BRITISH PHARMACOPOEIA COMMISSION

Working Party BIO-DPS: Alternative Approaches for Documentary and Physical Standards for Biotechnological Products.

MINUTES

A meeting of the Working Party was held at 10 South Colonnade, London E14 4PU on Wednesday 28th November 2018.

Present: Dr P Varley *(Chair)*, Dr A M Brady *(Vice Chair)*, Dr B Cowper, Dr V Ganeva, Dr B Jordan, Dr L Duhau, Dr M Wild, Mr C E Giartosio, Dr G Cook, Dr A Ramzan, Dr L Randon. Dr N Czeloth dialled in to part of the meeting by telephone.

In attendance: Mr A Gibb, Mr J Pound, Dr A Gardiner, Dr G Kemp.

Apologies: Dr C Burns.

Opening Remarks

Welcome The Chair welcomed everyone to the meeting and briefly stated the aims of the meeting. Members introduced themselves.

Confidentiality Members were reminded of the confidential nature of the papers, discussions and minutes of the meeting.

Declaration of Interests Members were asked to submit their Declaration of interest forms to the Secretariat if they had not already done so.

5 General matters **BIO-DPS(18)01 Annexes 1-6**

5.1 **Emergency exit** The emergency evacuation procedure was confirmed.

5.2 **Duties of members** Members had been provided details of their duties as experts on a British Pharmacopoeia Working Party.

5.3 **Working Party membership** The Working Party membership and contact details had been provided.

5.4 **Freedom of Information** Members were reminded that freedom of information requests should be referred to the Secretariat.

6 Minutes

The minutes and summary minutes of the meeting held on the 18th May were agreed.

The notes from the teleconference held on the 2nd October were agreed.

7 Matters arising from the minutes

None.

8 Discussion Papers **BIO-DPS(18)11**

8.1 a. Progress review

Dr Kemp presented an overview of the work party's objectives and progress to date. A matrix which mapped each of the agreed alternative approaches against a task list was prepared and key areas to be agreed by the working party in order to facilitate progress were highlighted.

Members noted that each of the alternative approaches were not necessarily mutually exclusive and the boundaries between each were unclear in certain instances – all agreed that open minds needed to be kept about how a final standard may look. Dr Varley agreed and stated that the group needed a starting point for the alternative approaches which are likely to evolve with time.

In addition to glycosylation and high molecular weight variants, Dr Varley raised the possibility of the charge variants quality attribute being investigated by the group as it was noted as being very important.

Dr Kemp noted that the scope of the structural class needed to be further defined (e.g. mAbs, IgG1s etc.) and that the functional class concept required more discussion as it was the least developed. Dr Kemp stated that a key milestone in the project is having draft standards agreed on paper before experimental evaluation.

8.2 b. Performance-based draft **BIO-DPS(18)12**
Annexes 1-4

Dr Kemp presented a draft performance-based standard which utilised the analytical target profile (ATP) concept. An overview of ATPs, measurement uncertainty and the analytical method lifecycle concept was given.

Dr Randon noted the overlap between the terms "performance" and "method capability" and suggested that the terminology needs to be further clarified. Dr Randon also mentioned that the high molecular weight variant test should specify the peak to be measured (e.g. "dimer").

Dr Cook highlighted that the context of the method is important – different techniques may be used depending on circumstance and one ATP may not be appropriate for all techniques. Mr Gibb questioned how true equivalence between methods could be demonstrated.

8.3 c. Method capability-based draft **BIO-DPS(18)13**
Annexes 1-2

Dr Cowper explained how the draft method capability standard was developed. He also presented a summary of the challenges of glycan analysis. In particular, he noted how multiple techniques may be required in order to fully characterise glycosylation of proteins. Dr Cowper noted that the draft limits included for the standard are based on the NISTmAb, however if the concept was officially agreed, it would be likely that a unique BP/NIBSC physical reference standard would be developed and fully characterised.

Dr Varley stated that there is no generally applicable consensus technique to use for glycan analysis. Members agreed that standard flexibility is essential, and some members noted that a class-based approach is a potential solution.

Mr Giartosio remarked that most quality attributes would not be applicable across “mAbs” as a class – most quality attributes would require further division into sub-classes of mAbs.

Dr Cowper questioned how sensitive analytical methods need to be (with regard to glycans) and commented that it wouldn't be productive to stipulate something which is not clinically significant in a given product. Dr Ramzan noted the potential for pharmacopoeial methods to be over prescriptive with respect to biological products.

Dr Cowper asked whether, or how much, guidance should be provided as part of the standard – it could be very useful for peak identification in glycan analysis and demonstrates the value of a well-characterised physical reference material. Dr Cowper mentioned that if a method was capable of resolving two or more particularly close-eluting peaks in a reference standard, then this could serve as an indication of the overall capability of method for peak resolution in general (i.e. system suitability). Dr Varley questioned whether the ability of a method to detect substances that are not in a product is indicative of the suitability of the method to detect unrelated peaks. Members raised the possibility of using defined glycan reference materials.

