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'Big Data' informed drug development: a case for acceptability

Neel Desai¹, neel.desai.13@ucl.ac.uk, A.J. Edwards², T.B. Ernest², C. Tuleu¹ and M. Orlu¹

Data, which help inform various stages of drug product development, are increasingly being collected using newer, more novel platforms, such as mobile applications, and analysed computationally as much larger 'Big Data' data sets, revealing patterns relating to human behaviour and interactions. Medicine acceptability gauges the ability and willingness of patients to take their dosage forms. It has become a crucial human component of drug product design. Vouching for the age appropriateness of medicinal products, acceptability related data are now expected by regulatory bodies. Shifting from traditional paper-based to electronic data-gathering platforms will allow the pharmaceutical industry to collect real-world, real-time, clinically relevant data, capable of informing current and future drug product development, reducing time and cost, and setting foundations for patient-centric drug product design.

Introduction

Data help inform the four stages of pharmaceutical product development [1]. Increasingly, drug product development is being driven by 'Big Data', extremely large data sets that can be analysed computationally to reveal patterns, trends, and associations, especially relating to human behaviour and interactions. 'Big Data' can also be characterised as the '5Vs' [2]: (i) value: data can only be of value when applied to make better and faster decisions; (ii) variety: whether the data that are available are structured, semistructured, or unstructured; (iii) velocity: the speed of data generation and analysis; (iv) veracity: the truthfulness of the data gathered; and (v) volume: the amount of data available.

Various platforms and technologies are already used within the pharmaceutical industry to collect and analyse 'Big Data', including the

use of artificial intelligence to optimise administration of controlled-release formulations [3] and predict drug behaviour using *in vivo*-*in vitro* correlations [4]. Mobile applications (apps) are another platform being explored, although current adoption, based on downloads, has not been so successful [4]. However, there remains an opportunity for the industry to develop apps, targeted at the increasing number of patients taking active measures towards understanding disease and medicines, which encourage and sustain behavioural changes to support a patient's needs [5].

The repurposing or adaptation of existing technological platforms, such as wearable devices used in conjunction with smartphone apps, provides an alternate approach for collecting 'Big Data'. Newer studies have incorporated biometrics and unique personal identifiers within wearable sensors for capturing various

unconscious physiological responses (e.g., heart rate, respiration rate, stress level, etc.) to stimuli [6].

A successfully developed drug delivery system has several key considerations: acceptability, efficacy, manufacturability, and safety. In recent years, acceptability has gained substantial focus from the pharmaceutical industry and regulatory bodies. The European Medicines Agency (EMA) defines acceptability as 'the overall ability of willingness of the patient to use and its caregiver to administer the medicine as intended' [7]. Acceptability of orally administered medicines, those most commonly available, requires recognising and considering characteristics of both the end-user and the medicinal product, including swallowability, palatability, and administration [8].

An unacceptable medicine could lead to medication rejection, a crucial issue for healthcare

providers and caregivers because the prescribed course of treatment is incomplete. Interpatient variability for medicine acceptability might also exist, where one formulation is better suited to a particular cohort over another (e.g., the use of orodispersible tablets in patients with dysphagia). This becomes problematic for patients with chronic disease because it can have prolonged effects on overall wellbeing.

Digital technologies could be used to collect medicine-acceptability 'Big Data' by the pharmaceutical industry, supporting real-time, informed drug product development while minimising the crucial issue of medication rejection because of unacceptable medicine administration. One way in which this could be achieved is in a manner analogous to patient-reported outcomes (PROs), which uses questionnaires to provide a direct response from the patient regarding their health condition, without a healthcare provider or caregiver interpretation [9].

PROs, similar to medicine-acceptability assessments, are often recorded using paper questionnaires, which are practical and easy, but can result, because of misinformation or misinterpretation, in unanswered questions, multiple responses to a single question, or answering beyond the nominated boundaries [10]. These errors can compromise recorded data because of the presence of missing values. Paper-based data collection also involves several time- and cost-expensive processes, including printing and packaging questionnaires and transcribing responses [10].

