems will allow scientists to produce more

knowledge. Chang's argument for pluralism is a doctrine about knowledge-building and not just knowledge evaluation (Chang, 2012: 284). Thus, Chang argues that scientific practices ought to have multiple systems to improve their knowledge-building capacity.

Chang's active normative epistemic pluralism aims to improve the acquisition of scientific knowledge by *actively* promoting plurality in scientific practices. Chang argues that a passive version of his pluralism would only point out the benefits of multiple systems, where Chang wants to go further and engage actively in cultivating multiple systems. In the following section I will examine what it means to be an active pluralist, expanding on Chang's argument that pluralists must actively promote multiplicities of systems in scientific practices.

5.1.4 How to be an Active Pluralist?

In the previous section I described the normative aspects of Chang's pluralism. In this section I focus on how to actively promote the presence of multiple systems of scientific knowledge. Chang asserts that:

> The main action point is to *proliferate*: to foster valuable alternative scientific systems of practice alongside the orthodox and the fashionable. I intend pluralism as a doctrine about knowledge-building, not just knowledge-evaluation. In a way, it is obvious that people who can best put pluralism into practice in science are practicing scientists. However, it is also likely that scientists are already being as pluralistic as their professional constraints allow, and at any rate it is unlikely that many scientists will be inclined to change the way they do science following some philosophical doctrine articulated from outside their own field. So it may well fall to those who are not professional scientists to undertake active pluralist work, and there are some distinct lines of useful work that historians and philosophers of science can plausibly carry out. (Chang, 2012: 284-285)

Thus, Chang argues that one way of actively proliferating multiple systems of practice is through pluralist historiography. Chang's pluralist historiography is a way to challenge triumphalism in history of science. As discussed in section 4.1.2, Chang argues that the history and philosophy of science must not focus on the 'heroes' of science, described in narratives in which one system of practice 'triumphs' over the other (as in the case of oxygenists triumphing over phlogistonists, where Lavoisier is named the father of chemistry). Although Chang's historical account of the chemical revolution is challenged (see Kusch 2015, Klein 2015), Chang's pluralistic historiography has an important lesson. Chang argues that our understanding of scientific practices (both historical and current) must be rid of monist assumptions. Triumphalist historiography, as defined by Chang, holds the assumption that the ultimate aim of science is to provide the monist account. Therefore, a plurality of systems is expected to end when one system is agreed to be right, in the sense that it is closer to the ultimate aim. As discussed in section 5.1.1, Chang argues against the notion that the monist account is the aim, therefore different systems of knowledge must not be judged based on their likeness to such account.

The task of pluralist historiography is to emphasise the plurality of systems of practices, underlining the plurality of aims of questions asked by different systems of practices. Moreover, Chang argues that the task of pluralists is to uncover the monist assumptions that underlie the received view of science and challenge them. Monist assumptions are recognised in multiple guises as I will discuss in section 5.2. Chang states that any unwarranted assumptions that lead to monism must be replaced by pluralist assumptions, and that the main task of pluralist history and philosophy of science is to encourage alternative systems to complement current practices. Chang summarises the active aspect of his pluralist argument as follows:

> To sum up: the ultimate aim of the active normative epistemic pluralism that I advocate is to improve science by cultivating

> multiple systems of knowledge. The most active service that history-and-philosophy of science can perform in this connection, going beyond description and commentary, is to address *scientific* questions that are not being dealt with by scientists because they are restricted by monist traditions—sometimes due to the necessities of normal science, sometimes for lack of imagination. History gives us an effective starting point, if we approach it with sufficient philosophical acumen to discern elements of the past that became discarded or hidden without good reason. (Chang, 2012: 290)

Chang's complementary science (Chang 2004) is an interesting approach that addresses questions no longer dealt with by scientists, unearthing forgotten methods and accounts to learn more about these systems of practices and phenomena itself. Here I wish to focus on Chang's argument for actively challenging monist assumptions. In the following section I define monist assumptions and question how to challenge them, using case studies from current debates from current debates in epidemiology and gene-centric biology.

5.2 What does it mean to be monistic?

Here I aim to identify monist assumptions that must be eliminated from our understanding of scientific inquiry (this might include from philosophical, historical and scientific policy perspectives as well as how scientific inquiry is conceptualised by scientists themselves). Chang argues that scientific inquiry should not be limited by monist assumptions: that is, monism about scientific knowledge and practices restricts the capacity of scientific inquiry to produce knowledge about the world. Chang characterises monism in the following way:

> monism about science springs from the notion that science is the search for the truth about nature; since there is only one world, there is only one truth about it, and only one science should seek it […] there is one right answer to each well-formed question, and science tries to find out that right answer,

> employing the one best scientific method known and employed by the relevant mainstream scientific community. (Chang 2012: 259)

Here I will identify three different monist assumptions in Chang's characterisation. The first is metaphysical, holding that the structure of the word is such that it can be explained in a single account. Chang rejects the metaphysical assumption asserting that the external reality as we know it through scientific practices is complex and abundant (see 4.1.2). The second assumption is epistemic considering the nature of scientific knowledge, holding that there is only one truth about the world that can be captured by a single complete and comprehensive account. Finally, there is what I call the methodological assumption, holding that there is one method that can provide such account. Chang seeks to challenge monist assumptions, and cultivate multiple systems of practice in any given field of science (2012: 260). Here, I am going to focus on epistemic and methodological assumptions, as Chang remains agnostic about the metaphysical view.

I agree with Chang that it is not necessary to commit to a metaphysical view to pursue epistemic and methodological pluralism. The starting position is scientific practices and their aims. Metaphysical monism is an ontological view on what constitutes phenomena and the way the world is. The argument for metaphysical monism can be constructed as follows: the nature or the structure of the external reality is such that it can be explained completely through the simplest and the most fundamental terms. I remain agnostic about metaphysical arguments for monism. I hold the assumption that nature or the structure of the external reality is an empirical question that cannot be answered *a priori*. Instead, the argument I pursue regards how we go about investigating and understanding the phenomena.

Epistemological assumptions, broadly construed, are the notion that the aim of science is to provide a single complete and coherent account of phenomena. Thus, scientific accounts of phenomena must be judged in terms of their proximity to the monist account, where the

aim is to get rid of the multiplicity of accounts leaving with the best (or as best as it can be). Although Chang makes it clear that his position is epistemic as opposed to metaphysical, he does not comment on his stance on methodology assumptions. I define methodological assumptions as that there is one way to achieve an aim. Methodological monism coupled with epistemic monism will argue that there is one way to achieve a single, complete and coherent account of phenomena. However, it is possible to separate methodological monism from epistemic assumptions. Herein I argue that a distinction between epistemic and methodological monism is important for active pluralism, especially if one defines active normative pluralism as the rejection of monist assumptions that restrict the potential of scientific inquiry to explain and explore different aspects of phenomena. Thus it is necessary to make the distinction between methodological and epistemic assumptions in monsim. It is possible for practitioners of a system to accept the plurality of aims in scientific practices, but adhere to a single methodology that can only explain and examine limited aspects of phenomena. Adherence to a given system based on epistemic assumptions leads to a disregard of other systems, compromising the plurality of systems of practices. Therefore, the normative pluralism I defend in this thesis is the rejection of epistemic assumptions (and to an extent methodological assumptions that compromise proliferation of other systems). This has direct consequences for promoting active pluralism. In section 5.2.1, I will focus on current debates in epidemiology, particularly Broadbent (2015), who summarises the POA, which is based on the epistemic assumption that the only causally relevant factors in epidemiology are those that can be intervened in, via well-specified interventions. I will argue that the epistemic assumption must be challenged from a normative pluralist point of view, and argue for plurality of causally relevant factors in epidemiology, promoting approaches that focus on different causal factors. In section 5.2.2, I shift to gene-centric biology, using Waters (2006) to argue that focus on gene-centred methods in molecular biology, in particular biological development, is based on the assumption that genes are difference-makers in cells. Therefore,

methods for manipulating genes such as gene knockout or RNAi are used in cellular biology research, based on the assumption that gene centred methods are the best way of studying biological development. Herein, I want to underline that monist assumptions are nuanced, and require close scrutiny. Moreover, I argue that only assumptions that lead to unnecessary limitations of scientific inquiry must be challenged and replaced.

5.2.1 Concepts of Causation in Epidemiology

Broadbent (2015) provides a critical overview of the potential outcomes approach (POA) developed recently in epidemiology. Although the POA has a long history, Broadbent focuses on contemporary developments in this field where the use of mathematical methods (such as *marginal structural models*) has led to reconsideration of the concept of causality. Broadbent identifies two papers important in the development of the POA, by Hernán and Taubman (2008) and Vander-Weele and Robinson (2014). Hernán and Taubman (2008) argue for a conceptual change in how epidemiologists think about causal inference. Vander-Weele and Robinson further the argument, arguing for a shift in conceptual frameworks beyond what is generally considered reasonable or plausible by epidemiologists, creating a division between established concepts and the POA. According to the POA (as put forward by Hernán and Taubman [2008] and Vander-Weele and Robinson [2014]), the only relevant causal factors are those that can be intervened in experimentally and in a well-specified way. Hernán and Taubman (2008) argue that obesity does not respond to a well-specified intervention, and therefore it is not a cause of death. Broadbent summarises Hernán et al.'s position as follows:

> obesity ought not to be treated as a cause of death. The reason – which is the real point of the paper – is that obesity does not correspond to a well-specified intervention. There is more than one way to reduce obesity, and these different methods all lead to different effects on mortality. From this striking and

> uncontestable point, they draw the conclusion that obesity itself is not a cause of death. (Broadbent 2015: 74)

Hernán and Taubman (2008) reach this conclusion using a comparative case study looking at the possible outcomes of experimental studies (different diet, exercise and combinations of diet and exercise) and retrospective data analysis. Hernán and Taubman suggest that although data analysis can provide the exact number of deaths attributable to obesity, only experimenters can give specific recommendations to reduce mortality. Broadbent summarises Hernán and Taubman's conclusions as follows:

> something is a cause only if it corresponds to a well-specified intervention, and that experimental studies are better than observational ones because they enforce the proper specification of an intervention; that much of the causal knowledge delivered by observational studies is either useless or illusory, or perhaps both; and, of course, that obesity is not a cause of death. (Broadbent 2015: 74)

Proponents of the POA argue that observational approaches are inadequate because they cannot enforce a proper intervention, moreover arguing that knowledge delivered by observation is useless. The POA relies on the epistemic assumption that something is a cause only if it corresponds to a well-specified intervention, therefore other approaches and systems of practice in epidemiology that focuses on causal factors that do not correspond to a well specified intervention must be discarded. Broadbent argues that the observational approaches in epidemiology have been crucial to understanding disease, causes and patterns, offering methods of intervention before the conception of the POA. Thus, it is normative pluralists' role to actively challenge this assumption and argue that observational approaches in epidemiology also produce useful knowledge about phenomena. For instance, racial differences are taken to be an important causal factor for some diseases (such as heart diseases). However, Vander-Weele and Robinson (following the assumption that

only causes that correspond to well-specified interventions are relevant) assert that that since race cannot be manipulated, there is no well-defined intervention; therefore, effects of race should not be considered as a cause by the epidemiologist.

On the one hand, the POA can be treated as a new tool for an epidemiologist that focuses on different aspects of disease causes. However, the epistemic assumption that these causes are the only relevant ones leads to a monist argument that the POA is the only approach worth pursuing in epidemiology. Broadbent argues that in these two papers (by Hernán & Taubman and Vander-Weele & Robinson), the POA is presented as a conceptual framework to understand causal concepts in epidemiology. Moreover, Broadbent makes a distinction between the *narrow sense of the POA,* that is the application of mathematical tools in epidemiology to analyse different aspects of phenomena, and *the broad sense of POA,* which he calls a methodological revolution. The narrow sense can be regarded as a new method in epidemiology that asks different questions about phenomena using mathematical tools, producing distinct accounts of alternative approaches in epidemiology. The narrow sense does not have any commitment to the epistemic assumption that the only relevant causes for epidemiologist are those that correspond to well-specified interventions. The broad sense of POA is the commitment to a new concept of causality based on the epistemic assumption that limits what can be considered as a cause in epidemiology (namely the causes that correspond to well-specified interventions). Moreover, Broadbent argues that broad POA can be thought of as a methodological revolution, aiming to replace the existing approaches in epidemiology that are based on observational studies with experimental studies. Broadbent states that:

> Epidemiology in its modern form is a discipline characterized by observational studies, carried out on exposures that are highly prevalent in the population, and which may not themselves be

> manipulable. It is also characterized by stories of detective-like informal reasoning. (Broadbent 2015: 75)

In contrast to observational practices, Broadbent states that:

> the potential outcomes approach strongly favours experimental studies–that is, studies where an intervention is performed. This is not only because of the advantages of randomization, widely discussed among philosophers and others elsewhere. It is also because there is a conviction that if you actually do an intervention, it is necessarily well- specified. (Broadbent 2015: 75)

Thus, the broad sense of the POA leads to epistemic monism, based on the epistemic assumption that 'causal questions are well-defined as long as interventions are well-specified'. The POA motto is not that the mathematical methods that constitute POA are better than others because of their own merits — rather, the POA allows the elucidation of causal questions that epidemiologists aim to answer. The POA, as defined in Hernán and Taubman (2008) and Vander-Weele and Robinson (2014), aims for a certain type of knowledge that is exclusionary of different systems of practices, namely observational studies in epidemiology. The POA takes the aim of epidemiology to be identifying well-specified interventions for diseases; therefore only the POA can produce knowledge that will fulfil this aim. However, observational studies, as argued by Broadbent, produce accounts of phenomena, revealing causal relations and helping the epidemiologist understand disease patterns. Thus, the role of active pluralism in this debate between the proponents of the POA and the traditional observational studies is to promote pluralism by challenging the epistemic assumption that the only relevant causal account of disease aetiology is the one that corresponds to well-specified intervention. Moreover, the role of pluralists is to argue that each approach produces a partiality of accounts and argue for the benefits of having multiple accounts to improve our understanding of disease aetiology.

5.2.2 Gene-Centric Biology

Gene-centric biology is another field in which we can draw a distinction between methodological and epistemic monism. Although I used case studies from gene-centric approaches in chapter 4 (sections 4.2 and 4.4), in this section I want to focus on Waters's (2006) account of gene-centric biology in order to argue that the decision to focus on genes is not due to an epistemic assumption that genes are causally fundamental in biological development. Instead, Waters argues that genes are at the centre of this field because of their utility. That is to say, genes are useful tools in manipulation developmental processes in order to reveal causal relations in development.

