BRITISH PHARMACOPOEIA COMMISSION

Expert Advisory Group BIO: Biological and Biotechnological Products

SUMMARY MINUTES

A meeting of the Expert Advisory Group was held at 10 South Colonnade, Canary Wharf, London E14 4PU on Friday 7th September 2018.

Present: Dr P Varley (*Chair*), Dr A M Brady *(Vice Chair)*, Mr S Gill, Dr B Patel, Mr L Randon, Dr R Thorpe, Dr E Griffiths.
J Hogwood and Dr E Gray contributed to the meeting by teleconference for item BIO(18)04.

In attendance: Mr A Gibb, Dr A Gardiner.

Apologies for absence were received from P Sheppard, Dr C Burns and Dr L Tsang.

Opening Remarks

Welcome The Chair welcomed everyone to the meeting and noted that Dr Radi had left the Agency since the Group's last meeting. Dr G Kemp was now supporting the EAG.

Dr Adrian Thomas The Chair noted the sad and untimely passing of Dr Thomas and gave some remarks regarding his enormous contribution to the group and the Agency as well as to him personally. A minute's silence was held by the group in respect of Dr Thomas.

Dr E Griffiths The Chair noted that it would be Dr Griffith's last meeting, as he had decided not to continue his membership for the following 4-year term. The Chair thanked Dr Griffiths for his valuable contributions over the several years of his membership.

Membership The Secretariat had been carrying out a membership review of all of the EAGs, panels and working parties of the British Pharmacopoeia and Dr Gardiner provided a verbal update relating to EAG BIO.

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

Mr Randon and Dr Patel declared an interest in one or more agenda items and appropriate action was taken.

326 General Matters BIO(18)01

Emergency exit The emergency evacuation procedure for the new building was confirmed.

BIO membership list Members were asked to inform the Secretariat of any changes to their contact details. The current contact details were circulated for checking at the meeting.

I MINUTES

327 The minutes of the meeting held on 17th November 2017 were confirmed.

II MATTERS ARISING FROM THE MINUTES

328 It was noted that all items arising from the minutes of the meeting of EAG BIO held on 17th November 2017 had been accounted for within the papers.

III EAG BIO STRATEGY

329 Agency Strategy for Pharmacopoeial Biological Standards BIO(18)02

The Secretariat updated members on the ongoing implementation of the MHRA's strategy for pharmacopoeial quality standards for biological medicines as well as the outcomes of the workshops held at the 2017 meeting of the EAG.

IV MONOGRAPHS IN PROGRESS

330 Erythropoietin Injection BIO(18)03

Members were reminded that the replacement of the BRP with two new EPCRS in the monograph had been discussed at the previous meeting. Members had endorsed the change in principle but raised concerns such as the concentrations used.

Identification B The concentration of EPCRS used had been amended in conjunction with colleagues from NIBSC. Members agreed with the proposed changes.

Dimers and related substances of higher molecular weight – method A The concentration of EPCRS used had been amended in conjunction with colleagues from NIBSC. Additionally, further minor changes to the method were suggested. Members agreed with the proposed changes.

Dimers and related substances of higher molecular weight – method B The group agreed the method should be retained.

Laboratory risk assessment In order to address whether laboratory evaluation would be required to introduce the EPCRS into the monograph methods, the Secretariat presented a laboratory risk assessment to the group. The group commended the use of the risk assessment tool but raised concerns about its application to biological medicines due to their complexity and unpredictability. They therefore recommended that a laboratory investigation was required to ensure the EPCRS was appropriate for the method.

331 Heparin Monographs BIO(18)04

ENOXAPARIN SODIUM INJECTION
DALTEPARIN SODIUM INJECTION
TINZAPARIN SODIUM INJECTION
HEPARIN INJECTION

Size exclusion chromatography identification method (Low molecular weight Heparins) Members agreed that the method should be updated in line with the European Pharmacopoeia low molecular weight heparin monograph as drafted. The revision replaced the existing calibration of the chromatographic system with the Broad Standard Table method, as well as changing the eluent buffer.

Zone electrophoresis identification method (Heparin Injection) The Secretariat noted that Identification C in the Heparin Injection monograph was outdated, and procurement of the necessary equipment was difficult which had led to user queries. The Secretariat agreed to investigate the feasibility of including the NMR method in the monograph.

Related substances – suggested column (All four monographs) Correspondence from a manufacturer had highlighted that there was a typographical error in both the pre-column and guard column suggested within the monographs. This had been verified by the Secretariat and group agreed that the error should be corrected.

Related substances – Injection volume (Heparin Injection) The Secretariat explained that solution (1) of the related substances method included different dilutions for the different strengths available of Heparin injection, resulting in a sample solution of either 5000 IU/mL or 1000 IU/mL, however in all cases the monograph gave an injection volume of 20 µL, leading to a discrepancy in the amount of sample loaded, which was not adjusted for when calculating the amount of impurities. The group agreed that the monograph should be amended.

Related substances - incorrect limit for dermatan sulfate and chondroitin sulfate (all four monographs) A number of user queries had highlighted a calculation error in the dermatan sulfate and chondroitin sulfate limits within the BP Heparin and LMWH Injection monographs, which the Secretariat had investigated. The Secretariat proposed wording to correct the error, which the group endorsed.