Regulatory bodies have recognised the transition to electronic data recording, with studies that have harnessed the Internet shown to lower costs associated with data collection [11], attractive for larger population-based studies used in clinical trials. The EMA has expressed support for the development of digital tools to support

the approval of medicinal products [12]. To ensure the safe and effective use of medicines, comprehensive advice will be provided, even at early conceptual stages [13]. As digitalisation of patient healthcare data increases, assisted by high-quality real-world evidence, the US Food and Drug Administration (FDA)-designed MyStudies App has the capability to improve the efficiency of clinical trials by enabling input of real-world data directly by patients, linked to their electronic health data records [14,15].

Legal and ethical issues for data capture and storage, and technical, reimbursement, and remuneration requirements are some of the barriers associated with these advanced technologies [11]. Importantly, the design and development of technologies and applications should not be in isolation of the desired end-user. Instead, collaboration between healthcare providers, academic institutions, and pharmaceutical companies will be essential to maximise the use of 'Big Data' to inform drug-product design [16]. Together, the collected 'Big Data' would enable informed development of current and future assets with all stakeholders benefiting from the result.

Here, we consider how data associated with patient acceptability are currently obtained, what additional data would be useful to obtain and, consequently, how 'Big Data' could be generated to inform drug product design.

Development data

'Big Data'-informed drug product development with associated technologies has the potential to reduce both time, approximately two decades, and cost, upwards of a billion US dollars, required to develop and release new active pharmaceutical ingredients (APIs). As described earlier, many drug discovery programs have been assisted through various implementations of 'Big Data' technology. Novel platforms could

be used to collect, store, and analyse data generated from the phases that follow drug discovery (Fig. 1), helping to accelerate the drug development process while improving the design of age-appropriate, patient-centric medicines. The individual phases where 'Big Data' for medicines acceptability exists are further discussed herein.

Preclinical trials

Preclinical APIs must pass safety assessments before formulation design is considered. For age-appropriate formulations, product life-cycles and requirements will vary depending on the target population. For paediatric formulations, the safety profile of the API will likely have been determined in association with the development of the adult drug product in pre-clinical and adult clinical studies. The right medication, dose, patient, time and route must be considered when administering an acceptable medicine [17]. In paediatric patients, this is especially important because any potential aversive reactions might prevent dose repetition if and/or when required.

Given that APIs are often bitter and require taste masking, the ambition is to develop formulations of neutral taste, because strong flavours might become unacceptable with repeated administration [7]. Excipients, such as taste-masking agents, sweeteners, and flavours, can be introduced where improvements are required. Care must be taken to ensure that the final product is not too attractive, particularly for children, because this is known to increase rates of accidental poisoning [7].

Sensory analysis studies help assess the acceptability of designed formulations. Nonhuman trials using the electronic tongue (e-tongue) [18] test formulations in a laboratory environment with optimisation of the 'best' performing products before human studies.

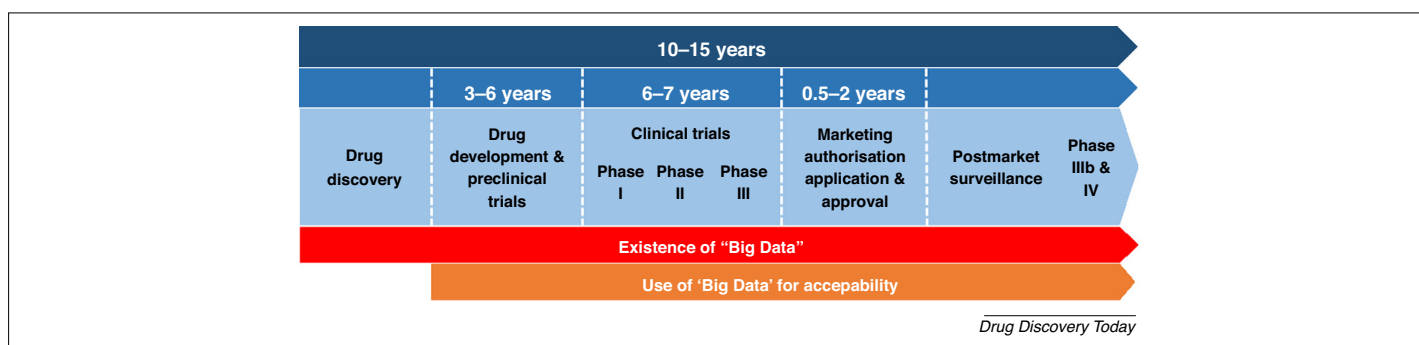


FIGURE 1

Diagrammatic representation of a typical drug development pipeline. The figure displays where 'Big Data' already exist (red) and a proposal for where 'Big Data' for patient acceptability could be captured to improve drug product development (orange).