Waters's argument involves defending gene-centrism against its critiques, namely the developmental systems theory (DST). I will not go into the details of this debate in order to keep my line of argument clear. The proponents of the DST claim that biological development is multi-factorial and that genes are no more significant as causal factors than others, such as epigenetic factors and environmental factors (see Oyama, Griffiths, and Gray 2001). The DST approach argues for a more holist understanding of biological development in which genes are part of a larger causal picture including epigenetics and environmental input. Thus, critiques of gene-centred biology argue that focusing on genes obscures aspects of biological development that cannot be revealed by gene-centric practices. Although these worries are warranted, Waters argues that closer studies of gene-centric practices reveal that genes are at the centre of some scientific practices not because they are regarded as causally fundamental but due to their pragmatic value. Waters argues that:

> Gene-centrism can be understood as a general scientific approach for investigating and modelling a broad range of biological processes. As such, it includes practical knowledge about various procedures, descriptive knowledge about the makeup and causal regularities of model organisms, and evaluative knowledge assessing the utility of procedures,

> materials, and ideas for further research. The functioning of this knowledge is structured not just by patterns of explanatory reasoning, but also by strategies for investigation. (Waters 2006: 199)

Here Waters underlines that focusing on genes is not justified by an epistemic assumption that genes are more fundamental in understanding biological development in comparison to epigenetic and environmental factors. That is to say, gene-centrism does not rely on the assumption that focusing on genes will lead to a fundamental account that can be used to explain all biological phenomena. Instead, Waters argues that gene-centrism is justified through its pragmatic value in that the set of methods allow further investigation of phenomena. Waters sums up this position in the following statement:

> Understanding gene-centrism as an approach centered on a set of open-ended strategies for investigating a broad range of biological phenomena, rather than as an explanatory enterprise centered on filling out the details of a central theory, makes it possible to entertain the idea that genes are at the center of attention because of their investigative utility, not because of their alleged explanatory power." (Waters 2006: 200

Waters argues that the focus on genes in molecular biology is because genes are regarded as *difference-makers* in the development processes (a term that will become clear in the following example), and thereby useful tools to investigate phenomena. For instance, gene-centric approaches focus on gene expression and protein synthesis, which involves the translation of genetic information into amino acid sequences. This is a complex process and takes place in multiple stages. First, genes (which are short DNA segments) are transcribed into RNA molecules, which get modified into messenger RNAs (mRNAs) and transported to special sites in cells called ribosomes, where they get translated into other amino acid chains. The whole process relies on multiple molecules and processes including transfer RNA, ribosomal RNA and many other enzymes, all causally relevant.

Moreover, gene expression is often a response to external stimuli from the environment (such as the presence of xenobiotics or absence of nutrients). Waters acknowledges that gene expression is a complex process that includes multiple factors that have different causal roles at different stages. Waters also acknowledges that it is wrong to say that genes direct the whole process. Nonetheless, Waters notes that most causal factors involved in DNA expression, except genes, are uniform in a given cell or cell structure at a given time. In simple terms this means that the translators remain the same, but the translated script (the genes) changes, therefore they are regarded as difference-makers in the whole process. Even if there are differences in these causal factors, the changes will be ubiquitous in the cell, i.e., every gene expressed will be affected by the difference in the gene expression mechanism. On the other hand, the difference in a gene will lead to a particular change in the end product i.e. the amino-acid chain.

Waters also argues that genes' capacity to bring about difference in the cellular processes is utilised by molecular biologist in order to manipulate biological processes. For instance, Waters uses the case of systems biologists investigating metabolic pathways by interfering with the related genes. Although the immediate causal agents under study are metabolites, Waters argues that the strategy to learn about metabolic patterns is to manipulate the related genes. In the case of HAT research discussed in the previous chapter (4.2), the genetic approach uses various methods (gene knockout or RNAi for instance) to manipulate genes to investigate whether a given metabolic pathway is essential for parasite survival. The aim is to understand the role of a given macromolecule (coded by a particular gene that is manipulated) in a parasite's metabolic pathways. Therefore, genes are mere tools in order to validate a causal factor, protein or RNA, as a drug target. I argue that gene-centric methods do not rely on the epistemic assumption that genes are the only relevant causal factor in biological development and the genetic approaches described above do not lead to monism (in this case epistemic and metaphysical). Waters sums this up as follows:

> Interpreting gene-centrism as one of a plurality of possible approaches leaves open the possibility that genes are the centre of attention not so much because of their explanatory value, but because of their investigative utility. I will argue that this is indeed the case, that genes provide a unique entry point for investigating and model a broad range of biological processes. (Waters 2006: 201)

Thus, gene-centric approaches in biology should not be thought of as epistemic monism, as long as they are not based on an epistemic assumption that genes are the only causally relevant factors in biological development, and therefore a gene-centred account of development is the only type of account scientists should seek to produce. Waters argues that gene-centric approaches focus on genes for pragmatic reasons, as genes can be manipulated in a way that can produce useful knowledge about developmental processes (and other metabolic activities) in living cells. 'Useful knowledge' is a loaded term that I will discuss in the following section, particularly focusing on pragmatic values.

In this section, I argued that normative pluralists must actively challenge epistemic assumptions that lead to monism (as in the case of the POA). Moreover, I argued that methodological assumptions in which one approach is favoured over another due to its utility lead to methodological monism. However, the argument for methodological monism does not hold that other approaches do not produce accounts of phenomena that are useful for different aims. Methodological monism can be understood as adherence to an approach that is thought to be the best way to accomplish a given aim. For instance, the aim of the WHO is to eliminate HAT by 2030, which can be done by developing new drugs. Therefore, anti-parasitic drug discovery is prioritised over other approaches that can also help eliminate HAT. Chapter 6 discusses the broader context of HAT, and argues that the socio-economic and political context leads to prioritisation of drug

discovery over other methods (such as environmental control or more holist epidemiological control) based on pragmatic values.

In summary, in this section I argued that the role of normative pluralists to identify monist assumptions. Moreover, I argued that monist assumptions are more nuanced and can be divided into different categories. It is necessary for active normative pluralists to challenge and replace assumptions that favour one set of approaches and accounts, thus limiting the potential of scientific inquiry to explain and explore different aspects of phenomena.

5.4 Monism v. Pluralism

The pluralism pursued in this thesis is a rejection of a monist ideal that can be realised in three different arguments: metaphysical, epistemic and methodological. In this chapter I mainly focus on epistemic and methodological assumptions, given the pluralist thesis I develop here mainly focuses on scientific practices and the accounts they produce to explain and explore the natural world.

Herein, I argued that the epistemic assumptions of monism are that the ultimate aim of scientific practices is to provide a single, complete and coherent account of the world in the sense that we can derive all knowledge from this account. Although this might be an exaggerated view, epistemic monism still influences historical accounts of science (triumphalism) and the way philosophers make sense of the multiplicity of accounts and practices in science (naïve reductionism discussed in chapter 4). Epistemic monism is a ‘conceptual hangover’ from the received view of science I discussed in chapter 2.

Rejecting epistemic monism strengthens the philosophy of science in practice approach, given that the first step in PSP is to understand the different aims of scientific practices. An important assumption that epistemic pluralism makes is that the multiplicity of aims and practices are ineliminable. This assumption is driven by direct engagement with scientific practices and not from a rational reconstruction of science.

In addition to epistemic assumptions, I identified methodological assumptions. The methodological monism can be thought of as adhering to a particular approach or system of practice based on the assumption that a given method or set of methods (genetic approaches in developmental biology for instance) is the best way to explain and explore phenomena. Herein, I asserted that an argument for methodological monism requires further justification.

Providing this analysis of the monist argument is to further the discourse on active pluralism. Understanding different arguments in detail allows me to make the point that active pluralists must challenge the epistemic assumptions and values that lead to monism in the sense that one system of practice that dominates a field of inquiry is to the detriment of other systems. Moreover, pluralists must emphasise the partiality of scientific knowledge. This is particularly important in debates in which different systems are compared and contested on the assumption that one is right. Pluralists' role in such cases is to highlight the merits of each system with regard to their distinct aim. The pluralist must act if a given approach is dominating the field based on aforementioned monist assumptions, especially if this is resulting in the termination of alternative systems.

Chang's work on the history of phlogiston shows how oxygen theory was favoured over phlogiston based on the assumption that it captured reality better The monist assumption leads to the killing of a system that was successful in its own terms. Moreover, Chang argues that phlogistonists were successful in engaging with certain aspects of the phenomena, demonstrated in his book *Is Water H_2O?* (discussed in section 4.1.2, pages 107 and 108). The task of the active pluralist is to challenge the most dominant assumptions and values. However, the only boundary to pluralism is not the assumptions I associated with the monist ideal. Herein, I argue that there are pragmatic values that arise from the context of inquiry that provides justification in prioritising certain systems over others. I presented the case of HAT where anti-parasitic drug discovery research as a system of practice is prioritised

over systems of practices such as environmental research or epidemiological research in achieving the goals set by the WHO.

I will further discuss pragmatic values in the following chapter, however it is necessary to make the distinction between the methodological assumptions I defined here and pragmatic values I will discuss in the following section. Although both methodological assumptions and pragmatic values lead to limitation of plurality of approaches in a given field. Methodological assumptions stipulate best way to explain and explore an aspect of phenomena (such as the use of gene-centred methods to study biological development). Pragmatic values define the best way a particular aim can be achieved taking the broader context. In the following chapter I will argue how the pragmatic aims limit the extent of plurality of approaches to eliminate HAT, where eliminating HAT by 2030 requires new drugs that match patients' needs.

The difference between Chang's argument and mine stems from the differences in our case studies. The HAT case study I am looking at is contemporaneous with an aim that has a strict timeframe. Chang, on the other hand, looks at history of chemistry over several centuries. Differences in the timeframes and the type of benefits we expect from plurality leads to two different conclusions. While Chang argues that pluralism must be promoted at all costs with regards epistemic values, I argue that there are cases in which the context of inquiry prompts plausible pragmatic boundaries.[36] These pragmatic boundaries and values are up for debate and philosophical scrutiny and the

[36] Chang's discussion does not directly consider the role of ethical values; however, he acknowledges that different values jostle with each other. Chang's project is mainly focused on epistemic values (and to an extent methodological values). Chang only acknowledges ethical values when he remarks that it is impossible to step away from ethical considerations in his own work (Chang 2012: 27). Chang does not give ethical values place in his overall argument. My analysis goes beyond Chang's, to include ethical values under pragmatic values, which I will get to discuss in detail in the following chapter.

responsibility to do this lies with pluralists. In the following chapter I focus on the broader context of the HAT case, demonstrating how these pragmatic values are constructed. Moreover, I argue that values have a fundamental role in science, particularly in shaping the aims of inquiry and setting the priorities and the direction of research. I borrow from the contemporary pragmatism debate to further develop the concept of pragmatic values identified in this chapter.

In this chapter, following Chang's active normative pluralism, I argued that the role of normative pluralists is to challenge assumptions that lead to monism. I separated monist assumptions into metaphysical, epistemic and metaphysical, focusing on the epistemic and methodological. I argued that normative pluralism promotes a multiplicity of accounts and approaches in scientific practices, allowing scientists to explain and explore different aspects of phenomena. Following Chang's call for active, normative pluralism, I argued that it is the role of normative pluralism to challenge any assumption that limits such plurality. In section 5.2.1 I suggested that an approach like the POA is based on an epistemic assumption that the only causally relevant factors in epidemiology are those that correspond to well-defined interventions. I argued that the proponents of the POA assert that observational studies in epidemiology produce inadequate accounts, given that the aim of epidemiology is to come up such interventions. That is, the proponents of the POA approach explored here are committed to the assumption that the aim of epidemiology is to come up with well specified interventions which only the POA can produce. Thus, it is the normative pluralists' role to challenge these assumptions to show that there are multiple aims in epidemiology and each approach in epidemiology produces partial accounts of phenomena (experimental or observational). In section 5.2.2, I shifted my focus to gene-centric approaches to understand biological development. I argued that gene-centric approaches are based on the assumption that genes can be utilised to manipulate developmental processes in cells. That is to say, in understanding biological development at a cellular level, genes are useful, given that they can

be manipulated in ways (gene knockout, RNAi etc.) that allow scientists to find out more about phenomena. It is important to note that the gene-centred approach in my discussion only relies on methodological assumptions and not epistemic assumptions; therefore, I argue that gene-centric approaches in biology are not problematic from a normative pluralist point of view, as long as they do not limit other approaches seeking to explain different aspects of biological development.

Chapter 6

6.1 Aims and Values in Scientific Practices

In the previous chapter, I argued that scientific practices ought to be pluralistic in order to explore and explain different aspects of phenomena. Moreover, I asserted that the role of normative pluralists is to challenge any monist assumption that lead to unnecessary limitation of plurality of approaches and accounts in scientific practices (following Chang's call to action). While I argue that the role of normative pluralist is to challenge monist assumptions, I also identify pragmatic values in scientific practices which pose boundaries to the extent of plurality. In this chapter I will return to Human African Trypanosomiasis. Here, I wish to argue that while current efforts to eliminate HAT involve a plurality of approaches working together, there is a limit to the extent of plurality. I will argue that the limits to plurality in this case are not due to epistemic assumptions, but pragmatic values. In the first half of this chapter I will provide a detailed discussion of current HAT research, focusing on the aims set out by the World Health Organisation. I will argue that the WHO's aims are shaped by the biomedical knowledge of HAT and the socio-economic and political context of the disease. Moreover, I will argue that while the aim (in this case elimination of HAT) promotes a plurality of approaches employed (particularly in anti-parasitic drug discovery process, as discussed in section 4.2), it also sets a boundary to which approaches will be employed in a given timeframe. In section 6.1.1 I will argue that scientific and medical practices working towards eliminating HAT involve multiple approaches (genetic engineering and organic chemistry to validate drugs, medicinal chemistry to develop drug candidates, structural biology to determine drug-target interaction etc.) with particular aims (target validation, synthesis and development of drug candidates, determining pharmacodynamics properties etc.). However, these multiple approaches are governed by the overarching aim of eliminating HAT by 2030. I will further argue that the aim limits

the extent of plurality by favouring certain approaches over others. In particular approaches involved in anti-parasitic drug discovery and development process are prioritised over approaches involving environmental control and vector control (two approaches proven effective by colonial administrations, discussed in 3.1). I will argue that limits to plurality are posed by pragmatic values, which define the best way to achieve elimination. In 6.1.2, and 6.1.3, I will further discuss the origins of the pragmatic values that determine how elimination can be achieved in the way specified by WHO. My aim in the first part of this chapter is to flesh out the justificatory narrative put forward by WHO to prioritise active screening campaigns over other methods (such as vector control and environmental approaches), thus prioritising approaches linked to anti-parasitic drug discovery.

