AN EVALUATION OF THE cGMP MANUFACTURING PROCESS ECONOMICS AND HIGH-THROUGHPUT CHARACTERISATION OF TARGETED SECRETION INHIBITORS

Andy Hooker[a*], Andrew Splevins[a], Peter Horrocks[a], Paul Dalby[b], Suzanne Farid[b]

[a]Ipsen Bioinnovation Limited, Oxford, UK; [b]University College London, London, UK

*Corresponding author: Ipsen Bioinnovation Limited, Oxford, OX14 4RY, UK.
E-mail address: andy.hooker@ipsen.com

Introduction and Objectives:

Targeted Secretion Inhibitors (TSIs) are a novel class of recombinant biotherapeutics, using protein engineering to re-target Botulinum neurotoxins for treatment of diseases with secretion disorders. SXN101959 has been successfully manufactured by Ipsen to cGMP standards and is an example of an emerging recombinant TSI manufacturing platform. SXN101959 is a multi-domain, multi-functional recombinant protein expressed within *Escherichia coli*, composed of a light chain (LC/D) endopeptidase domain and a heavy chain (H_N/D) domain with a growth hormone releasing hormone (GHRH) targeting peptide ligand.

The Engineering and Physical Sciences Research Council (EPSRC) within the UK has established a Centre for Innovative Manufacturing in Emergent Macromolecular Therapies at University College London. The Centre provides an international lead in delivering biopharmaceutical manufacturing innovations for next generation advanced therapies, which has included an evaluation of SXN101959. We present an assessment of SXN101959 using two research workstreams:
Workstream 1 – an assessment of the process economics and manufacturability of SXN101959, including cost of goods; and
Workstream 2 – the development of rapid biophysical characterisation decisional tools that assess aggregation propensity and facilitate formulation development.

Methods:

Workstream 1: Process and economic data from the cGMP manufacturing of SXN101959 were collated and combined into a spreadsheet-based mathematical model, in order to determine the key cost factors and allow future improvements that would reduce manufacturing costs.

Workstream 2: The aggregation properties of SXN101959 were studied by Size Exclusion High Performance Liquid Chromatography (SE-HPLC), Static Light Scattering (SLS), Intrinsic Fluorescence and monitoring binding of fluorescent dyes. These studies were performed in various buffers.

Results and Conclusions:

We present the key outcomes from the two SXN101959 research workstreams:
Workstream 1: Successful generation of a mathematical spreadsheet-based tool, able to identify key costs in the manufacturing process, and estimate effects of manufacturing scale on costs of goods; and
Workstream 2: A suite of analytical tools able to provide data on the aggregation propensity of SXN101959, and so identify solvent conditions for minimizing aggregation.

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Keywords:

Botulinum Neurotoxin (BoNT);
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