BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group BIO: Biological and Biotechnological Products

SUMMARY MINUTES

A meeting of the Expert Advisory Group was held at 151 Buckingham Palace Road, Victoria, London SW1W 9SZ on Thursday 6th November 2014.

Present: Dr L Tsang (*Chair*) (part of meeting), Dr P Varley (*Vice-chair*), Dr A Bristow, Prof D H Calam, Dr L Findlay, Mr S Gill, Dr E Griffiths, Dr B Patel, Mr P Sheppard, Dr A Thomas, Mr W Tarbit, Dr R Thorpe.

In attendance: Dr R A Pask-Hughes, Mr A Gibb.

Mr M Whaley and Mr S Young attended the meeting for items BIO(14)04 and BIO(14)22.

Apologies for absence were received from Dr J Cook, Dr A M Pickett, Mr T Pronce, Mr I Rees, Dr T Sesardic and Dr J Tettey.

Dr Tsang chaired the discussions on Items BIO(14)1 to 16 and BIO(14)22.

Dr Varley chaired the discussions on Items BIO(14)17 to 28.

Opening Remarks

Welcome The Chair welcomed everyone to the meeting. Members introduced themselves and gave brief overviews of their background experience in relation to the work of the EAG.

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

Declaration of Interests The Chair asked members to declare any interests at the start of the meeting and prior to the relevant agenda item.

I MINUTES

228 The minutes of the meeting held on 5th November 2013 were confirmed.

II MATTERS ARISING FROM THE MINUTES

229 A list of matters arising from the minutes of the meeting of EAG BIO held on 5th November 2013 had been provided. A copy is attached.

III REPORTS AND CORRESPONDENCE

230 General Matters BIO(14)1

Emergency exit The emergency evacuation procedure was confirmed.

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

Retention of past papers/minutes The Secretariat highlighted relevant guidance concerning the retention and disposal of all papers. Retained papers were to be stored in a secure and confidential manner and, when no longer required, to be securely destroyed.

EAG membership review A review of the membership of all BP groups had taken place and members would be contacted directly regarding their appointment. The membership term of new and re-appointed members was to start on the 1st January 2015 and last for 4 years.

Specialist membership A number of "specialist" members would be appointed for EAG BIO. These members would be provided with all of the EAG papers and correspondence items, but would only be invited to attend meetings if the agenda included items related to their area of expertise.

BIO membership list Members were asked to inform the Secretariat of any changes to their contact details.

BP Annual Report This report was available on the MHRA website.

231 Work Programmes: Ph Eur and BP Biologicals Update BIO(14)2

Work Programme The current work programme was noted.

BP 2015 The new and revised texts related to the work of the EAG that had been published in the BP 2015 were noted.

European Pharmacopoeia The current work programmes relevant to the work of EAG BIO were noted.

232 BP 150th Anniversary BIO(14)3

The events marking 150th Anniversary of the BP had taken place during the week starting 7 April 2014 and the Secretariat highlighted specific activities that had occurred as part of this. These meetings had included a number of bilateral meetings with other pharmacopoeial authorities.

233 Bacterial Endotoxin Testing – BP Policy BIO(14)4

Ph. Eur. policy The EDQM had published in the September 2014 issue of 'Pharmeuropa: Useful information' a policy document related to bacterial endotoxins policy in the Ph. Eur. related to substances for pharmaceutical use. This policy had been approved at the June 2014 Ph. Eur. Commission meeting and had been supported by the UK Delegation and the UK representative of the Ph. Eur. Working Party BET. The policy was also applicable to biological and products derived from fermentation processes.

BP Policy Members agreed that the BP policy should be aligned, as far as possible, with that adopted by the Ph. Eur. Commission. For new BP Monographs, if the use of a specific method was required, this should be included without a corresponding limit. For existing BP monographs that included a test and limits, no change was necessary.

234 Biological Qualifiers BIO(13)5

The EAG noted the consultation document published by the WHO concerning the development of a system of assignment of Biological Qualifiers to biological substances.

235 Vaccine Abbreviation BIO(14)6

A new Ph. Eur. monograph for Diphtheria, Tetanus and Pertussis (Acellular Component) Vaccine (Adsorbed, Reduced Antigen(s) Content) had been published in Supplement 8.2 and included in the BP 2015. Members endorsed that the proposed abbreviation, dTaP, should be included in the BP header to the monograph, subject to confirmation from the Immunological section at the Department of Health. It was noted that the use of a lowercase 'd' distinguished the product as being a lower strength dose of the diphtheria toxoid, used for the primary immunisation in individuals 10 years old or over. Higher strengths of the diphtheria toxoid were used for primary immunisation of children under 10 years of age.

The background to the inclusion of abbreviations was briefly discussed. National abbreviations were used due to the long names of multicomponent vaccines and the consequential risk of the wrong vaccine being dispensed and used. Information was provided that there had been no further developments in the development of a WHO international vaccine abbreviation scheme.

236 Insulin Glargine Injection BIO(14)7

The monograph had been published in the BP 2015. With the approval of the Chair and Vice-chair a number of changes had been made to the monograph prior to publication and these were highlighted to members.