In section 6.2, I will shift my focus to the philosophical debate on values in science, aiming to further articulate the role of pragmatic values in scientific practices. I will provide an overview of arguments that a broad range of values (not just so-called epistemic values) play an important role in scientific practices. In section 6.2.1 I will provide an overview of Longino (1990 & 1996) and Douglas (2000 & 2009), who both argue that epistemic and non-epistemic values are used by scientists. This is in line with my argument that the values from the socio-economic and political context of HAT guide the scientific practices involved in its elimination. Longino argues that scientists require values to bridge the gap between theory and evidence, where Douglas argues scientists require values to assess the inductive risk linked to decisions they make. Both Longino and Douglas argues (broadly) that scientists use values to make sense of evidence in hand. In section 6.2.2 I wish to argue further that values play an integral role in scientific practices, following Brown's (2013) argument against the lexical priority of evidence, arguing that values in science only play an indirect role in scientific practices (assessing evidence for example). Instead, I will argue that, instead of regarding values as an afterthought, we must understand the relationship between values and evidence in a pragmatic framework. My main aim in the second part of

this chapter is to define and further articulate the pragmatic values. Here I will argue that pragmatic values are specific to the broader context of scientific practices, moreover I will argue that they allow determine the aims of inquiry and they shape and guide scientific practices. I will develop the concept of pragmatic aims following Brown's (2012) account of Dewey's logic of science, who provides an account of scientific inquiry focusing on the links between scientific practices and their broader context.

6.1.1 Elimination of HAT

In section 3.2, I built an account of current efforts to control and eliminate HAT. These efforts are organised by the WHO and supported by organisational bodies such as Médecins Sans Frontières (MSF), the United Nations Development Programme (UNDP), and the World Bank (WB). The current efforts led by WHO are a partnership with a diverse group of stake holders with their own set of aims and values guiding their operations. However, in the efforts lead by the WHO, partners share overarching values and the broad aim. These values are the result of the difficulties in implementing the existing control methods in the disease endemic regions. There are existing control methods that have proven effective in some disease-endemic regions, but ineffective in others. One key problem for implementing these control measures is the inadequacy of the diagnostic tools and drugs. As described above, diagnostic tools for the second stage of this disease are invasive and painful, and the drugs available for treatment have high toxicity and a long treatment period (section 3.1).

To address the need for new drugs in HAT treatment, the Drugs for Neglected Disease working group was established in 1999 by MSF to build strategies for developing new medicines that match the needs of the target populations (section 3.3). This working group led to the establishment of the Drugs for Neglected Disease Initiative (DNDi) in 2003. DNDi was established through the contributions of five public institutions (Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the

Ministry of Health of Malaysia and the Pasteur Institute), with MSF and WHO, UNDP and the World Bank acting as permanent observers.

WHO's aim is to eliminate HAT in two stages. The first stage is:

> detection of less than 1 new case per 10 000 inhabitants in at least 90% of endemic foci reporting less than 2000 new cases annually at continental level by 2020. (WHO 2012b: 11)

Followed by the second and final stage of elimination:

> reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, as a result of deliberate efforts; continued actions to prevent re-establishment of transmission may be required. (WHO 2012b: 12)

The main strategy to achieve elimination is active screening campaigns. These campaigns involve screening populations in disease-endemic areas, and providing treatment to those who test positive. However, there are major barriers to patient participation to these campaigns. Anthropological studies (discussed in 6.1.2) have shown that drug toxicity and cost are the two main barriers to implementing current control methods in disease-endemic areas, highlighting the need for new medicines. Therefore, the focus of the scientific practices involved in the efforts to eliminate HAT has been anti-parasitic drug discovery. Herein I argue that the context of this disease and the aims set out by the WHO and DNDi provide a way of understanding why some scientific practices are prioritised over others. Moreover, efforts to develop new drugs are guided by target product profiles, defining the desired properties of new medicines. I argue that the TPP determines the constitution of scientific practices involved in the drug discovery and development process, where multiple approaches (such as genetic and chemical approaches) are used to study different aspects of parasite metabolism in answering questions determined by the TPP (e.g. whether a drug candidate can treat both forms of *T. brucei,* or can be formulated to an orally bioavailable drug).

In section 4.2, I demonstrated the multiplicity of approaches in anti-parasitic drug discovery, arguing for the benefits of plurality in this field. While a plurality of approaches is favoured in anti-parasitic drug discovery and development, anti-parasitic drug discovery is prioritised in research and development in current efforts to eliminate HAT, to overcome the limitations of the screening programmes. In summary, the timeframe, specific needs and restricted resources make it necessary to promote a set of approaches (anti-parasitic drug discovery) over others (such as environmental control or vector control).[37] This R&D landscape with a limited plurality of approaches is a result of pragmatic values (as opposed to epistemic assumptions). The focus on the set of approaches under anti-parasitic drug discovery is not due to the assumption that they will provide an account of phenomena that fulfils the monist criteria (as discussed above). Instead, the pragmatic values lead to prioritisation of the anti-parasitic drug discovery to fulfil the aims of WHO within the given timeframe and the socio-economic context of HAT. In the absence of these pragmatic values, there is no justification of prioritising anti parasitic drug discovery over other approaches, given that approaches such as environmental control and vector control were effective in the past (section 3.1).

For instance, there is a body of historical evidence to argue that elimination can be achieved using environmental control. Historical data (number of new cases of HAT versus population screened) presented in WHO (2000) (see figure 3) shows that partial elimination was achieved through control measures, using current diagnostics, drugs and environmental methods (discussed in 3.1). Although control and elimination are hypothetically possible using current methods, they

[37] It is important to underline that I am focusing on the R&D priorities that shape scientific practices. These practices are different from day-to-day medical practices in disease-endemic areas, where the aim and priority is to screen people and provide treatment. The focus here is the R&D priorities leading to the promotion of certain approaches over others.

are not sustainable for various reasons in practice in the given time frame. The first reason is the aforementioned barriers for patient participation caused by current diagnostics and drugs. The second reason is the cost of current measures, since the current support to fight HAT (and other NTDs) is not long term and bound to stop at some point . The third reason is the difficulty of building infrastructure and sustaining active control methods due to political instability in disease-endemic regions. Moreover, a lack of infrastructure makes it difficult to preserve and administer current drugs. Therefore, the reason for prioritising anti parasitic drug discovery and development is primarily pragmatic values as opposed to primarily epistemic values, i.e. the boundaries of plurality are set by pragmatic values (although it is necessary to underline that the two sets of values are related, see section 6.2).

In chapter 5, I put forward a normative argument for pluralism, asserting that scientific practices are ought to be pluralistic in order to explain and explore different aspects of phenomena. Moreover, I argued that the role of pluralists is to challenge any assumptions that lead to monism. However, in this case, I argue that the limits to pluralism are rooted in pragmatic values that derive from the socio-economic and political context of HAT. It must be noted that pragmatic values here lead to a focus on the biomedical causes of HAT. Yet note too that it is possible to conceptualise the causes of HAT epidemic as environmental (changes in the physical environment or increased overlap between tsetse and human habitats) or socio-political (as a result of colonisation and consequent changes in social, economic and political structures). Here I argue that in addition to challenging assumptions that lead to monism, it is also the normative pluralists' task to scrutinise pragmatic values that limit plurality. In the rest of this section I will argue the need for prioritising one approach over others by looking at the broader context of scientific practices.

As discussed in sections 3.2 and 3.3, there is a need to develop new tools to achieve sustainable elimination by 2030. Here, I argue that

there is a need to develop new tools in order to achieve elimination in the given time period with limited resources, and that plurality in scientific practices is limited by pragmatic values. In the rest of this chapter I will focus on arguments for the need to develop new drugs. Simarro et al. (2015) argue that there are two main challenges in protecting the population in disease-endemic areas.

> Concerning the population at risk, the challenge for the future is twofold. First, to prevent the 43.4 million people presently living in low and very low risk areas from sliding back into a situation of higher risk through effective surveillance and response. Second, to set up appropriate and sustainable control strategies to reduce transmission in the areas where 13 millions of people are still living at moderate to very high risk of infection. If met, these targets will enable to reach the 2020 goal of eliminating g-HAT as a public health problem. (Simarro et al. 2015: 11)

Moreover, Simarro et al. (2015) list several obstacles: (1) possible donor fatigue; (2) competing health priorities in disease-endemic areas; and (3) social unrest and gaps in the coverage of the population at risk. In addition, Simarro et al. assert that that current control methods have difficulties in integrating the control programmes with national healthcare systems and mustering resources to fund necessary research.

Rock et al. (2017) make a similar argument using a mathematical model to predict the success of current control methods in achieving WHO goals. Rock et al. report an estimate of new infections using reported case data and active screening levels in order to predict transmission rates. Rock et al. assert that it is necessary to focus on the transmission rate instead as the number of cases reported is not reliable due to underreporting (see 3.1.5). As discussed in chapter 3, it is difficult to estimate the real disease burden based on the new cases reported due to underreporting. Therefore, there is a need for other indicators such as the transmission rate in order to assess the progress towards elimination. Based on the rate of transmission

extrapolated from the mathematical model, Rock et al. conclude that it is not possible to achieve this within the timeframe set by the WHO:

> It is very unlikely that the 2030 full elimination target will be met by continuing with strategies which screen only low-risk members of the population and with no vector control. The predicted elimination year is 2236 for mean screening, and 2121 for maximum screening. This demonstrates how the current strategy is unlikely to impact HAT transmission sufficiently to reach full elimination by 2030. (Rock et al. 2017: 8)

Hasker et al. focused on the shortcomings of the current control methods in DRC (see section 3.2). The current control programme Programme National de Lutte contre la Trypanosomiase Humaine Africaine (PNLTHA) in Democratic Republic of Congo relies on active screening funded through bilateral funding from Belgium. Hasker et al. (2011) argue that with the prospect of this funding being phased out and no other prospective funding, the screening and monitoring activities will be gradually reduced. Given that 89% of the new cases reported in 2013 were in the DRC, it is important to maintain active screening campaigns in this region to achieve elimination. Active screening is particularly important in this context given that average annual attendance to the healthcare services is less than 0.15 visits per inhabitant. However, whether active screening campaigns are running or not, the population in disease endemic areas must be persuaded to participate in these campaigns.

Hasker et al., Rock et al. and Simarro et al. here all focus on the shortcomings of the tools currently available for use in the active screening campaigns. The three papers discussed here all argue that the current methods are not sustainable in long term to achieve elimination (in the way defined by WHO). The main point here is that there is a need for new tools, particularly new therapeutic tools that can be deployed by the active screening teams to treat patients effectively in the disease endemic area. Due to the lack of infrastructure and the lack of long term funding for these campaigns, and more importantly

due to high toxicity of current drugs, makes the development of new drugs a priority in the effort to eliminate HAT.

So far, I only discussed the shortcomings of the diagnostic and therapeutic tools from a medical and an economic perspective. In the following section I wish to shirt my focus to social factors, particularly patient's perspectives, that render current tools deficient to use. In chapter 3 I considered health-seeking behaviour of patients living in disease-endemic regions, toxicity, the cost of HAT treatment and intrusive diagnostic tools as factors that negatively influence patient participation in the screening campaigns. In the following section I aim to discuss social taboos and barriers to patient participation, underlining how contextual values are taken into consideration in determining the properties of the new drugs. I aim to show how the social and economic values in particular play a part in shaping the Target Product Profile, therefore playing an important role in scientific practices.

6.1.2 Social Taboos and Barriers

Understanding the patients' perspective and the patients' perception of the screening campaigns is necessary to encourage effective participation of communities living in the disease endemic regions. In this section I focus on social taboos and barriers to community participation in HAT control. Robays et al. (2007) and Mpanya et al. (2015) argue that social taboos and barriers negatively affect patient participation in active screening campaigns and following treatment. In section 6.1.1 (and in chapter 3) I argued that lack of participation is due to inadequate diagnostic tools and costly and toxic treatments, thus creating a need for the development of new diagnostic and therapeutic tools to eliminate HAT. Given lack of patient participation (and problems due to lack infrastructure and political will), the current control methods are not sufficient to eliminate HAT by 2030. In this section I focus on anthropological works, suggesting how the current tools used by the mobile screening teams to diagnose and treat HAT patients generate social barriers, preventing patient participation directly or

indirectly in the form of social taboos linked to the disease and how it is treated. My broader argument here is that the WHO's aim to eliminate HAT by 2030 requires new tools, and therefore leads to the prioritization of some sets of practices over others. Moreover, I argue that, in order to have a better understanding of scientific practices and their aims it is necessary to look at the social context in which these aims are constructed. The social barriers and taboos described contributed to how the WHO and other scientists understand and address HAT.

Mpanya et al. (2015) identify 'taboos' as a mixture of local beliefs and medical advice, referring to a set of rules to follow during HAT treatment. In other words, taboos are amixture of medical recommendations and local customs. The taboos identified by Mpanya et al. are specific to two provinces of DRC; however, similar issues are observed in related social contexts (Kovacic et al. 2016, Simarro et al. 1999). Some of the taboos identified by Mpanya et al. have a long and complex history:

> most were originally intended to reduce the incidence of adverse drug effects caused by melarsoprol, without any firm evidence base. The prohibitions originating from the health care providers were amplified at community level and merged with traditional nosological interpretations of a symbolic nature. (Mpanya et al. 2015: 9-10)

It is important to note that community perceptions and taboos vary geographically due to cultural heterogeneity in the disease-endemic regions and the epidemiological history (see Chappuis et al. 2004, Kovacic et al. 2016) These taboos and restrictions to lifestyle deter people from participating in the screening campaigns. Mpanya et al. describe a list of taboos identified in the two regions of DRC, which include avoiding sun during the treatment period, avoiding spicy food, abstaining from sexual intercourse and an additional rest six-month rest period after treatment ends. These taboos have considerable social effects, abstinence from sex being the most reported problem

with serious consequences for families. Moreover, the six-month rest period has severe economic consequences for the individual and the family as the resting patient (who may be the main breadwinner) is reliant on their family for resources and care.

A similar study conducted in Western Uganda by Kovacic et al. (2016) questions how memories of HAT control and treatment measures are preserved in communities in disease-endemic areas. Kovacic et al.'s objective was to understand how memories of past experiences and potential trauma influence current generations' participation in the current control measures. They state their aims as follows:

> By examining elders' memories in this study we aimed to explore what memories have been preserved in relation to colonial HAT control measures and more recent interventions implemented by MSF. (Kovacic et al. 2016: 3)

Kovacic et al. argue that the memories of elders are well-preserved in these communities, and inform current attitudes towards screening campaigns and treatment. They argue that:

> The study is especially relevant in the context of new diagnostic tools and treatment of HAT, which are expected to be introduced in the next couple of years. Understanding of the community experiences of previous programs may greatly impact on how these new tools are accepted and utilized. (Kovacic et al. 2016: 3)

Kovacic et al. argue that elders recall diagnostic procedures, treatment duration and side effects from the early 1990s. Kovacic et al. argue that preservation of these memories has a negative effect on participation, particularly in communities that currently live in the low-risk areas. Kovacic et al. also report that recent advancements in treatment, like the use of NECT, received a very positive response. Kovacic et al.'s work highlight the importance of taking participants' perceptions of treatment into consideration when developing new treatments and measures. In other words it is necessary to consider

the broader context of a given disease while determining the aims of scientific practices. Kovacic et al. summarise this as follows:

> The beneficiary community should be the first stakeholder to be informed about the changes occurring in global HAT control strategies, hence transparent communication and frequent dialogue is necessary not only for keeping all the information updated, but also to prevent future negative experience with disease control programs. As shown in our study, negative experiences will remain a part of the collective memory for a long time. (Kovacic et a. 2016: 14)

In order to assure the success of the active control campaigns it is necessary to address the barriers to patient participation. Robays et al. Mpanya et al. and Kovacic et al. all argue that patients experience with the diagnostic and therapeutic tools can have negative consequences in community participation for a long time. Moreover, the social and economic strains on communities as a result of resting period (and period in which sexual activity is forbidden) required during and after the treatment negatively effect the rate of community participation in the control programmes. In order to achieve the elimination aim set by WHO (see section 6.1.1) it is necessary to make sure the factors leading to the barriers to the community participation in control programmes are eliminated by developing new tools such as drugs with tolerable toxicity and shorter treatment periods. Studies such as Robays et al. Mpanya et al. and Kovacic et al. allow highlight the patients' needs from new drugs developed to be used in the control programmes in order to eliminate HAT.