8.4 d. Structural class-based draft(s) **BIO-DPS(18)14 Annex 1**

Dr Wild presented a draft standard which combined structural class, performance and method capability concepts as applied to the glycosylation quality attribute. The standard was based on a large study which investigated the variation of glycan values using different techniques in different laboratories. Dr Wild noted that the group had been considering standards in terms of products or classes, but questioned whether the quality attributes should be the starting point instead.

Dr Ganeva highlighted that common guidelines (e.g. ICH Q2) are currently applied to methods and questioned at what stage in the product lifecycle, such standards would be used (e.g. characterisation, development, post-authorisation). Mr Pound stated that pharmacopoeial standards are only applicable to authorised products. Dr Cook noted that although they are not legally applicable, pharmacopoeial standards can be useful to manufacturers pre-authorisation, and an understanding of the requirements is very useful for planning ahead.

Dr Jordan noted that Amgen had been working with the USP on method capability type approaches and raised the possibility of a standard containing several methods – of which one could be chosen by the manufacturer to demonstrate compliance (a so called “menu”). He

noted that the Ph. Eur. Infliximab Concentrated Solution monograph prescribed methods and that manufacturers needed to provide justification if those methods were not used. Mr Pound raised the possibility of including ATPs for each technique, as opposed to specific methods for each technique.

8.5 e. Functional/Structural class-based draft **BIO-DPS(18)15 Annex 1**

Dr Randon presented his ideas for a class-based monograph. The concept was based on categorising molecules by common quality attributes and utilised a modular ("building-block") approach. Information from prior knowledge would be included in the standard and guidance would be provided indicating the appropriate types of control and analytical techniques/methods. The benefits of such an approach were listed as being: mutual understanding of relevant quality attributes, forms part of a control strategy to ensure quality, facilitating alignment between regulatory assessors and minimising justification of each quality attribute in each product. Dr Randon stated that a class-based pharmacopoeial standard could provide more detail to regulators/manufacturers than current regulatory guidelines. Dr Ganeva noted that the criticality of quality attributes should be determined by regulatory assessors who can consider the product as a whole, rather than being determined by pharmacopoeias.

Dr Randon highlighted that this was a "top-down" approach, as opposed to traditional monograph approaches which were considered "bottom-up". Members agreed that prior knowledge was an essential part of the development process and that the pharmacopoeia could add value by further supporting knowledge management. Members considered that this support of knowledge management would not need to include reproducing other publicly available guidelines, but could offer more insightful/specific information. Mr Pound emphasised that the purpose of the pharmacopoeia was not entirely to facilitate regulatory submissions by industry and included other important applications as a common quality standard (e.g. use by OMCLs, customs checks etc.).

Dr Jordan presented his ideas for a class-based monograph. Dr Jordan suggested that a class-based concept didn't have to be restricted to mAbs but could apply broadly to all biologics. He suggested that a class-based approach could describe specific, defined quality requirements in some areas and broader guidance in others. Members noted the overlap with Dr Randon's presentation and the modular approach. Dr Jordan presented an inverted pyramid style approach with a broad requirement for certain quality attributes at the top and more specific requirements at the lower tip of the pyramid. Specific, functionality-based tests could be situated at the tip of the pyramid.

Dr Ganeva remarked that the approach was similar to how license assessors review regulatory submissions by picking out critical quality attributes. Members suggested that this approach would promote standardisation across regulators.

Members noted that the presented approach was not mutually exclusive with performance/method capability concepts. Members also commented that an alternative standard should provide the answers to at least two key questions in order to ensure a minimum level of quality: are you analysing the correct things? And, is your method

performing correctly? Members agreed that each of these questions could be addressed by a pharmacopoeial quality standard which provided defined attributes to analyse (e.g. as described in a class-based approach) and method performance criteria (e.g. accuracy/precision as described in a performance-based approach).

Dr Varley highlighted the need for testing the approach with a real worked example. A pilot laboratory study on a licensed product would present several benefits, including: enabling any unforeseen issues to arise, provide scientific data to justify an alternative standard and providing a clear example that users would be able to follow.

8.6 f. Laboratory evaluation draft plan **BIO-DPS(18)16 Annex 1**

Dr Kemp presented a stimulus plan for how the laboratory evaluation phase of the project could look, using multiple products, methods and laboratories.

Dr Cook noted that the Secretariat should refer to other standards institutes for guidance on how to carry out any experimental work. He also stated that the purpose of the laboratory work should be clearly defined up front. Members agreed in principle to donating laboratory resource and samples, once a laboratory protocol was finalised.

Members agreed to keep the scope relatively simple to start with and suggested to limit work to IgG1s for the moment. Members identified that there were likely to be challenges to overcome, but it was noted that the learning gained would help develop the approaches.

Mr Pound noted that this would be a good opportunity to examine how broad and generic an ATP could be.

Mr Giartosio noted that the plan looked at what the method could achieve, not whether it was fit for purpose. He stated the need to look at the method in conjunction with the quality attributes to determine if the method was controlling what it needed to control.

ACTION: The Secretariat to work with MHRA colleagues and Working Party members to further develop “top-down” and “bottom-up” approaches. The latest iterations of these concepts would be discussed at the next face-to-face meeting in May 2019 (date tbc).