Related substances – disregard limit (all four monographs) Members were reminded that inclusion of a disregard limit had been endorsed at the 2017 meeting of EAG BIO, to align with the Ph. Eur. heparin monographs. The revision had been put on hold while the dermatan sulfate and chondroitin sulfate limit matter was being resolved. Members agreed that these peak areas were too small to be practicable and agreed that the current wording should be retained. It was acknowledged that the change of wording from Ph. Eur. was included to make the requirement clearer, rather than due to any technical difficulties users had experienced in meeting it.

The Secretariat noted that publishing a notice of intent on the BP website to alert users of the planned changes would be helpful, this was supported by the group.

332 Interferon Alfa-2b Injection BIO(18)05

Members discussed issues relating the Interferon Alfa-2b Injection monograph and recommended the monograph be put forward for omission.

333 Interferon Beta-1a Injection BIO(18)06

Members were reminded that at the 2017 meeting of EAG BIO, the Secretariat reported that a new BCPRS had been established in conjunction with NIBSC. The monograph had been revised to include the BPCRS in the BP2019. Stakeholder comments had been received and the group discussed proposed revisions to several sections of the monograph.

BPCRS concentration The laboratory assessment of the BPCRS had identified an error within the concentration of the BPCRS required. The monograph had stated 0.01% BPCRS, which the Laboratory found was insufficient. It was discovered that the intended concentration should have been 2%, which was verified in the Laboratory. The group were informed that the monograph had been amended to reflect the correct concentration. The information had also been included in the BPCRS leaflet to aid users.

Injection volume It had been noted that volume injection given in the monograph, "*Inject a volume of each solution containing 20 μg of digested protein"* was not applicable to the BPCRS. The BP Laboratory had found that an injection volume of 70μL was appropriate, and the group agreed this information should be included within the monograph.

Oxidised forms limit The limit in the monograph had been based on the amount of the oxidised form of the peptide fragment 34 to 45. The group agreed that the limit should be clarified to specify the 34 to 45 fragment.

Characteristics A manufacturer requested that as the solution of interferon might appear slightly yellow or opalescent wording of this section is changed from to "Clear or slightly opalescent, colourless or slightly yellowish liquid". The group endorsed this change.

Specific strength limit changes The manufacturer highlighted that for both the test for dimers and the content assay, their lowest strength product had wider specifications than the monograph. Members agreed it was important that the monograph limits were in line with the licensed specifications of the products on the UK market. The group recommended specifying within the monograph wider limits for products with a low strength.

334 Oxytocin Injection, Ergometrine and Oxytocin Injection BIO(18)07

The group were informed that the Oxytocin Injection and Ergometrine and Oxytocin Injection monographs contained an outdated assay method and no control of oxytocin related substances. There were 6 UK MAHs for oxytocin injection and 1 UK MAH for the combination product.

User queries Several queries from users had highlighted issues with meeting the system suitability requirement for the assay method. The BP Laboratory had been asked to carry out the method to determine whether the requirement should be changed. The Secretariat would communicate with members by correspondence when the Laboratory recommendation had been received.

Monograph update The Secretariat had contacted the UK MAHs of the products to request their in-house Assay and Related substances methodology in order to update the monograph. Two datasets had been received. A laboratory risk assessment had been carried out and the group had recommended the methodology be confirmed in the BP Laboratory.

VII WORK PROGRAMME AND EUROPEAN PHARMACOPOEIA

335 Work Programmes: BP and Ph. Eur. Biologicals Update BIO(18)08

New and revised BIO monographs included in the BP2019 Members were informed that two new and six revised BIO monographs had been included in the BP 2019. The edition was published on August 1st and will be implemented on 1st January 2019.

Work Programmes The work programmes of the expert group, as well as the relevant European Pharmacopoeia expert groups had been included in the papers for the meeting.

336 Comments from the British Pharmacopoeia Commission BIO(18)09

Members noted that comments from the BP Commission had been sent to Strasbourg on proposals for new and revised Ph. Eur. texts included in Pharmeuropa Volumes 29.3 and 30.2.

337 Comments Requested from Members on Draft Texts BIO(18)10

Members were thanked for their comments into Pharmeuropa documents over the past year. It was noted that Pharmeuropa 30.3 did not contain any texts relevant to the group.

338 Texts adopted at the 159th, 160th and 161st Sessions BIO(18)11

Lists of the documents relevant to the Group that had been adopted at the 159th, 160th and 161st Sessions of the EPC were provided to members for information.

339 European Pharmacopoeia Commission update – Biopharmaceutical Finished Product Monographs BIO(18)12

The Secretariat updated the group on the outcomes of EDQM's biopharmaceutical finished product monographs pilot phase.

340 Groups of Experts: Formal reports BIO(18)13

The most recently available formal reports and summaries of decisions of Groups of Experts 6 and 15, and Working Parties BET, CTP, MAB and P4BIO had been made available to members electronically. Members noted that if they wished to receive previous reports the Secretariat should be informed.

VIII ANY OTHER BUSINESS

Date of Next Meeting: to be announced.

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