In the following section I will argue that patients' needs should be translated into Target Product Profile (TPPs) by DNDi in order to develop drugs that will help eliminate HAT by 2030. In the following section I wish to revisit TPPs, to show that the social taboos and barriers identified in the disease-endemic region are taken into consideration in determining the TPP. The purpose is to show how the

broad socioeconomic and political context (including idiosyncratic community responses) are formulated into scientific guidelines.

6.1.3 Target Product Profile

The TPP is a tool which considers the broader socio-economic and political context of a disease and what is already known biologically and medically about the disease in order to specify the properties of the desired drug. In this section I will focus on the role of TPP's linking the broader context of HAT (discussed above in 6.1.1 and 6.1.2) and the scientific practices aiming to develop anti-parasitic drugs.

As stated above the anti-parasitic discover and development projects for HAT are facilitated by DNDi (see section 2.2.4). DNDi claim to have patients' needs as a fundamental part of their daily practice and overall organisation. That is, research and development process is guided by TPP, developed by experts from disease-endemic countries, researchers, clinicians, disease control programme managers, and patient representatives (DNDi, 2014). An example of a generic patient-orientated TPP is given in table 2: answers to the questions listed constitute the TPP.

- Indications: Which disease(s)?
- Population: Which type of patients and where?
- Clinical Efficacy: Does it treat the infection effectively?
- Safety and Tolerability: What is the level of acceptability for adverse events?
- Stability: How long is the shelf-life of the drug(s) and what are the storage conditions?
- Route of Administration: What is an acceptable way to administer the treatment?
- Dosing Frequency and Treatment Duration: How often and how long must it be given?
- Cost: Will it be affordable to the target population or health system?

Table 2. adapted from DNDi (2014). TPPs are updated in the light of new evidence and findings to keep up-to-date with the needs of patients.

In order to assess whether patients' needs are addressed by the scientific inquiry it is necessary to look at the role of TPP in scientific practices. The role of TPP can be best understood as a tool for guiding and informing scientific practices. Wyatt et al. (2011) assert that TPPs are used for linking the chemical properties to the patients' needs, describing a TPP as a strategic planning tool. For example, the clinical efficacy, stability and route of administration of a drug is linked to the atomic composition and the size of the molecule; therefore smaller molecules with chemical composition that allows them to be absorbed into the blood stream through ingestion, pass the blood brain barrier and have a stable formulation (as a pill or suspension that can be administered orally without specialised equipment) are selected as drug candidates when possible.[38] TPP's define the desired efficacy, route of administration, provisions available to store drugs and so forth, thus prescribing which chemical entities that can be developed into drug candidates (that have the desired properties listed in the TPP). Wyatt et al. use the following TPP for HAT in table 3. Wyatt et al. assert that TPP's are used to assess project feasibility, monitor progress and guide drug discovery and development. Moreover, TPP's are used as a communication tool between different actors, among scientist themselves and among scientists and medical professionals, policy makers etc. TPP can be considered as the set of values that guide the anti-parasitic drug discovery and development process, serving as a decision-making tool in the drug discovery pipeline (discussed in section 2.2.2.1) (This includes selecting drug targets [section 4.2], and informing the drug optimisation processes, designing *in vitro* studies in animals and clinical trials [both cases discussed sections 2.2.2 and 3.3.1]).

[38] See Lipinski et al. (2001) for more details how the pharmacological properties of a

- Active against T.b. gambiense and T.b. rhodesiense
- Active against Melarsoprol refractory strains
- Efficacy against early and late-stage disease desirable
- Formulation (oral against early stage desirable; parenteral against late stage acceptable)
- Curative in 14 days (late stage) or less (early stage)
- Cost less than current treatment for early stage disease ($100-140)
- Safe in pregnancy
- Stable under tropical conditions

Table 3. adapted from Wyatt et.al. (2011) listing TPP used for HAT

In short, TPPs describe a drug with the right attributes that matches patients' needs. It is a set of values that allow scientists to make decisions in the drug discovery process.[39] Wyatt et al. state that:

> Clearly defining a TPP and using it to define criteria for progression from one phase of the drug discovery process to another helps to deliver benefits from better decision making, faster development times and higher approval success rates to bring a drug to market. Most importantly this approach helps to define targets and compound series which will never achieve the TPP and therefore never benefit patients, facilitating the rapid closure of such projects and allowing the realignment of valuable resource into potentially more productive areas. (Wyatt et al. 2011: 1276)

The importance of TPPs becomes even clearer when we consider the broader context of NTD research. As described in section 2.2.2, HAT has received limited interest from profit-driven pharmaceutical research, and current resources put into public-private partnerships are limited and lack longevity. Approximately 0.1% of global research budgets are spent on NTD drug research (Wyatt et al. 2011: 1275). The failure rate of drug discovery and projects is significant: 1 in 50 projects successfully yield an approved drug that can be used in humans. The reasons for such a high rate of failure are many, but one reason is due to selecting poorly-validated targets and sets of compounds (HITS) that interact with the target. Using TPP from the beginning of the process, scientists determine specific criteria to examine the prospect of success at different stages of the drug discovery and development processes to deliver the desired product. Wyatt et al. focus on six criteria they use to link the chemical properties

[39] The benefits of TPP described by Wyatt et al. is a heuristic tool used with the *hope* to lower the attrition rates in the drug discovery pipeline while delivering a drug that matches patients' needs. Whether the use of TPP's lower the attrition rate requires further assessment.

of a potential drug target to a TPP: *(1) large validation; (2) druggability; (3) assay feasibility; (4) toxicity; (5) resistance potential; and (6) structural information.* Scientists, as described by Wyatt et al., use these six criteria to identify strengths and weaknesses of different targets and assess the performance of project at different stages. A TPP is a heuristic tool for decision-making, aimed at keeping attrition rates low while making sure that the patients' needs are met. Moreover, a TPP is a communication tool between different actors involved in the process: scientists involved in drug discovery and development, healthcare providers, policy-makers etc. Wyatt et al. emphasise the importance of TPPs as follows:

> in this still under resourced area of drug discovery, there needs to great clarity around the aims and goals of the mission and clear decision making associated with each project. To this end Therapeutic Product Profiles are coming to the fore, allowing the unmet medical need and the properties required of the clinical drug and its usage to be clearly defined. Using this information, the criteria for transition from each stage of the drug discovery process can be clearly defined, even back to making assessments on whether a target could eventually deliver candidates which could satisfy the TPP. (Wyatt et al. 2011: 1282)

In previous chapters I argued that in order to understand the aims of a particular field in scientific practice, it is necessary to understand the context of inquiry. Looking at the broader context of HAT, it is clear that the scientific practices involved in this field are informed and guided by patients' needs. As argued above (section 4.2), a TPP promotes the plurality of approaches employed to study a given phenomenon within set boundaries. To understand these boundaries it is necessary to look at the broader context. Eliminating HAT by 2030 requires development of new therapeutic and diagnostic tools, which are in turn required to meet the specifications listed in TPP in order to meet patients' needs.

At this point it is necessary to refer back to Chang's active normative epistemic pluralism and Chang's statement that the normative argument for pluralism must start with identifying aims and values in science. Chang continues to say that, given the aims of science, pluralism is always beneficial. Herein, I argued that any assessment of whether pluralities are beneficial must understand aims and values in their broader context. While the aim of eliminating HAT promotes plurality of approaches in anti-parasitic drug discovery, it also leads to the exclusion of some other approaches (environmental, epidemiological etc.). In summary, the boundaries of the plurality of approaches employed to eliminate HAT are determined by its context.

In the next section I shift my focus to values in science literature. So far, I have argued that aims and values promote or limit plurality in scientific practices. In the following part I link my argument with the broader discussion of values in science by providing a critical appraisal of this literature, arguing there it is a need to go beyond the argument against the notion that the science is value-free to argue that values are essential in scientific practice.

6.2 Values

Section 2.1.1 presented Hacking's analysis of the traditional view in philosophy of science, in which there is a sharp distinction between context of justification and context of discovery. The context of discovery is thought to include intuitive and irrational processes that help in the generation of new theories, methods etc. The context of justification, on the other hand, includes the verification and testing of new theories using logical reasoning. According to this distinction, values have no role to play in rational processes, and are therefore irrelevant for philosophy of science given that philosophers of science are only concerned with rational processes. Another way of putting this is philosophy of science is concerned with the internal processes of science, which are purely rational, free from any external influences.

In section 2.2.1 I challenged the distinction between context of discovery and context of justification, arguing that values are relevant to internal scientific processes therefore philosophers of science must take values into consideration. For instance, Kuhn (1977) identifies a set of epistemic values (including accuracy, simplicity etc.) arguing that these values are used by scientists in accepting new theories. However, while Kuhn recognised that epistemic values were used in internal scientific processes (such as evaluating theories in light of evidence), epistemic values were meant to be particular. That is, only epistemic values were thought to be important for scientific practices, while non-epistemic values were thought irrelevant to the internal processes of science; moreover, non-epistemic values are thought to be eliminated from internal scientific processes.

Here I will look at two accounts that challenge the idea that non-epistemic values ought to be eliminated from internal processes of science. Both Longino and Douglas argue that non-epistemic values play important roles in what are considered the internal processes of science. In the previous section I argued that values from the socio-economic and political context of HAT play an important part in scientific practices involved in its elimination. Longino (1990) argues that values in science are used to address the underdetermination problem i.e. how we can bridge different evidence and theories (or hypothesis). Douglas (2000 & 2009) points to a different use of values in science, in which they are used to assess the inductive risk related to scientific practice and its products. The values literature is rich and has a long history, but for the purposes for my argument I will focus on these two main themes with reference to other topics in the field when relevant.

Both Longino and Douglas provide strong arguments for the relevance of non-epistemic values in science. After I describe the arguments put forward by Longino and Douglas I will move on to discuss Matt J. Brown's (2013) criticism of the values debate. Brown argues that the values debate has focused on rejecting the value free ideal. Both

Longino and Douglas argue that values play an important but an indirect role in assessing and evaluating different forms of evidence. While this should not be taken as an argument for values having lesser role in scientific practices, these accounts do not provide a framework to understand how value judgements are employed in scientific practices at all stages. In particular, understanding the integral role values play in scientific practices: in defining aims of inquiry and defining the ways in which these aims can be best achieved with respect to broader context. Brown (2013) argues that it is necessary to move beyond to build a pragmatic framework in which we can treat values as an integral part of scientific practices and discourse (including policy and wider discussions). This is important, given that my argument emphasises the role of context in shaping and guiding scientific practices. Brown proposes a pragmatic framework to study the role of values in scientific practices, using John Dewey's logic of science to show how values interact with evidence and theories. Dewey's logic of science provides a detailed inquiry that is situated in a particular context. Dewey also articulates the roles of values, facts and ideas in an inquiry. According to Brown, Dewey's account provides 'a middle path between atomism and holism, and it replaces universalism with a form of contextualism' (Brown 2012: 268).

The pragmatic framework I present here supports my argument for the limits of pluralism. Here I wish to argue that pragmatic values play an important role in defining the aims of scientific practices; moreover, they help determine which accounts to employ. In the following section I will provide a detailed overview of arguments that both epistemic and non-epistemic values play an important role in scientific practices by Longino and Douglas. Using the two arguments put forward by Longino and Douglas, I will argue that the distinction between epistemic and non-epistemic values is futile; that epistemic values are not more important than other values; and that the terms 'epistemic' and 'non-epistemic' are only analysts' categories. That is to say, although I reject the epistemic and non-epistemic distinction posed by the value free ideal, I do not argue that we cannot differentiate between distinct types

of values in scientific inquiry and the different roles they play. Here I argue that a broad range of values (epistemic, pragmatic, ethical, aesthetic etc.) play part in science. I will later argue that all values that play part in scientific inquiry must be understood in a pragmatic framework; a framework I develop using Brown (2012 & 2013)

6.2.1 Two arguments for non-epistemic values

Underdetermination

Longino's contextual empiricism holds that empirical data gathered through observation and experimentation forms the ground from which to assess scientific theories. Moreover, Longino states that given that data underdetermines theory, the bridge between data and theory can never be merely formal. Thus, Longino argues that the evidential relevance of data to theories, models and hypotheses relies on values and background assumptions.

Based on their role in forming these evidential bridges between data and theory, values cannot be eliminated from science. Part of Longino's project is to look at how values and assumptions are used in science and what controls and prevents background assumptions from rendering scientific theories entirely subjective. Longino (1990, 1996) argues that what prevents theories from being entirely subjective is critical interaction among scientists. Longino coins the term intersubjective interaction, describing critical assessment of evidence, theories, values and assumptions at community level in recognised fora. For this to happen, there must be public standards. Longino describes this process:

> There must be publicly recognized standards by reference to which theories, hypotheses and observational practices are evaluated and by appeal to which criticism is made relevant to the goals of the inquiring community. Such standards serve as ideals regulating normative discourse in a community. That is, by explicitly or implicitly professing adherence to those standards individuals and communities adopt criteria of

> adequacy by which their cognitive activity may be evaluated. The satisfaction of goals of inquiry is not ascertained privately, but by evaluation with respect to shared values and standards. This evaluation may be performed by anyone, not just by members of the community sharing all standards. Furthermore, standards are not a static set, but may themselves be criticized and transformed, in reference to other standards, goals, or values, held temporarily constant. Indeed, the presupposition of reliance on such standards is that they have survived similar critical scrutiny. (Longino 1996: 40)

Longino argues that when theories, evidence, values assumptions etc. are subject to community scrutiny, it is difficult for idiosyncratic, subjective preferences of individuals to be incorporated into scientific practices and knowledge. The process described by Longino where idiosyncratic assumptions are scrutinised by a scientific community, is a process in which an overarching set of values are constructed in scientific inquiry. On a more normative point, Longino argues that intersubjective interaction is necessary for scientific cognition given that it eliminates idiosyncratic assumptions and makes it difficult for sets of values and assumptions to dominate a field because they are commonly held.