Human sensory assessments rely on small cohort responses collected using paper-based questionnaires. Combined, these tests produce both qualitative and quantitative data, which with time, could enable the generation of 'Big Data' for different formulations. These larger data sets could be used to create predictive models capable of selecting the most acceptable formulation composition, demonstrating the capacity and ease of 'Big Data' technologies and platforms for data capture, storage, and analysis.

Clinical trials

A drug product entering clinical trials will be assessed by a diverse cohort, increasing in number and heterogeneity through each phase: Phase I, healthy volunteers; and Phases II and III, patients with the targeted disease. Clinical trials offer greater insights into medicine-acceptability profiles and potentially provide a rich resource of 'Big Data' used to inform future drug product development.

Early Phase I trials determine drug product tolerability. Data obtained from these assessments combined with the preclinical data set could enhance predictions of the overall acceptability and tolerability of a drug product in healthy participants, helping to eliminate earlier, less successful, future formulation candidates.

Phases II and III are likely to generate the greatest volume of medicine-acceptability data because of recruitment numbers, and the possibility that the disease state might alter characteristics essential to acceptability profile determination. Age can also influence the perception and acceptability of a particular drug product, important in paediatric and geriatric cohorts.

From the 'Big Data' collected, it might be possible to make incremental changes to a formulation (e.g., change in flavour) during Phase III. If the asset is too far into development and changes cannot be made, the data can be useful for either the future of the life cycle of this API (e.g., use of the product in different patient populations) or different APIs in development with similar acceptability. If an age-appropriate formulation was not acceptable, a project team might decide to delay the product to get it correct for first launch.

Given that real-time, continuous monitoring of patients in real-world environments is less likely to be achieved with traditional paper-based methods (discussed earlier), where measured outcomes are an infrequent snapshot of the participant within an unnatural environment [19], Phases II and III provide the optimal envi-

ronment to use 'Big Data' technologies and platforms to collect, store, and analyse clinically relevant, real-time data sets. Furthermore, these technologies do not depend on manual transcription of data into appropriate databases and, therefore, do not suffer from a lack of data entry and validation.

Marketing application authorisation and approval

The final application for a formulated drug candidate must present evidence that the API provides the required effects during trials when prescribed as recommended for the wider patient population affected by the disease. Guidance issued by the EMA states patient acceptability must be a fundamental component of paediatric formulation development and must be described in the paediatric investigation plan (PIP) [20].

Digital technologies and platforms can accelerate the filing of new applications through real-time, real-world qualitative and quantitative drug product attribute data, automatic storage in cloud databases, and subsequent data analyses. This provides a significant advantage compared with paper-based data collection methods and also makes documentation of this requirement far easier. Overall, these modern 'Big Data' technologies could reduce costs associated within both clinical trial Phases and marketing authorisation processes, and have been recognised by regulatory bodies [12,13,15], further encouraging their use in drug product development.

Postmarketing surveillance

Postmarketing surveillance allows for extensive data collection of medicinal and consumer health products and devices because of further increases in population size and diversity; in addition, time for data collection is greater than in the stages discussed thus far. The two main forms of post-marketing surveillance are: (i) monitoring of adverse drug reactions (ADRs); and (ii) detection of falsified medicinal products under the Falsified Medicines Directive (FMD), 2013 (Directive 2011/62/EC) [21].