237 Heparin and Low-Molecular Weight Heparins: Related Substances BIO(14)8

It was recommended that, in line with BP policy, the monographs for Dalteparin Sodium Injection, Enoxaparin Sodium Injection, Heparin Injection and Tinzaparin Sodium Injection should be revised to include a test for Related substances.

Heparin Flush preparations Further information and the approach for quality control would be sought.

238 Bovine Heparins BIO(14)9

Further information would be sought on the need to develop a monograph.

IV NEW MONOGRAPHS

239 Danaparoid Sodium Injection BIO(14)10

The draft monograph would be included in a future BP publication, subject to comments from manufacturers.

V MONOGRAPHS IN PROGRESS

240 Interferon Alfa-2b Injection BIO(14)11

The draft monograph would be included in a future BP publication, subject to comments from manufacturers.

241 Interferon Beta-1a Injection BIO(14)12

The draft monograph would be included in a future BP publication, subject to comments from manufacturers.

242 Follitropin Injection BIO(14)13

The draft monograph would be included in a future BP publication, subject to comments from manufacturers.

243 Desmopressin Nasal Spray BIO(14)14

The draft monograph would be included in a future BP publication, subject to comments from manufacturers.

244 Desmopressin Oral Powder BIO(14)15

The draft monograph would be included in a future BP publication, subject to comments from manufacturers.

245 Pancreatin Preparations BIO(14)16

The draft monographs would be included in a future BP publication, subject to comments from manufacturers.

VI REVISION OF MONOGRAPHS

246 Enoxaparin Sodium Injection BIO(14)17

Sodium (limits) The Secretariat had examined the published limits of 11.3 to 13.5%, which were harmonised with those in the Ph. Eur. monograph for Enoxaparin Sodium, following a user query. As the quantity of drug substance used in the manufacture of the formulation was adjusted to achieve the necessary potency, the resulting product might fail to meet the narrow Sodium limits in the formulation monograph.

In order that products produced from drug substance at the upper and lower limits were accounted for in the formulation monograph the following revised wording was accepted:

‘***Sodium***
10.2 to 16.9% per mg of Enoxaparin Sodium, when determined by atomic absorption spectrophotometry, Appendix II D Method I. For the purposes of this test, assume that 100 U of anti-factor Xa is equivalent to 1 mg of Enoxaparin Sodium.’

The revised test would be published in the BP 2016, subject to comments from manufacturers.

Sodium (method details) Sample preparation and other method details, such as measurement wavelength, were not included in the published monograph. This was consistent with the approach taken in the monograph for Enoxaparin Sodium but inconsistent with the details included for atomic emission spectroscopy methods in other monographs. The Secretariat undertook to investigate if further information should be included.

247 Insulin Aspart Injection BIO(14)18

Identification A member of the BP Commission had noted that the Identification requirement consisted of a single HPLC Assay cross-reference and had suggested that an alternative method should be included.

It was agreed that the suggestion be noted and included in any future laboratory requisition placed for the formulation.

Related proteins No disregard limits had been included in the published test, which was based on that in the Ph. Eur. monograph for Insulin Aspart. The Secretariat had contacted the manufacturer and the EDQM to seek the reason for the absence of the limit and to seek appropriate limits for inclusion in the monograph.

248 Goserelin Implants BIO(14)19

A revised monograph had been published in the BP 2015 to include changes to the preparation of the solutions used in Related substances tests A, B and C.

Following advice from a manufacturer further revision proposals had been drafted for discussion.

Drug release The published instruction to measure the average absorbance had been considered ambiguous. The instruction had been revised to specify that individual absorbance readings should be recorded at 1 nm intervals and the average taken of these readings. This approach was stated to improve the signal-to-noise ratio.

Related substances (tests A, B and C) Solution (2) had been revised to replace the use of *goserelin EPCRS* with a dilution of the test solution. This was in-line with the usual BP Commission policy for limit solutions. The manufacturer had confirmed that a dilution of the test sample was suitable for quantification of impurities.

Related substances (test A) For the convenience of the analyst, the approximate retention time of goserelin had been included together with the relative retention of 4-D-Ser-goserelin.

Related substances (tests B and C) A limit for the sum of impurities observed in tests B and C was included in the published monograph but no corresponding disregard limits had been included. The tests had been revised to include a 0.05% limit of quantification and solutions at the corresponding concentration.

The drafted changes were accepted for inclusion in the BP 2016, subject to any further comments from manufacturers.

249 Heparin Injection: Identification and Assay BIO(14)20

The Ph. Eur. method for the Assay of Heparin (2.7.5, BP Appendix XIV J B2) had been revised in Supplement 8.3 of the 8th Edition of the Ph. Eur. The delayed clotting of recalcified citrated sheep plasma method had been replaced with the determination of anti-factor IIa activity and ratio to anti-factor Xa activity.

Comments had been received from a manufacturer confirming the suitability of the revised method to Heparin Injection. Other manufacturers did not anticipate issues in applying the revised method to their products. A draft revision, including consequential changes to Identification A, was accepted.