The important point Longino makes in her work is to point out that cognitive practices have social dimensions. In other words, the evidential link between theory and data requires further extra-theoretical interpretation that is subject to intersubjective discussion. This interaction among scientists is regulated by public standards. For Longino, public standards include cognitive and pragmatic values, as well as substantive assumptions grounded in metaphysical or social and political commitments. Longino's argument is in line with the argument I present in this thesis; where I argue that the scientific practices are directly influenced by the broader socio-economic and political context of inquiry. Intersubjective interaction can be seen as the process in which overarching values are constructed and

scrutinised. This is similar to process in which TPP's are constructed (using values from the broader context of HAT in order to determine the desired features of the potential product) and modified in light of further evidence or changes in the relevant circumstances in the broader context.

While Longino distinguishes cognitive values as a category separate from the rest, she argues that non-cognitive values can serve as cognitive values too. This might sound contradictory; however Longino (1996) is responding to a literature in which cognitive values are thought be a definitive category only containing privileged values that is shared across the board by scientists. The point Longino is making against this form of thinking is that we might recognise a group of values that are used by scientists to regulate the discursive and material interactions in the scientific community, but these values differ in time and context and are not esoteric to science.

While cognitive values can be interpreted in different ways, Longino focuses on the debate in which cognitive values are put forward as a solution to underdetermination. For instance, Kuhn identifies five values that scientists use to guide their judgement while choosing between alternative theories: accuracy, simplicity, consistency (internal and external), scope and fruitfulness. Kuhn presented these values as an objective ground for justification while choosing between competing theories. While there are many other renditions and interpretations of these values, Longino focuses on Kuhn for brevity. I will follow suit as my main aim here is to illustrate Longino's argument against the dichotomy between cognitive and non-cognitive values in science.

Longino (1996) contrasts Kuhn's cognitive values (I will use cognitive and epistemic values to mean the same thing) with sets of feminist values. Longino defines feminist values as empirical adequacy, novelty, ontological heterogeneity, mutuality of interaction, applicability to current human needs and diffusion of power. The cognitive values in the traditional sense are taken to serve the aims of science, which can be thought of in the abstract as the construction of rational beliefs

about nature. Longino, on the other hand, argues that the feminist set of values serve the cognitive aims of feminist inquiry. Moreover, Longino argues that the feminist cognitive aims are scientific as well as their broader political and social aims. As soon as we realise the aims of scientific practices in their broader context, the dichotomy between cognitive and non-cognitive values become questionable. Longino states that by identifying the values of a particular scientific community, it is possible to highlight the features of the values traditionally thought to be cognitive. While the socio-political aspect of feminist values are immediately obvious to many, the same cannot be said about the cognitive values described by Kuhn for example. While feminist values have clear social and political role, they also have cognitive roles influencing scientific practices and judgement. Kuhn's epistemic value son the other hand, have clear cognitive roles but their social or political role are not as clear. This ambiguity arises from the lack of attention to the aims of science in a broader context. That is to say it is difficult to give a precise answer as to what aims the cognitive values identified by Kuhn serve. The best answer we can give is either a contraction of rational belief or some abstract realist argument about the truth of theories. However, once we move beyond to discuss scientific practices in context, we see that cognitive values are not divorced from the broader social and political context. Moreover, values that are not thought to be relevant to science become highly important for scientists in their decision-making about models, theories, hypotheses etc.

To sum up Longino's position, her contextual empiricism states that the main ground on which to assess a theory is using empirically-attained data. However, in order to make the evidential links between the theory and data, scientists use sets of values. The traditional group of values, termed cognitive (or epistemic) values, were identified as a privileged set that guided the decision-making process in science. Longino argues that the traditional cognitive values are not purely cognitive set of values shared by all scientist's independent of the broader context of the scientific inquiry (Longino 1996: 54). Moreover, looking at the

values of particular scientific communities, we see that there are different sets of values used based on the specific aims of that community (Longino 1996: 55). Longino furthers the underdetermination argument to show that values have a place in science, taking the argument further to show that both cognitive and non-cognitive values play an important role in scientific inquiry.

Inductive Risk

The second argument underlining the importance of the values in scientific inquiry can be traced back to the concept of inductive risk, first introduced by Carl Hempel in order to explain the extent to which values can be part of scientific reasoning (Hempel 1965). According to Hempel, inductive risk is the chance that a scientific hypothesis can be wrongly accepted or rejected. Hempel states that, given that evidence cannot establish a hypothesis with certainty, scientists must have rules for accepting and rejecting hypotheses, and in determining these rules scientists must decide how different outcomes are valued. Hempel asserts that values played no logical role in scientific reasoning, but scientists make use of these rules in accepting and rejecting hypotheses. Inductive risk argument shows that values have a role in science, guiding scientists in accepting and rejecting hypotheses. Like the underdetermination problem, the inductive risk argument is based on the notion that scientists can never have certainty in accepting or rejecting hypotheses, theories, models etc.

Heather Douglas uses the concept of inductive risk to argue for the importance of values in scientific reasoning. However, it is important to note that Douglas's position in this debate is different in the sense that she argues for dismantling the value-free normative standard for science. Unlike Hempel, Douglas argues that values are necessary for rational processes in scientific reasoning (Douglas 2000: 578). Following, Douglas aims to understand how and why scientific disputes occur by focusing on the role of values in scientific decision-making processes (Douglas 2000: 564). Douglas's position is different to Hempel in the sense that Hempel does not consider the practical

outcomes of research, but only the epistemic aims of research, which he takes to be 'the attainment of an increasingly reliable, extensive, and theoretically systematised body of knowledge' (1965: 93). Douglas does not restrict her argument to epistemic aims but looks at scientific practices in their broader context. Douglas argues that it is necessary to look at the practical aims and non-epistemic values while considering inductive risk, given that the consequences of decision taken by scientist have non-epistemic consequences:

> Where science is 'useful' it will have effects beyond the development of a body of knowledge. In many contexts, if a scientist affirms something as true, or accepts a certain theory, that statement is taken as authoritative and will have effects, potentially damaging ones, if the scientist is wrong. (Douglas 2000: 563)

Similar to Longino, Douglas's argument supports the overarching argument I present in this thesis where values from the broader context of scientific inquiry has a direct influence in shaping scientific practices. Douglas argues that judgment involved at different stages of scientific practices entails consideration of both evidence and values together. Before moving on to discuss how these two are used by scientists, it is necessary to clarify how Douglas defines values (statements of norms, goals and desires) and evidence (descriptive statements about the world). [40] While empirical evidence describes things in the world, Douglas argues that value judgements are required to determine the accuracy of descriptive statements and assess whether errors can arise from accepting these statements. Values do not directly influence the argument on which theory is 'true'[41], but they are used in assessing

[40] However, Douglas adds that descriptive statements are also value-laden in their origins (since they are produced by a value laden process).
[41] Here I am using Douglas's term: I am not making a realist claim on what makes theories true.

the consequences of accepting or rejecting a theory as true. On this Douglas states the following:

> because error is always a possibility, we are required to consider the consequences of error alongside the arguments concerning evidence. And the consideration of the consequences of error require the consideration of values, both epistemic and non-epistemic. The role for values is there, even if it is not direct. (Douglas 2000: 564)

Douglas also argues that values are involved at different stages of scientific practices when inductive risk is relevant. While Hempel focuses on inductive risk at the point of accepting and rejecting theories, Douglas argues that there are multiple stages in the course of scientific practices at which inductive risk is relevant. That is to say, Douglas argues that we must go beyond looking at theory choice and look at all instances where scientists must make a choice. For instance, Douglas identifies three stages, including choice of methodology, gathering and characterisation of data, and interpretation of data where inductive risk is relevant. In virtue of this, Douglas's analysis of inductive risk moves beyond theories, but looks at decision-making processes in scientific practices more broadly. Moreover, Douglas stresses that whenever inductive risk has non-epistemic consequences, scientists must consider non-epistemic values in their decision-making:

> The scientist will need to consider both the quantity of evidence or degree of confirmation to estimate the magnitude of inductive risk and the valuation of the consequences that would result from error to estimate the seriousness or desirability of the consequences. The weighing of these consequences, in combination with the perceived magnitude of the inductive risk (i.e., how likely one is to be wrong), determines which choice is more acceptable. Where non-epistemic consequences follow from error, non-epistemic values are essential for deciding

> which inductive risks we should accept, or which choice we should make. (Douglas 2000: 565)

To illustrate the importance of non-epistemic practices in scientific practice, Douglas uses the example of methodological choice regarding an appropriate level of statistical significance. Douglas argues that the deliberate choice of statistical significance requires deliberate choice of which risks to tolerate. Her example is the statistical significance levels in toxicology studies, demonstrating the role of values.

Determining the level of statistical significance is a balancing act between two types of errors: false positives and false negatives. Douglas articulates this as follows:

> False positives occur when one accepts an experimental hypothesis as true and it is not. False negatives occur when one rejects an experimental hypothesis as false and it is not. Changing the level of statistical significance changes the balance between false positives and false negatives. If one wishes to avoid more false negatives and one is willing to accept more false positives, one should lower the standard for statistical significance. If one wishes, on the other hand, to avoid false positives more, one should raise the standard for statistical significance. For any given experimental test, one cannot lower both types of error; one can only make trade-offs from one to the other. (Douglas 2000: 566)

Determining a suitable level of statistical significance determines whether we tolerate more false positives or false negatives. In toxicology studies, for instance questioning the carcinogenic effects of dioxin exposure, an excess of false positives will lead to the conclusion that dioxins are more toxic than they actually are, while an excess of false negatives will lead to the conclusion that dioxins are safer than they are. Douglas argues that an excess of false positives will lead to

over-regulation of chemicals; false negatives will lead to under-regulation; and both outcomes have non-epistemic consequences:

> Overregulation presents excess costs to the industries that would bear the costs of regulations. Underregulation presents costs to public health and to other areas affected by damage to public health. Depending on how one values these effects, an evaluation that requires the consultation of non-epistemic values, different balances between false positives and false negatives will be preferable. (Douglas 2000: 567)

Douglas has an extensive and sophisticated account demonstrating how both epistemic and non-epistemic values are used by scientists. Here, I used a small part of her account to illustrate how Douglas (similar to Longino) responds to values literature arguing for the importance of both epistemic and non-epistemic values in scientific practices. In summary, Douglas argues that values are necessary for scientists to assess the inductive risks linked to their decisions about methodology, data collection and interpretation. Douglas points out that these decisions have both epistemic and non-epistemic consequences, and therefore the scientist much consider both epistemic and non-epistemic values.

Both underdetermination and inductive risk arguments are strong, showing the importance of values in scientific practices, particularly in how scientists reason. Both arguments also question the dichotomy between epistemic and non-epistemic values: each show that sets of values used by scientists (or scientific communities) differ depending on their aims and the context in which their inquiry takes place.

6.2.2 Lexical Priority of Evidence

At the core of the values debate is the normative question on the role values ought to play in scientific practice. So far I have focused on two arguments that reject the value-free ideal and demonstrate how scientific communities use a range of values to assess scientific theories, evidence and the risks involved in decisions made by

scientists in accepting or rejecting hypotheses. The third argument I want to present here is that of Brown (2013), who argues that both Longino and Douglas share a flawed premise, wherein both arguments prioritise evidence over values. Brown argues that both Longino and Douglas build strong arguments against the value-free ideal of science; however both accounts maintain a lexical priority of evidence over values to an extent, where values play an indirect role in scientific practices. Brown argues that empirical evidence is given higher epistemic status in both traditional values literature and their critiques; and that values have a more integral role as opposed to being auxiliary to evidence. Brown goes on to show how this flawed premise does not do justice to the important role played by values in science. Brown's argument promotes a new kind of thinking about the role of values, demonstrating their importance for scientific practices and supporting the argument I presented in section 6.1.1, where I argued that the socio-economic and political context of HAT plays an important role in determining the aims of scientific practices and which approaches are employed to achieve these aims. This goes a step beyond the traditional debate on the role of values in science, by shifting the focus to value judgements.

The under-determination argument holds that values are relevant in the gap between evidence and theory. Brown states that if we follow the gap argument, we must accept that in cases where the gap is narrow, the role for values is reduced. In the inductive risk argument, values indirectly dictate the decision by determining the level of acceptable uncertainty. In both cases values are auxiliary, occupying the space left over once the evidence is settled. Brown articulates this as follows:

> The reason that values must play a role is that uncertainty remains once the evidence is in. In a relatively weak version of this argument, social values fill in the space between evidence and theory because something has to, so it might as well be (and often is) social values […] The arguments of these two general forms all assume the lexical priority of evidence over

> values. The premise of lexical priority guarantees that even in value-laden science, values do not compete with evidence when the two conflict. […]This is often defended as an important guarantor of the objectivity or reliability of the science in question. (Brown 2013: 834)

The hierarchy between values and evidence is thus seen as a leftover from the value-free ideal in which where the lexical priority is a rhetorical device. This hierarchy can be seen clearly in Douglas's work when she argues that values only influence decision-making indirectly once the evidence is determined. Brown argues that these arguments are good for undermining the value-free ideal and establish that values play a major role in scientific practices. However, Brown argues that these are unfit grounds for further development of understanding the role of values in science.

Brown identifies two main problems with the lexical priority of evidence. First, giving lexical priority to evidence over values requires taking an uncritical stance towards evidence: 'in testing we ask, *given the evidence*, what should we make of our hypothesis? Framed this way, values only play a role at the margins." (Brown 2013: 836, emphasis mine). That is to say, once evidence is in place, values play a role in determining what to make of that evidence. Brown argues that an uncritical view of evidence is not favourable, given that evidence can be unreliable, laden with unfit background assumptions that may be irrelevant in a given context.[42] In addition, Brown argues that lexical priority reduces the role of value judgment to an expression of preference, as opposed to a nuanced judgement. Brown argues that value judgement must not be thought as mere expression of preference, stating:

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[42] The history and philosophy of science and social studies of science provided us with many examples calling for the critical scrutiny of evidence, such as eugenics and its racist assumptions, or the design of clinical trials to favour different interest groups.