The former allows ADR reports to be collected by local regulatory agencies, analysed to identify and categorise ADRs, and assess incidence. Mobile technologies are already used for ADR reporting to local healthcare agencies or regulatory bodies, although data are not immediately transferred to market authorisation holders unless product recall is necessary. The latter aims to prevent entry of falsified medicinal products into supply chains, minimising the risk

of such products reaching patients. Subsequently, two safety features on medical product packaging anticipated for human use and/or consumption, as stipulated by the Commission Delegated Regulation (EU) 2016/161 [22] were introduced: (i) a unique identifier: a 2D data matrix barcode (QR codes) scanned along the medicine/device supply chain to determine authenticity; and (ii) an anti-tamper device (ATD).

Real-time transfer of information simultaneously to local regulatory bodies and market authorisation holders to enable capture, storage, and analysis of data for future drug product design could be achieved with the compulsory technologies defined within the FMD. This is important because the mass distribution of products to increasingly diverse global populations could reveal the possible introduction of falsified medicines into the supply chain. Additionally, previously unexplored insights during the premarket stages, including use and/or performance as intended, reporting of pharmacovigilance issues, and understanding the effects of patient preference on repeated dose products could be further analysed. Postmarket acceptability assessments could, with time, collect data to aid determination of the most acceptable formulations for a specific patient population, rather than targeting the general population during product launch (Fig. 2)

Wanted: new acceptability data

The growing number of patient-centric drug products necessitates the consideration and use of patient medication-acceptability data to support informed drug product development throughout the pipeline, as outlined in the previous section. Acquiring these data will be easier for certain routes of administrations and formulation types, such as oral drug products. The various oral formulation acceptability profiles have been extensively studied, as reviewed by Mistry and Batchelor [23].

Although regulatory authorities, including the EMA [7,24], FDA [25], and the International Council for Harmonisation (ICH) [26], highlight the importance of developing medicinal products suited to the characteristic of targeted patient groups, especially paediatric and frail geriatric populations [27], there remains an absence of 'recognised' pharmacopoeia testing for determining medicines acceptability. The current qualitative assessments are laborious, time consuming, and conducted on smaller groups of trained panellists [28], unrepresentative of the final patient population.