The drafted changes were accepted for inclusion in the BP 2016, subject to any further comments from manufacturers.

VII FUTURE OF BIOLOGICAL MATERIALS IN THE BRITISH PHARMACOPOEIA

250 Future of Biological Materials in the British Pharmacopoeia BIO(14)21

A draft policy was discussed and further information would be sought.

251 1. MHRA merger with NIBSC BIO(14)22

Proposed work to increase collaboration between the BP and NIBSC was discussed.

252 2. Review of the mechanism of monograph development BIO(14)23

A draft policy was discussed and further information would be sought.

253 3. Collaboration with other pharmacopoeias BIO(14)24

Feedback was given on collaborative activities discussed with other pharmacopoeial authorities.

VIII EUROPEAN PHARMACOPOEIA

254 Comments from the British Pharmacopoeia Commission BIO(14)25

Members noted that comments from the BPC had been sent to Strasbourg on proposals for new and revised Ph. Eur. texts included in Pharmeuropa Volumes 25.3, 25.4 and 26.1.

255 Comments requested from members on draft texts BIO(13)26

Members were thanked for the comments they had submitted on the monographs published in Pharmeuropa 26.3. Members were reminded that comments on draft texts included in

Pharmeuropa Volume 26.4 should be submitted by 31 December 2014 either by using the BP Website forum or contacting the Secretariat directly.

Pharmeuropa 26.4 included the draft text for the new General Chapter 5.2.12 Raw materials for the production of cell-based and gene therapy medicinal products.

256 Texts adopted at the 147th, 148th and 149th Sessions BIO(13)27

Lists of the documents relevant to the Group that had been adopted at the 147th, 148th and 149th Sessions of the EPC were provided to members for information.

257 Groups of Experts: Formal reports BIO(13)28

The formal reports and summaries of decisions relevant to the work of EAG BIO were noted.

IX ANY OTHER BUSINESS

258 EDQM 50th The BP Secretariat highlighted some of the discussions that had taken place at the EDQM's 50th anniversary celebrations related to biologicals.

Date of Next Meeting: Thursday 3rd September 2015.

British Pharmacopoeia Commission
Panel of Experts BIO: Biological and Biotechnological Products

II – MATTERS ARISING

Matters arising from the Minutes of meeting held 5th November 2013
(other than those appearing on the Agenda)

Minute 201	**Similar Biological Medicinal Products (Biosimilars)**	The Secretariat were continuing to investigate what changes were necessary to the BP guidance in the Supplementary Chapter III B (Monograph Development: Mechanisms) and Supplementary Chapter IX (Similar Biological Medicinal Products) following the replacement of the UK specific Black Triangle Scheme with the EU Additional Monitoring Scheme. Any changes proposed were to be put to EAG BIO for discussion at a future meeting.
Minute 204	**Viral safety of urine derived materials in the pharmacopoeia**	The production statement in the BP monograph for Menotrophin had been amended in the BP 2015 to more closely match the approach taken in the Ph. Eur. urine-derived material monographs. The Secretariat had confirmed with the EDQM that inconsistencies in the specific viral antigen tests included in the various monographs was as a result of the monographs being written independently and at different periods of time. The approach taken to reviewing the viral antigen tests included in the monographs was to be reconsidered once the draft EMA Guideline on the adventitious agent safety of urine-derived medicinal products had been adopted.
Minute 214	**Desmopressin tablets** (revision)	**Uniformity of content** The correction to the mobile phase was to be included in material for the BP 2016 edition.
Minute 223	**Recombinant DNA Technology revision request**	The UK request for revision had been made.

List of Acronyms/Synonyms for use by BP Secretariat

Acronym/Synonym	Name
BAN	British Approved Name
BP	British Pharmacopoeia
BP (Vet)	British Pharmacopoeia (Veterinary)
BPC	British Pharmacopoeia Commission
BPCRS	British Pharmacopoeia Chemical Reference Substance
BRP	Biological Reference Preparation
BSP	Biological Standardisation Programme
CHM	Commission on Human Medicines
CRS	Chemical Reference Substance
EAG	Expert Advisory Group
EDQM	European Directorate for the Quality of Medicines & HealthCare
EPBRP	European Pharmacopoeia Biological Reference Preparation
EPC	European Pharmacopoeia Commission
EPCRS	European Pharmacopoeia Chemical Reference Substance
EU	European Union
FIP	International Pharmaceutical Federation
FOI	Freedom of Information
GC	Gas chromatography
ISO	International Organisation for Standardisation
LC	Liquid chromatography
LD	Licensing Division
LGC	Laboratory of the Government Chemist, Teddington
LR	BP Laboratory Report
MHRA	Medicines and Healthcare products Regulatory Agency
NIBSC	National Institute for Biological Standards and Control
NOAH	National Office of Animal Health
NPA	National Pharmacopoeial Authority
OMCL	Official Medicines Control Laboratory
Ph. Eur.	European Pharmacopoeia
TGA	Therapeutic Goods Administration, Australia
TLC	Thin layer chromatography
UK	United Kingdom
UKD	United Kingdom Delegation [to the European Pharmacopoeia]
USP	United States Pharmacopeia