> It is crucial to distinguish between preferences or valuing and value judgments or evaluations […] Valuing may be the expression of a preference, but value judgments are reflective decisions about what to value and are better and worse on the basis of reasons. Value judgments may even be open to empirical test because they hypothesize relationships between a state or course of action to prefer and pursue and the desirability or value of the consequences of pursuing and attaining them. (Brown 2013: 836)

Brown further argues that if we consider value judgements to be adopted for good reason and subject to scrutiny, it is unreasonable to think of them as 'having lower epistemic status' in comparison to evidence. Thus, Brown argues that the lexical priority is an unreasonable presumption, and that philosophers of science should emphasise the joint necessity of evidence and values. The arguments presented by Longino and Douglas (as discussed above) focus on showing that values are necessary in scientific practices but do not allow us to further analyse the value judgements that take place in scientific inquiry. Brown argues that value judgements have a pragmatic function, stating that this allows us to recognise the different roles played by evidence, theory and values in inquiry. The pragmatic aspect of Brown's account is described as follows, in which Brown links functionality to the resolution of a problem:

> According to such an account [pragmatic], not only must evidence, theory, and values fit together in their functional roles, but they must do so in a way that actually resolves the problem that spurred the inquiry. (Brown 2013: 837)

Brown further argues that the relationship between evidence, theory and values is defined by the problem or question that led to the inquiry. That is to say, the aims of the inquiry define how evidence and values relate to one another. Brown's conclusion can be better understood by looking at his earlier paper (Brown 2012), where he focuses on John Dewey's theory of inquiry. Brown states that Dewey's work is

particularly relevant to the contemporary debate in philosophy of scientific practice, given the shared interest in the processes that make up scientific inquiry and the social aspect of science (discussed in what follows).

The argument against the lexical priority of evidence is significant for the pluralist argument I put forward in my thesis. So far, I have argued that the aims of scientific practices see the boundaries of the extent of plurality in approaches employed to achieve a given aim. Moreover, I argued that particular aims in science must be understood by taking the broader context into consideration, and understanding how values guide the scientific practices. For instance, in section 6.1 I argued that the anti-parasitic drug discovery research is prioritised to develop new therapies to eliminate HAT by 2030. I argued that the socio-economic and political context of the disease determine the Target Product Profile, and thus that values play an important role in determining the boundaries of inquiry, providing ways to assess the performance and the outcome of inquiry, as well as determining questions that scientist pursue within a system of practice. The important role values play in all parts of the inquiry must be analysed in a pragmatic framework. Following from Longino and Douglas, I argued that the traditional distinction between epistemic and non-epistemic values does not hold, where I demonstrated that broad range of values play various roles scientific practices. Moreover, I argued against the rhetoric where evidence has a lexical priority over values, where values are given only an external role determining the aim of inquiry, or only having an indirect role in the internal processes of science. That is to say the values in science debate must be reframed in order to understand the role of values in scientific practices at different stages of inquiry and the value judgements that take place in scientific inquiry. In the following section I focus on Brown's account of Dewey's logic of science to develop a pragmatic framework with which to understand the pluralities in scientific practices and, more importantly, the limits of pluralities in a given field of science.

6.3 A pragmatic framework for values

Brown provides a detailed account of Dewey's logic of science, which is mainly concerned with the epistemic and methodological issues in science. Brown presents Dewey's logic of science as the study of inquiry, in which an inquiry is defined as a process of a perplexity or problematic situation being resolved through a series of organised and intentional processes. Dewey's notion of inquiry is a complex and a dynamic process that is interlinked with its wider context. Brown underlines the key points in Dewey's logic that are directly relevant to the contemporary debate on pluralism and values in science. Using Brown's work on Dewey, I will further articulate my notion of pragmatic values in order to demonstrate how the pragmatic framework is useful for understanding the role of values in scientific practice, particularly the way they determine the extent of plurality in any field of science.

Dewey acknowledges the link between scientific inquiry and its context. A key aspect of Dewey's logic is situationism, in which a situation is defined as the contextual whole that forms the background of experiences and judgement. Brown states that Dewey's situationism avoids following,

> 'atomistic particularism' and the 'analytic fallacy' on the one hand and 'unlimited extension or universalization' on the other, by way of 'contextual situations' that preserve that 'connection and continuity' present in the experienced world while providing 'limiting conditions' for any generalization. (Brown 2012: 268)

A situation can be simply understood as an interaction or relation between agents and their environments, where that environment contains both animate and inanimate objects as well as social and cultural objects. Therefore, situations are particular to agents and practices, defined by the specific interactions between the agents and a specific environment. What counts as relevant in an inquiry depends on this interaction. Brown states that 'anything that is causally connected to a situation is potentially relevant thus potentially part of

the situation – there is no way to rule out anything out *a priori*' (Brown 2012: 273). This is best understood as the context of inquiry where the relevance of causal factors depends on the question in hand.

For Dewey, inquiry consists of 'complex pattern[s] with multiple phases' centred around a problematic situation. Brown describes Deweyan inquiry as an attempt to overcome an indeterminate situation or a perplexity (Brown 2012: 274). In Dewey's words:

> Inquiry is the controlled or directed transformation of an indeterminate situation into one that is so determinate in its constituent distinctions and relations as to convert the elements of the original situation into a unified whole. (Brown 2012: 274).

Inquiry begins with an implicit or poorly-expressed perplexity redefined as a problem statement that is the explicit formulation of the perplexity at hand. Dewey uses the following metaphor to illustrate this point:

> When an alarm of fire is sounded in a crowded assembly hall, there is much that is indeterminate as regards the activities that may produce a favorable issue. One may get out safely or one may be trampled and burned. The fire is characterized, however, by some settled traits. It is, for example, located somewhere. Then the aisles and exits are at fixed places. Since they are settled or determinate in existence, the first step in institution of a problem is to settle them in observation. There are other factors which, while they are not as temporally and spatially fixed, are yet observable constituents; for example, the behavior and movements of other members of the audience. All of these observed conditions taken together constitute "the facts of the case." They constitute the terms of the problem, because they are conditions that must be reckoned with or taken account of in any relevant solution that is proposed. (Brown 2012: 284)

Inquiry is embedded in a specific context where the initial problem (what to do when one hears the fire alarm) is formulated into an explicit situation (fire in a crowded assembly hall), which can be resolved

through either exiting in an orderly way using the designated routes or causing panic and chaos. Dewey's metaphor allows us to flesh out the role of values and evidence (evidential data) or facts in scientific inquiry. There are many relevant factors in this case including facts, ideas and values. For Dewey, the main role of facts in an inquiry is to determine what the problem is. Brown defines the Deweyan notion of fact as follows:

> Facts capture the fixed conditions with which inquiry must cope. They provide the resources for locating and formulating the problem of inquiry. The facts also suggest certain hypotheses for solving the problem […] facts for Dewey are not always singular or particular matters. Nor are there "atomic" or "basic" facts that transcend particular inquiries. (Brown 2012: 288)

In addition to facts, Dewey also identifies ideas, which refers to any conceptual-theoretical material that plays a part in an inquiry. The important distinction between facts and ideas is that facts capture the present state of affairs, whereas ideas indicate possibilities. Both facts and ideas are operational; however, they are not the only important factors in inquiry. For Dewey, inquiry is a socially-conditioned practice, in which broader interests and values shape the inquiry by defining the problems addressed and the standards of a solution. Scientific practices are governed by normative values determining how scientists ought to 'pursue their inquiries, what they may count as evidence, and what they are entitled to believe in specific situations' (Brown 2012: 301). Going back to the fire alarm example, facts can be thought of as the number of people in the room and where the exits are; the ideas are different ways one can exit the building (run ahead; get in an orderly queue; run around in a chaotic way, smashing windows and screaming for help), then values allow us make judgements at every step. According to Dewey, values play part in each stages of inquiry; however, it is important to note that the values are subject to change depending on the situation. Brown describes the role of values as follows:

> The selection of data is an active and evaluative enterprise. Inquirers must decide which instruments and techniques to use, which operations of observation to perform, which data to select as relevant, and which tolerances to set and errors to control. All inquiry requires experiments, which are at base practical operations of making and doing, which as a type of practical activity require values. […] In many parts of inquiry, explicit judgments of value, or evaluations, are required. And indeed, the inability to make good judgments about value would severely impair the ability to do science well. (Brown 2012: 301)

I agree with Brown's that Dewey's characterisation of inquiry is useful in the sense that it provides for an alternative understanding of scientific practices in which values play an integral role, along with other relevant factors in a given context. Dewey's situationism and concept of inquiry provides links between pragmatism literature and the contemporary pluralism debate I argue for in my thesis.

Earlier in section 5.2 and 5.3, I argued that the limits of pluralism are defined by pragmatic values. In section 6.1 I argued that the pragmatic values are linked to the aims of a particular set of scientific practices in specific contexts. The role of these values is to allow scientists (and other parties such as policy experts and medical professionals) involved in scientific practices to make judgements as to how they can fulfil their aim. In other words, in order to understand this, we need to understand how agents determine which approaches to employ to achieve a certain aim. Using Dewey's account in the case of HAT, the WHO and DNDi are the actors determining the course of inquiry using facts and ideas to identify the problem and formulate certain sets of values that direct scientific practices to address this problem. The colonial history and the current socio-economic and political context of HAT, combined with our biomedical and environmental understanding of this disease provides alternative ways in which HAT can be controlled and eliminated. In order to understand how WHO selected and supported a given approach to the control and elimination of HAT

it is necessary to look at different values. Here, I focused on epistemic and pragmatic values, but it is necessary to note that there are broader political and ethical values at play.

As I argued in chapter two, both epistemic and non-epistemic values play an important role in scientific practices. The epistemic and non-epistemic distinction in value free ideal is to argue that internal processes in science (such as theory choice) is free from non-epistemic. Using Longino's and Douglas's argument, I argued that scientists used both epistemic and non-epistemic values in all stages of scientific inquiry; thus, rejecting both the epistemic/non-epistemic distinction and the value free ideal. However, distinguishing between different sets of values is useful as long as such distinctions do not rely on the value free ideal. Moving beyond the value free ideal, I propose a new distinction between values: pragmatic and epistemic. Epistemic values are those that see the ultimate aim of scientific practices as to generate knowledge regardless of their context, whereas pragmatic values are thought to be values that asses the products of scientific practices with regards to particular aims that are products of their broader context. This distinction is instrumental, posed to differentiate the pragmatic limitations on scientific practices from *a priori* monist assumptions. Using the distinction between pragmatic and epistemic values, I argued that although plurality is valuable to scientific practices regarding the epistemic values, pluralism cannot be encouraged without limits. These limits are posed by the pragmatic context of inquiry.

Chapter 7

Conclusions

Throughout this thesis, I aimed to provide a philosophical account of pluralities in scientific practices, arguing that the multiplicities of accounts and approaches in scientific practices are an important characteristic of scientific inquiry. I argued that scientific practices ought to be pluralistic in order to explain and explore different aspects of phenomena. Whilst I acknowledge the benefits of plurality, I also argue that the extent of plurality in scientific practices is limited by pragmatic aims and values. Pragmatic values ought to be understood in the broader context of inquiry, with respect to particular aims of scientific practices. Herein, I supported my argument using examples from the scientific practices involved in current efforts to combat Human African Trypanosomiasis (HAT), headed by the WHO. Here, I provide a quick overview of the argument I put forward here, before providing the concluding remarks to my thesis.

My work was primarily framed by scholars from philosophy of science literature, particularly philosophers with the philosophy of science in practice approach. Following Ankeny et al. (2011) I argue that the subject matter of philosophy ought not to be limited to scientific theories and rational processes in which these theories are confirmed. Here, I take scientific practices and the accounts they produce as the main subject matter of philosophy of science. The shift from understanding scientific inquiry through rational reconstructions of scientific reasoning to focusing on actual scientific practices reveals the multiplicity in accounts and approaches used by scientists to study the natural world. Moreover, the shift in subject underlines the role of a broad range of values in scientific practices and the plurality of aims in scientific inquiry.

Following the philosophy of science in practice perspective, I focused on the scientific practices involved in the current efforts to combat HAT

as my main case study for investigating pluralities in scientific inquiry. The current control methods consist of active and passive screening campaigns, under which communities living in the disease-endemic regions are tested and patients diagnosed positive are treated. However, the current control methods have several limitations. The first is that the diagnostic and therapeutic tools are inadequate: diagnostic methods are invasive and painful, requiring specialised equipment for definite diagnosis. Furthermore, existing drugs are highly toxic, difficult to administer and have a long therapeutic window. Moreover, there are social taboos and barriers in the disease-endemic regions that negatively affect community participation in control campaigns. In addition to active and passive screening campaigns, there are other approaches (including environmental approaches and vector controls) that can be used to eliminate HAT. Some of these approaches were used usefully by different colonial administrations in the first half of the twentieth century, and the number of new cases reported fell below 10,000 in the 1960s, thus providing a principle of proof that sustained efforts can lead to significant reduction and partial elimination of HAT. The reason for prioritising active and passive screening campaigns is based on the fact that environmental and vector control approaches require large-scale interventions with the physical nature of the disease-endemic regions, and these efforts must be sustained over a long period of time. On the other hand, treating the human population (which is the only known reservoir for *T.b. gambiense*) is likely to lead to elimination after several rounds of screening campaigns. However, the success of these campaigns relies on the development of new diagnostic and therapeutic tools. In this thesis, I focused on the drug discovery process, aiming to develop anti-parasitic drugs that match patients' needs and are suitable for use in the local medical systems. Using anti-parasitic drug discovery, I argued that the scientist employs multiple approaches and accounts to develop drug candidates from scratch. Moreover, I argued that scientific practices are guided by set of overarching values listed in target product profiles (TPPs).

Using the HAT case study developed in chapter 3 and additional case studies from life sciences, in chapter 4 I developed the philosophical account of the apparent pluralities in scientific practices. The pluralist account I developed here was built on three arguments, put forward by Kellert et al., Chang and Mitchell. I mainly focused on these three arguments, given that they had a similar approach in that they all study scientific practices directly, in line with the philosophy of science in practice approach I employ here. Following these authors, I argued that pluralism is first and foremost a rejection of monist assumptions about scientific practices and their aims. I argued against the assumption that the aim of science is to provide a single, complete and coherent account of phenomena. Instead, I argued that there are multiple aims in science: different approaches have distinct aims, focusing on different aspects of phenomena; and each account is particular to the specific questions and aims of a particular approach.

In chapter 4, I discussed possible objections to the pluralist argument I develop here. An argument that is often put forward to undermine pluralism comes in the form of integration and reduction, a process in which plurality of accounts and approaches are eliminated by reducing higher level accounts to more fundamental level explanations. Herein, I provided a pluralist argument for both integration and reduction, not as a way to remove plurality, but regarding both processes as part of scientific practices allowing ad hoc interaction between different accounts. I argued that neither integration or reduction as they happen in scientific practices remove plurality, but instead add to the multiplicity of accounts and approaches by proliferating new accounts of phenomena (in the case of reductive explanations in molecular biology, or integrative approaches in homology modelling for protein structures).

The HAT case study showed that epistemic and methodological pluralism is required in order to explore and explain phenomena. Here, I argued that HAT has a complex aetiology and must be understood in its broader socio-economic and political context. As a consequence,

we saw that a plurality of approaches and accounts (both historical and current) had played a role in our efforts to study, control and eliminate HAT. Here, I argued that these pluralities are an important characteristic of scientific practices in this field that must inform philosophy of science.