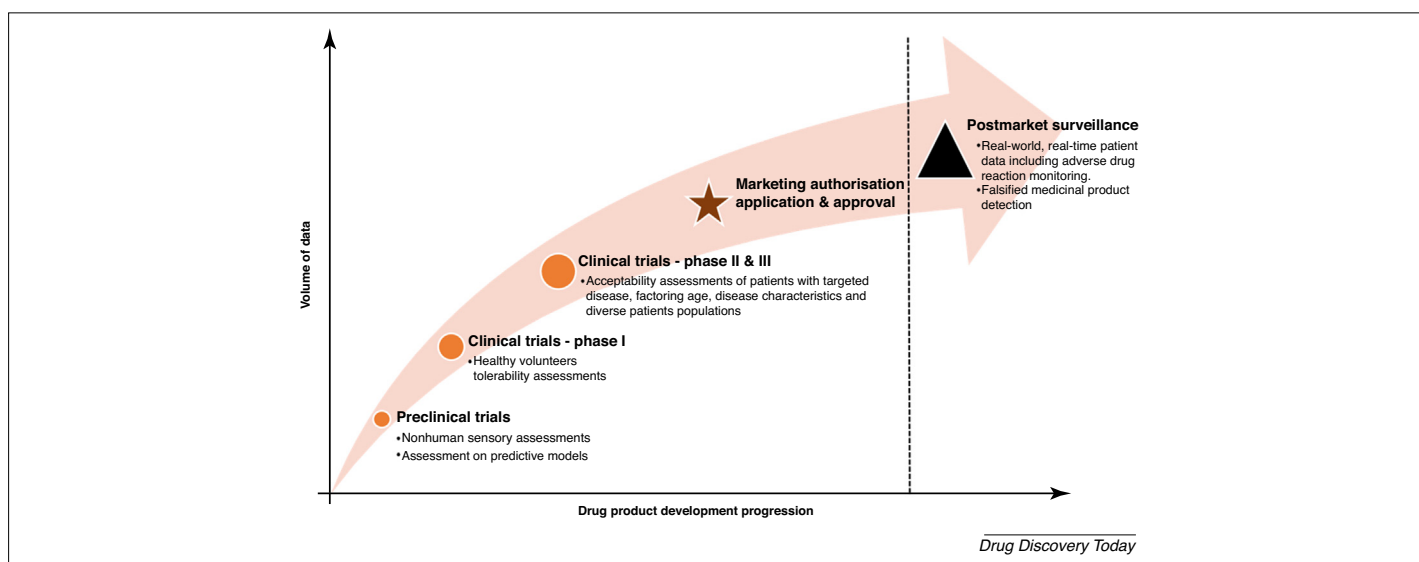


FIGURE 2

Summarised representation of the volume and availability of data throughout the drug product pipeline, which could aid informed drug product design of future, acceptable medicinal products. The figure is divided into premarketing, with the key stages of marketing authorisation, and application and approval, followed by post marketing.

The platforms and technologies described earlier provide an ideal opportunity to reach end-users to obtain real-world, real-time acceptability data during drug product development or post marketing, helping to inform both processes separately. The Noldus FaceReader® provides an example of facial recognition and video analytic technologies that has been used to assess drug palatability of postmarketed medicines in children [29,30]. Through appropriate recruitment and platform customisation, assessments of medicine acceptability may inform future prescribing practices through observations of patient compliance and/or adherence during chronic treatment regimens. It might also be possible to identify potential relationships, previously unknown, between medication adherence and physiological measures, using digital feedback systems and ingestible sensors located within pill-sized electronics that confirm tablet swallowing for patients with chronic conditions [31]. Further analyses could help reduce rising costs and inefficiencies troubling healthcare systems, associated with unused medicines and poly-pharmacy.

Randomised controlled trails remain the gold standard. However, use of real-world patient data could accelerate drug approval processes, reducing time to market and support treatment recommendations and guidelines [32,33]. 'Big Data' could enable regulatory bodies to make informed decisions from analysis of non-randomised patient data [33], particularly for drug repurposing. As personalised medicine

becomes increasingly important, acceptability data will drive the future of medicine manufacture through informed drug product development.

Concluding remarks

With regulatory bodies increasingly recognising the importance of medicine-acceptability data for drug product development, and the use of mobile technologies for capturing data throughout clinical trials, the pharmaceutical industry needs to continue adopting the shift away from traditional paper-based practices to electronic technologies and platforms. The collection of real-world, real-time, clinically relevant data during the various stages outlined herein could culminate in 'Big Data' data sets capable of informing drug product development. Importantly, medicine-acceptability data could allow for meeting the requirements of wider patient populations and reducing medication rejection, laying the foundations for future patient-centric drug product design. Together, both time and cost to the pharmaceutical industry might be reduced through the collection of language normalised data, while also accelerating the availability of more patient-tailored pharmaceuticals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- 1 Amarji, B. *et al.* (2018) Four stages of pharmaceutical product development: preformulation, prototype development and scale-up, biological aspects, and commercialization. *Dosage Form Des. Considerations* 1, 637–668
- 2 Pramanik, M.I. *et al.* (2017) Smart health: Big Data enabled health paradigm within smart cities. *Expert Syst. Appl.* 87, 370–383
- 3 Hassanzadeh, P. *et al.* (2019) The significance of artificial intelligence in drug delivery system design. *Adv. Drug Delivery Rev.* 151, 169–190
- 4 Sun, Y. *et al.* (2003) Application of artificial neural networks in the design of controlled release drug delivery systems. *Adv. Drug Delivery Rev.* 55, 1201–1215
- 5 Istas, A. (2019) Four things to know about digital health. *DIA Global Forum* 11 March
- 6 Fuentes, S. *et al.* (2018) Development of a biosensory computer application to assess physiological and emotional responses from sensory panelists. *Sensors (Switzerland)* 18 (9), 2958–295
- 7 EMA (2013) *Guideline on Pharmaceutical Development of Medicines for Paediatric Use Guideline on Pharmaceutical Development of Medicines for Paediatric Use*. EMA
- 8 Kozarewicz, P. (2014) Regulatory perspectives on acceptability testing of dosage forms in children. *Int. J. Pharmaceutics* 469, 245–248
- 9 FDA (2019) *Learn about FDA Patient Engagement*. FDA
- 10 Ebert, J.F. *et al.* (2018) Paper-or web-based questionnaire invitations as a method for data collection: Cross-sectional comparative study of differences in response rate, completeness of data, and financial cost. *J. Med. Internet Res.* 20, e24