It is important to underline again one of my principal claims throughout this thesis: that the plurality of approaches in scientific practices is an important characteristic of scientific inquiry. Furthermore, I have argued in this thesis that in order to explain and explore different aspects of phenomena, scientific practices ought to be pluralistic. Following Chang's normative and active claims, I asserted that the role of pluralism is to actively challenge and replace the monist assumptions that unnecessarily limit scientific practices. I describe these limitations as unnecessary given that they are only justified through *a priori* assumptions regarding the aims of science, the nature of the world or the nature of the scientific knowledge.

I make a clear distinction between monist assumptions and pragmatic values. While both sets of assumptions and values limit the extent of plurality, unlike monist assumptions, pragmatic values are justified through the broader context of scientific practices. Here I argued that the extent of plurality in current efforts to eliminate HAT is due to limitations such as lack of resources, a short time-period in which to achieve the aim, and the particular patients' needs.

Here I do not wish to argue that limiting plurality using pragmatic values must not be questioned or rejected. Instead I want to argue that our philosophical analysis of scientific practices must distinguish between monist assumptions and pragmatic values in understanding the limits of plurality, and challenge them in different terms. In the HAT case, for instance, it is important to scrutinise the justificatory narrative provided by the WHO and DNDi to prioritise the screening campaigns, therefore justifying the prioritisation of anti-parasitic drug discovery and limiting the extent of approaches employed in scientific practices in this field.

Here I provided a philosophical argument that takes pluralities in scientific practices as necessary for exploring and explaining different aspects of phenomena. Moreover, I argued that the plurality of approaches and accounts employed in each case is limited by the pragmatic values of the broader context of inquiry. Herein I provided a discussion of a pragmatic framework in which we can understand scientific practices within their broader context. My argument in this thesis focused mainly on one particular case study, and in the future I aim to revisit my philosophical claims using other case studies. My argument for pluralism provokes the question: *what makes science different from other forms of inquiry?* This question can be answered through describing what makes scientific inquiry epistemically privileged (for example the use of empirical evidence in assessing its central beliefs and assumptions). Or it can be approached from a Science and Technology Studies point of view to understand how the boundaries of science are constructed by different social actors including scientists themselves. The pragmatist framework I provide here can be used in a third way to understand what makes scientific inquiry different from other forms of inquiry, by using Dewey's approach to understand the role of scientific practices within the broader context of inquiry. However, the details of this question must be addressed in future work in detail.

My main claim here regards the role of philosophers of science. Here I argue that philosophers of science must engage with scientific practices, putting analytical tools of philosophy to use in understanding the state of affairs in scientific practices, scrutinising justificatory narratives and reflecting on the nature of scientific knowledge. Here I argued that the role of pluralist philosopher to go beyond asserting that in science 'many things go', to asking, 'what goes and why?'

Bibliography

Ahn, A. C., M. Tewari, C.-S. Poon, and R. S. Phillips. 2006. "The Limits of Reductionism in Medicine: Could Systems Biology Offer an Alternative?" *PLOS Medicine* **3** (6):e208.

Ankeny, R., H. Chang, M. Boumans, and M. Boon. 2011. "Introduction: philosophy of science in practice." *European Journal for Philosophy of Science* **1** (3):303.

Barnes, B. 1982. *TS Kuhn and social science*: Columbia University Press New York.

Barrett, M. P., R. J. S. Burchmore, A. Stich, J. O. Lazzari, A. C. Frasch, J. J. Cazzulo, and S. Krishna. 2003. "The trypanosomiases." *The Lancet* **362** (9394):1469-1480.

Beck, A. 1971. "The role of medicine in German East Africa." *Bulletin of the History of Medicine* **45** (2):170.

Berrang-Ford, L., J. Lundine, and S. Breau. 2011. "Conflict and human African trypanosomiasis." *Social Science & Medicine* **72** (3):398-407.

Bird, A. 2005. "Naturalizing Kuhn." *Proceedings of the Aristotelian Society* **105**:99-117.

Blum, J., C. Schmid, and C. Burri. 2006. "Clinical aspects of 2541 patients with second stage human African trypanosomiasis." *Acta Tropica* **97** (1):55-64.

Broadbent, A. 2015. "Causation and prediction in epidemiology: A guide to the “Methodological Revolution”." *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* **54**:72-80.

Brown, M. J. 2012. "John Dewey's Logic of Science." *HOPOS: The Journal of the International Society for the History of Philosophy of Science* **2** (2):258-306.

Brown, M. J. 2013. "Values in Science beyond Underdetermination and Inductive Risk." *Philosophy of Science* **80** (5):829-839.

Brun, R., J. Blum, F. Chappuis, and C. Burri. 2010. "Human African trypanosomiasis." *The Lancet* **375** (9709):148-159.

Bunnage, M. E. 2011. "Getting pharmaceutical R&D back on target." *Nature Chemical Biology* **7**:335.

Burri, C., and R. Brun. 2003. "Eflornithine for the treatment of human African trypanosomiasis." *Parasitology Research* **90** (1):S49-S52.

Butterfield, J. 2011. "Emergence, Reduction and Supervenience: A Varied Landscape." *Foundations of Physics* **41** (6):920-959.

Cartwright, N. 1999. *The Dappled World: A Study of the Boundaries of Science*. Cambridge: Cambridge University Press.

Cartwright, N., J. Cat, L. Fleck, and T. E. Uebel. 1996. *Otto Neurath: Philosophy between Science and Politics*, *Ideas in Context*. Cambridge: Cambridge University Press.

Cat, J. 2017. "The Unity of Science." The Stanford Encyclopedia of Philosophy,Retrieved from https://plato.stanford.edu/archives/spr2017/entries/scientific-unity/

Last accessed September 1, 2017.

Chang, H. 2004. *Inventing Temperature: Measurement and Scientific Progress*: Oxford University Press, USA.

Chang, H. 2012. *Is Water H2O*, *Boston Studies in the Philosophy and History of Science*. London: Springer.

Chang, H. 2014. "Epistemic Activities and Systems of Practice. Units of Analysis in Philosophy of Science After the Practice Turn." In *Science After the Practice Turn in the Philosophy, History, and Social Studies of Science*, edited by L. Soler, S. Zwart, M. Lynch and V. Israel-Jost. Taylor & Francis.

Chappuis, F., L. Loutan, P. Simarro, V. Lejon, and P. Büscher. 2005. "Options for field diagnosis of human African trypanosomiasis." *Clinical microbiology reviews* **18** (1):133-146.

Checchi, F., J. A. Filipe, D. T. Haydon, D. Chandramohan, and F. Chappuis. 2008. "Estimates of the duration of the early and late stage of gambiense sleeping sickness." *BMC Infectious Diseases* **8** (1):16.

Comini, M. A., S. A. Guerrero, S. Haile, U. Menge, H. Lünsdorf, and L. Flohé. 2004. "Valdiation of Trypanosoma brucei trypanothione synthetase as drug target." *Free Radical Biology and Medicine* **36** (10):1289-1302.

Dickson, M. 2006. "Plurality and Complementarity in Quantum Dynamics." In *Scientific Pluralism*, edited by Stephen Kellert, Helen Longino and Kenneth Walters. Mineapolis, London: University of Minesota Press.

Dizadji-Bahmani, F., R. Frigg, and S. Hartmann. 2010. "Who's Afraid of Nagelian Reduction?" *Erkenntnis* **73** (3):393-412.

DNDi. 2011. 2011-2018 Business Plan. Geneva: Drugs for Neglected Diseases Initiative

DNDi. 2014. DNDi Model Report. Geneva: Drugs For Neglected Disease Initiative

Douglas, H. 2000. "Inductive Risk and Values in Science." *Philosophy of Science* **67** (4):559-579.

Douglas, H. 2009. *Science, Policy, and the Value-Free Ideal*: University of Pittsburgh Press.

Dupre, J. 1993. *The Disorder of Things*. Harward: Harward University Press.

Fehr, C. 2006. "Explanations of the Evolution of Sex: A Plurality of Local Mechanisms." In *Scientific Pluralism*, edited by Stephen Kellert, Helen Longino and Kenneth Walters. Mineapolis, London: University of Minesota Press.

Fenn, K., and K. R. Matthews. 2007. "The cell biology of Trypanosoma brucei differentiation." *Current Opinion in Microbiology* **10** (6):539-546.

Ford, J. 1971. "The role of the trypanosomiases in African ecology. A study of the tsetse fly problem." *The role of the trypanosomiases in African ecology. A study of the tsetse fly problem.*

Frearson, J. A., P. G. Wyatt, I. H. Gilbert, and A. H. Fairlamb. 2007. "Target assessment for antiparasitic drug discovery." *Trends in Parasitology* **23** (12):589-595.

Galison, P. 1987. *How Experiments End*: University of Chicago Press.

Galison, P., and D. Stump, eds. 1996. *The Disunity of Science: Boundaries, Contexts, and Power*. Stanford: Stanford University Press.

Giblin, J. 1990. "Trypanosomiasis control in African history: an evaded issue?" *The Journal of African History* **31** (01):59-80.

Giere, R. 2004. "How Models Are Used to Represent Reality." *Philosophy of Science* **71** (5):742-752.

Giere, R. 2006. "Perspectival Pluralism." In *Scientific Pluralism*, edited by Stephen Kellert, Helen Longino and Kenneth Waters. Mineapolis: University of Minnesota Press.

Giere, R. 2009. "An agent-based conception of models and scientific representation." *Synthese* **172** (2):269.

Gutting, G. 1980. "Science as Discovery." *Revue Internationale de Philosophie* **34** (131/132):26-48.

Hacking, I. 1983. *Representing and Intervening*: Cambridge University Press.

Hanson, N. R. 1958. *Patterns of Discovery: An Inquiry into the Conceptual Foundations of Science*: Cambridge University Press.

Hasker, E., C. Lumbala, F. Mbo, A. Mpanya, V. Kande, P. Lutumba, and M. Boelaert. 2011a. "Health care-seeking behaviour and diagnostic delays for human african trypanosomiasis in the democratic republic of the congo." *Trop Med Int Health* **16**.

Hasker, E., C. Lumbala, F. Mbo, A. Mpanya, V. Kande, P. Lutumba, and M. Boelaert. 2011b. "Health care-seeking behaviour and diagnostic delays for Human African Trypanosomiasis in the Democratic Republic of the Congo." *Tropical Medicine & International Health* **16** (7):869-874.

Headrick, D. R. 2014. "Sleeping Sickness Epidemics and Colonial Responses in East and Central Africa, 1900?1940." *PLoS Negl Trop Dis* **8** (4):e2772.

Hempel, C. 1965. "Science and Human Values." In *Aspects of Scientific Explanation and other Essays in the Philosophy of Science*, 81-96. New York: The Free Press.

Hernan, M. A., and S. L. Taubman. 2008. "Does obesity shorten life? The importance of well-defined interventions to answer causal questions." *Int J Obes* **32** (S3):S8-S14.

Holmes, P. H. 1997. "New approaches to the integrated control of trypanosomosis." *Veterinary Parasitology* **71** (2):121-135.

Hotez, P. J., D. H. Molyneux, A. Fenwick, J. Kumaresan, S. E. Sachs, J. D. Sachs, and L. Savioli. 2007. "Control of Neglected Tropical Diseases." *New England Journal of Medicine* **357** (10):1018-1027.

Howard, D. 2006. "Lost Wanderers in the Forest of Knowledge: Some Thoughts on the Discovery-Justification Distinction." In *Revisiting Discovery and Justification: Historical and philosophical perspectives on the context distinction*, edited by Jutta Schickore and Friedrich Steinle, 3-22. Dordrecht: Springer Netherlands.

Hoyningen-Huene, P. 1987. "Context of discovery and context of justification." *Studies in History and Philosophy of Science Part A* **18** (4):501-515.

Hull, D. L. 1972. "Reduction in Genetics--Biology or Philosophy?" *Philosophy of Science* **39** (4):491-499.

Hunter, W. N. 2009. "Structure-based ligand design and the promise held for antiprotozoan drug discovery." *Journal of Biological Chemistry* **284** (18):11749-11753.

Iliffe, J. 1979. *A modern history of Tanganyika*: Cambridge University Press.

Jordan, A. M. 1986. *Trypanosomiasis control and African rural development*. Vol. 357: Longman London; New York.

Kaiser, M. 2012. "Why It Is Time to Move Beyond Nagelian Reduction." In *Probabilities, Laws, and Structures*, edited by Dennis Dieks, Wenceslao J. Gonzalez, Stephan Hartmann, Michael Stöltzner and Marcel Weber, 245-262. Springer Netherlands.

Kaiser, M. I. 2011. "The Limits of Reductionism in the Life Sciences." *History and Philosophy of the Life Sciences* **33** (4):453-476.

Kellert, S., H. Longino, and K. Waters, eds. 2006. *Scientific Pluralism*, *Minnesota Studies in the Philosophy of Science*. Mineapolis: University of Minnesota Press.

Kennedy, P. G. E. 2006. "Human African trypanosomiasis–neurologicalaspects." *Journal of Neurology* **253** (4):411-416.

Kitcher, P. 1984. "1953 and all That. A Tale of Two Sciences." *The Philosophical Review* **93** (3):335-373.

Kitcher, P. 2003. *Science, Truth, and Democracy*: Oxford University Press.

Kordig, C. R. 1978. "Discovery and Justification." *Philosophy of Science* **45** (1):110-117.

Kovacic, V., I. Tirados, J. Esterhuizen, C. T. N. Mangwiro, M. J. Lehane, S. J. Torr, and H. Smith. 2016. "We Remember… Elders' Memories and Perceptions of Sleeping Sickness Control Interventions in West Nile, Uganda." *PLOS Neglected Tropical Diseases* **10** (6):e0004745.

Kuhn, T. S. 1970. "Logic of Discovery or Psychology of Research." In *Criticism and the Growth of Knowledge: Proceedings of the International Colloquium in the Philosophy of Science, London, 1965*, edited by Imre Lakatos and Alan Musgrave. Cambridge: Cambridge University Press.

Kuhn, T. S. 1977. "Objectivity, value judgment, and theory choice." *Arguing About Science*:74-86.

Kuhn, T. S. 2012. *The structure of scientific revolutions*. 4th ed. Chicago: University of Chicago Press.

L'Hermitte, J. 1910. *La maladie du sommeil et les narcolepsies*: Severeyns.

Lacey, H. 2005. *Is science value free?: Values and scientific understanding*: Psychology Press.

Lakatos, I., and A. Musgrave, eds. 1970. *Criticism and the Growth of Knowledge: Proceedings of the International Colloquium in the Philosophy of Science, London, 1965*. Vol. 4. Cambridge: Cambridge University Press.

Laudan, L. 1984. *Science and values: The aims of science and their role in scientific debate*: University of California Press.

Lejon, V., and P. Büscher. 2005. "Cerebrospinal fluid in human African trypanosomiasis: a key to diagnosis, therapeutic decision and post-treatment follow-up." *Tropical Medicine & International Health* **10** (5):395-403.