- 11 Scott, A. *et al.* (2011) A randomised trial and economic evaluation of the effect of response mode on response rate, response bias, and item non-response in a survey of doctors. *BMC Med. Res. Methodol.* 5 126–126
- 12 EMA (2020) *Questions and Answers: Qualification of Digital Technology-Based Methodologies to Support Approval of Medicinal Products*. EMA
- 13 Cerreta, F. *et al.* (2020) Digital technologies for medicines: shaping a framework for success. *Nat. Rev. Drug Discovery* 19, 573–574
- 14 FDA (2019) *FDA's MyStudies Application (App)*. FDA
- 15 Rogers, J. (2020) *Google Cloud and FDA MyStudies: Harnessing Real-World Data for Medical Research*. Google Cloud
- 16 Jain, S.H. *et al.* (2014) Is big data the new frontier for academic-industry collaboration? *JAMA* 311, 2171–2172
- 17 Ladak, S.S.J. *et al.* (2007) Right medication, right dose, right patient, right time, and right route: how do we select the right patient-controlled analgesia (PCA) device? *Pain Manage. Nurs.* 8, 140–145
- 18 Gupta, H. *et al.* (2010) E-Tongue: a tool for taste evaluation. *Recent Pat. Drug Delivery Formulation* 4, 82–89
- 19 Dobkin, B.H. and Dorsch, A. (2011) The promise of mHealth: daily activity monitoring and outcome assessments by wearable sensors. *Neurorehabil. Neural Repair* 25, 788–798
- 20 EMA (2013) *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*. EMA
- 21 EMA (2011) *Amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use, as Regards the Prevention of the Entry into the Legal Supply Chain of Falsified Medicinal Products*. EMA
- 22 EMA (2016) *Supplementing Directive 2001/83/EC of the European Parliament and of the Council by Laying Down Detailed Rules for the Safety Features Appearing on the Packaging of Medicinal Products for Human Use*. EMA
- 23 Mistry, P. and Batchelor, H. (2017) Evidence of acceptability of oral paediatric medicines: a review. *J. Phar. Pharmacol.* 69, 361–376
- 24 EMA (2020) *Reflection Paper on the Pharmaceutical Development of Medicines for Use in the Older Population*. EMA
- 25 FDA (2012) *Food and Drug Administration Safety and Innovation Act. S.3187*. FDA
- 26 EMA (2017) *ICH E11(R1) Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population*. EMA
- 27 Vallet, T. *et al.* (2018) A decision support tool facilitating medicine design for optimal acceptability in the older population. *Pharm. Res.* 35 136–136
- 28 Stone, H. *et al.* (2012) *Sensory Evaluation Practices (4th edn)*. Elsevier
- 29 FaceReader. <https://www.noldus.com/facereader> [Accessed December 16, 2020].
- 30 Kearns, G.L. *et al.* (2019) Use of facial recognition technology to assess drug palatability in pediatric patients: a pilot study. *J. Appl. Biopharm. Pharmacokinet.* 7, 37–49
- 31 Browne, S.H. *et al.* (2015) Let visuals tell the story: medication adherence in patients with type II diabetes captured by a novel ingestion sensor platform. *JMIR Mhealth Uhealth* 3, e108
- 32 Bate, A. *et al.* (2016) Designing and incorporating a real world data approach to international drug development and use: what the UK offers. *Drug Discovery Today* 21, 400–405
- 33 Bell, H. *et al.* (2016) *The Use of Real World Data for the Estimation of Treatment Effects in NICE Decision Making*. Decision Support Unit, SCHARR

Neel Desai^{1,*}

A.J. Edwards²

T.B. Ernest²

C. Tuleu¹

M. Orlu¹

¹*Department of Pharmaceutics, UCL School of Pharmacy, University College London, London, WC1N 1AX, UK*

²*GlaxoSmithKline, David Jack Centre, Park Road, Ware, SG12 0DP, UK*

*Corresponding author.