Lindh, J. M., P. Goswami, R. S. Blackburn, S. E. Arnold, G. A. Vale, M. J. Lehane, and S. J. Torr. 2012. "Optimizing the colour and fabric of targets for the control of the tsetse fly Glossina fuscipes fuscipes." *PLoS neglected tropical diseases* **6** (5):e1661.

Lipinski, C. A., F. Lombardo, B. W. Dominy, and P. J. Feeney. 2001. "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings1." *Advanced Drug Delivery Reviews* **46** (1–3):3-26.

Longino, H. E. 1990. *Science as Social Knowledge*. Princeton: Princeton University Press.

Longino, H. E. 1994. "In search of feminist epistemology." *The Monist* **77** (4):472-485.

Longino, H. E. 1996. "Cognitive and Non-Cognitive Values in Science: Rethinking the Dichotomy." In *Feminism, Science, and the Philosophy of Science*, edited by Lynn Hankinson Nelson and Jack Nelson, 39-58. Dordrecht: Springer Netherlands.

Longino, H. E. 2004. "How values can be good for science." In *Science, values, and objectivity*, edited by Peter Machamer and Gereon Wolters, 127-142. Pittsburg.

Longino, H. E. 2011. "Knowledge for What? Monist, Pluralist, Pragmatist Approaches to the Sciences of Behavior." In *Philosophy of Behavioral Biology*, edited by K.S. Plaisance and T. Reydon. Springer Netherlands.

Longino, H. E. 2013. *Studying Human Behavior: How Scientists Investigate Aggression and Sexuality*: University of Chicago Press.

Lyons, M. 2002. *The Colonial Disease: A Social History of Sleeping Sickness in Northern Zaire, 1900-1940*: Cambridge University Press.

MacGregor, P., B. Szöőr, N. J. Savill, and K. R. Matthews. 2012. "Trypanosomal immune evasion, chronicity and transmission: an elegant balancing act." *Nat Rev Micro* **10** (6):431-438.

Maull, N. L. 1977. "Unifying science without reduction." *Studies in History and Philosophy of Science Part A* **8** (2):143-162.

Maxwell, G. 1962. "The ontological status of theoretical entities." In *Minnesota studies in the philosophy of science Vol.3, Scientific explanation, space and time*, edited by Herbert Feigl and Grover Maxwell. Minneapolis: Minneapolis : University of Minnesota Press.

Mazzocchi, F. 2008. "Complexity in biology. Exceeding the limits of reductionism and determinism using complexity theory." *EMBO Reports* **9** (1):10-4.

McCann, P., C. Bacchi, A. Clarkson Jr, J. Seed, H. Nathan, B. Amole, S. Hutner, and A. Sjoerdsma. 1981. "Further studies on difluoromethylornithine in African trypanosomes." *Medical biology* **59** (5-6):434-440.

McEvoy, J. G. 2015. *The Historiography of the Chemical Revolution: Patterns of Interpretation in the History of Science*: Taylor & Francis.

McMullin, E. 1982. "Values in Science." *PSA: Proceedings of the Biennial Meeting of the Philosophy of Science Association* **1982**:3-28.

Mitchell, S. 2002. "Integrative Pluralism." *Biology and Philosophy* **17** (1):55-70.

Mitchell, S. 2003. *Biological Complexity and Integrative Pluralism*, *Cambridge Studies in Philosophy and Biology*. Cambridge: Cambridge University Press.

Mitchell, S., and A. M. Gronenborn. forthcoming. "Why after 50 Years are Protein X-ray Crystallographers Still in Business?" *British Journal for the Philosophy of Science*.

Molyneux, D. H. 2004. ""“Neglected” diseases but unrecognised successes—challenges and opportunities for infectious disease control." *The Lancet* **364** (9431):380-383.

Mpanya, A., D. Hendrickx, S. Baloji, C. Lumbala, R. I. da Luz, M. Boelaert, and P. Lutumba. 2015. "From Health Advice to Taboo: Community Perspectives on the Treatment of Sleeping Sickness in the Democratic Republic of Congo, a Qualitative Study." *PLOS Neglected Tropical Diseases* **9** (4):e0003686.

Nagel, E. 1961. *The structure of science : problems in the logic of scientific explanation*. London: London : Routledge and Kegan Paul.

Nagel, E. 1998. "Issues in the Logic of Reductive Explanations." In *Philosophy of Science: The Central Issues*, edited by M. Curd and J.A. Cover. W.W. Norton.

Nickles, T., ed. 2003. *Thomas Kuhn*: Cambridge University Press.

Nwaka, S., and R. G. Ridley. 2003. "Virtual drug discovery and development for neglected diseases through public-private partnerships." *Nature Reviews Drug Discovery* **2** (11):919-928.

Opigo, J., and C. Woodrow. 2009. "NECT trial: more than a small victory over sleeping sickness." *The Lancet* **374** (9683):7-9.

Oyama, S., P. E. Griffiths, and R. D. Gray. 2001. "Introduction: What is developmental systems theory." In *Cycles of contingency: Developmental systems and evolution*, 1-11. MIT Press.

Pink, R., A. Hudson, M. A. Mouriès, and M. Bendig. 2005. "Opportunities and challenges in antiparasitic drug discovery." *Nature Reviews Drug Discovery* **4** (9):727-740.

Pope, W. 1924. "Synthetic Therapeutic Agents." *The British Medical Journal* **1** (3297):413-414.

Popper, K. 1970. "Normal Science and its Dangers." In *Criticism and the Growth of Knowledge: Proceedings of the International Colloquium in the Philosophy of Science, London, 1965*, edited by Imre Lakatos and Alan Musgrave. Cambridge: Cambridge University Press.

Popper, K. 2002. *The Logic of Scientific Discovery*. London: Routledge.

Priotto, G., C. Fogg, M. Balasegaram, O. Erphas, A. Louga, F. Checchi, S. Ghabri, and P. Piola. 2006. "Three Drug Combinations for Late-Stage Trypanosoma brucei gambiense Sleeping Sickness: A Randomized Clinical Trial in Uganda." *PLoS Clinical Trials* **1** (8):e39.

Pyle, A. 2000. "The Rationality of the Chemical Revolution." In *After Popper, Kuhn and Feyerabend: Recent Issues in Theories of Scientific Method*, edited by Robert Nola and Howard Sankey, 99-124. Dordrecht: Springer Netherlands.

Raadt, P. d. 2005. "The History of Sleeping Sickness." World Health Organisation,Retrieved from http://www.who.int/trypanosomiasis_african/country/history/en/index.html

Last accessed September 1, 2017.

Reichenbach, H. 1938. *Experience and prediction: An analysis of the foundations and the structure of knowledge*. Chicago, IL, US: University of Chicago Press.

Richardson, A. 2006. "Freedom in a Scientific Society: Reading the Context of Reichenbach's Contexts." In *Revisiting Discovery and Justification: Historical and philosophical perspectives on the context distinction*, edited by Jutta Schickore and Friedrich Steinle, 41-54. Dordrecht: Springer Netherlands.

Robays, J., P. Lefèvre, P. Lutumba, S. Lubanza, V. Kande Betu Ku Mesu, P. Van der Stuyft, and M. Boelaert. 2007. "Drug toxicity and cost as barriers to community participation in HAT control in the Democratic Republic of Congo." *Tropical Medicine & International Health* **12** (2):290-298.

Rock, K. S., S. J. Torr, C. Lumbala, and M. J. Keeling. 2017. "Predicting the Impact of Intervention Strategies for Sleeping Sickness in Two High-Endemicity Health Zones of the Democratic Republic of Congo." *PLOS Neglected Tropical Diseases* **11** (1):e0005162.

Rosenberg, A. 1985. *The Structure of Biological Science*: Cambridge University Press.

Rouse, J. 2002. "Kuhn's Philosophy of Scientific Practice." In *Thomas Kuhn*, edited by Thomas Nickles, 101-121. Cambridge: Cambridge University Press.

Ruse, M. E. 1971. "Reduction, Replacement, and Molecular Biology." *Dialectica* **25** (1):39-72.

Sand, M., M. A. Kron, and R. B. Brown. 1985. "Prentamidine: a review." *Reviews of Infectious Diseases* **7**:627–634.

Sarkar, S. 1992. "Models of reduction and categories of reductionism." *Synthese* **91** (3):167-194.

Schaffner, K. 2012. "ERNEST NAGEL AND REDUCTION." *Journal of Philosophy* **109** (8/9):534.

Schaffner, K. F. 1993. *Discovery and explanation in biology and medicine*. Chicago: Chicago : University of Chicago Press.

Schickore, J., and F. Steinle. 2006. *Revisiting Discovery and Justification: Historical and philosophical perspectives on the context distinction*. Dordrecht: Springer Netherlands.

Sent, E.-M. 2006. "Pluralisms in Economics." In *Scientific Pluralism*, edited by Stephen Kellert, Helen Longino and Kenneth Walters. Mineapolis, London: University of Minesota Press.

Simarro, P. P., G. Cecchi, J. R. Franco, M. Paone, A. Diarra, G. Priotto, R. C. Mattioli, and J. G. Jannin. 2015. "Monitoring the Progress towards the Elimination of Gambiense Human African Trypanosomiasis." *PLOS Neglected Tropical Diseases* **9** (6):e0003785.

Simarro, P. P., G. Cecchi, J. R. Franco, M. Paone, A. Diarra, J. A. Ruiz-Postigo, R. C. Mattioli, and J. G. Jannin. 2014. "Mapping the capacities of fixed health facilities to cover people at risk of gambiense human African trypanosomiasis." *International Journal of Health Geographics* **13** (1):4.

Simarro, P. P., G. Cecchi, J. R. Franco, M. Paone, E. M. Fèvre, A. Diarra, J. A. Ruiz, R. C. Mattioli, and J. G. Jannin. 2011. "Risk for human african trypanosomiasis, central africa, 2000-2009." *Emerg Infect Dis* **17**.

Simarro, P. P., J. R. Franco, P. Ndongo, E. Nguema, F. J. Louis, and J. Jannin. 2006. "The elimination of Trypanosoma brucei gambiense sleeping sickness in the focus of Luba, Bioko Island, Equatorial Guinea." *Tropical Medicine & International Health* **11** (5):636-646.

Simarro, P. P., J. A. Ruiz, J. R. Franco, and T. Josenando. 1999. "Attitude towards CATT-positive individuals without parasitological confirmation in the African Trypanosomiasis (T.b. gambiense) focus of Quicama (Angola)." *Trop Med Int Health* **4**.

Sneader, W. 2005. *Drug Discovery: A History*: Wiley.

Soff, H. G. 1969. "Sleeping Sickness in the Lake Victoria Region of British East Africa, 1900-1915." *African Historical Studies* **2** (2):255-268.

Steverding, D. 2010. "The Development of drugs for treatment of sleeping sickness: a historical review." *Parasites & Vectors* **3** (15).

Stuart, K., R. Brun, S. Croft, A. Fairlamb, R. E. Gürtler, J. McKerrow, S. Reed, and R. Tarleton. 2008. "Kinetoplastids: related protozoan pathogens, different diseases." *The Journal of Clinical Investigation* **118** (4):1301-1310.

Suppes, P. 1978. "The Plurality of Science." *PSA: Proceedings of the Biennial Meeting of the Philosophy of Science Association* **1978**:3-16.

Thagard, P. 1990. "The Conceptual Structure of the Chemical Revolution." *Philosophy of Science* **57** (2):183-209.

Torrie, L. S., S. Wyllie, D. Spinks, S. L. Oza, S. Thompson, J. R. Harrison, I. H. Gilbert, P. G. Wyatt, A. H. Fairlamb, and J. A. Frearson. 2009. "Chemical Validation of Trypanothione Synthetase: A POTENTIAL DRUG TARGET FOR HUMAN TRYPANOSOMIASIS." *The Journal of Biological Chemistry* **284** (52):36137-36145.

Toulmin, S. 1970. "Does the distinction between normal and revolutionary science hold water?" In *Criticism and the Growth of Knowledge: Proceedings of the International Colloquium in the Philosophy of Science, London, 1965*, edited by Imre Lakatos and Alan Musgrave. Cambridge: Cambridge University Press.

Trouiller, P., E. Torreele, P. Olliaro, N. White, S. Foster, D. Wirth, and B. Pécoul. 2001. "Drugs for neglected diseases: a failure of the market and a public health failure?" *Tropical Medicine & International Health* **6** (11):945-951.

Uebel, T., ed. 1991. *Rediscovering the forgotten Vienna Circle : Austrian studies on Otto Neurath and the Vienna Circle*. Dordrecht

Boston: Kluwer Academic Publishers.

van Fraassen, B. 2010. "Scientific Representation: Paradoxes of Perspective." *Analysis* **70** (3):511-514.

van Riel, R. 2011. "Nagelian Reduction beyond the Nagel Model*." *Philosophy of Science* **78** (3):353-375.

VanderWeele, T. J., and W. R. Robinson. 2014. "On the Causal Interpretation of Race in Regressions Adjusting for Confounding and Mediating Variables." *Epidemiology* **25** (4):473-484.

Waters, C. K. 1990. "Why the anti-reductionist consensus won't survive: The case of classical Mendelian genetics." PSA: Proceedings of the Biennial Meeting of the Philosophy of Science Association.

Waters, C. K. 2006. "Pluralist interpretation of Gene-Centred Biology." In *Scientific Pluralism*, edited by S.H. Kellert, H.E. Longino and C.K. Waters. University of Minnesota Press.

Watkins, J. 1970. "Agaist 'Normal Science'." In *Criticism and the Growth of Knowledge: Proceedings of the International Colloquium in the Philosophy of Science, London, 1965*, edited by Imre Lakatos and Alan Musgrave. Cambridge: Cambridge University Press.

WHO. 2000. Report on Global Surveillance of Epidemic-prone Infectious Diseases. Geneva: World Health Organization Department of Communicable Disease Surveillance and Response

WHO. 2012a. Accelerating work to overcome the global impact of neglected tropical diseases – A roadmap for implementation. WHO

WHO. 2012b. Report of a WHO meeting on elimination of African trypanosomiasis (Trypanosoma brucei gambiense). WHO

WHO. 2013. Neglected tropical diseases: Prevention, control, elimination and eradication. World Health Organisaiton

Worboys, M. 1994. "The comparative history of sleeping sickness in east and central Africa, 1900–1914." *History of Science* **32** (1):89-102.

Wyatt, P. G., I. H. Gilbert, K. D. Read, and A. H. Fairlamb. 2011. "Target Validation: Linking Target and Chemical Properties to Desired Product Profile." *Current Topics in Medicinal Chemistry* **11** (10):1275-1283.

Wyllie, S., S. L. Oza, S. Patterson, D. Spinks, S. Thompson, and A. H. Fairlamb. 2009. "Dissecting the essentiality of the bifunctional trypanothione synthetase-amidase in Trypanosoma brucei using chemical and genetic methods." *Molecular Microbiology* **74** (3):529-540.