Work plan for the Biostatistics Working Party (BSWP) for 2018

Chairperson: Anja Schiel

Status of the work plan: December 2017 – Adopted

The activities outlined in the work plan for 2018 have been agreed considering the respective business priorities, as well as the Agency’s relocation as a result of the UK’s exit from the EU and its impact on the Agency’s business continuity, and may be subject to further review and reprioritisation in accordance with the business continuity plan of the Agency.

1. Meetings scheduled for 2018

Face-to-face meetings are planned for the following dates

- 08-09 March 2018
- 04-05 October 2018

Virtual meeting dates:
- 16 January 2018
- 13 February 2018
- 13 March 2018
- 17 April 2018
- 22 May 2018
- 19 June 2018
- 12-13 July 2018
- 17 July 2018
- 11 September 2018
- 09 October 2018
• 06 November 2018
• 04 December 2018

The above mentioned dates may be modified as needed. Additional virtual meetings may be organised ad hoc to respond to time-sensitive requests on products and to progress guidelines, as required.

2. Guidelines

2.1. New EU Guidelines

Action: Lead

Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013)

Target date: Final guideline expected to be released in Q2 2018
Comments: Comments received during the 2014 public consultation and discussed at the EMA. Working parties or SmPC Advisory Group to be consulted.

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017)

Target date: Comments on the reflection paper received during the public consultation will be discussed in 2018
Comments: The reflection paper was developed in collaboration with the CHMP Biologics working Party (BWP), the Biosimilar Medicinal Products Working Party (BMWP), the Quality Working Party (QWP) and the Scientific Advice Working Party (SAWP). The Pharmacokinetics Working Party (PKWP) will also contribute to further discussion related to this RP focussing on sections 4.3 (Other settings and generic developments) and 6.3 (Specific issues for generic/hybrid developments and dissolution comparisons).

Action: Specialised input

Reflection paper on the investigation of suicidal ideation and behaviour

Leading group: Central Nervous System Working Party (CNSWP)
Target date: Draft reflection paper to be released for a 3-month public consultation Q3 2018
Comments: New reflection paper to reflect on current scientific developments. Contribution to the development of this reflection paper.
Reflection paper on extrapolation of efficacy and safety in medicine development (EMA/199678/2016)

Leading group  Extrapolation Working Group
Target date  Final reflection paper to be published in Q2 2019
Comments  Draft reflection paper was published in October 2017. Contribution to the development of this reflection paper.

Draft reflection Paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) (EMA/CHMP/197320/2017)

Leading group  Gastroenterology drafting group (GDG)
Target date  Draft Reflection Paper to be released in Q2 2018
Comments  Concept paper on the need for the development of a reflection paper released in June 2017. Contribution to the development of this reflection paper (i.e. on clinical trial design).

Addendum to the guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products on terminology in pharmacogenomics

Leading group  Pharmacogenomics working party (PGWP)
Target date  Draft addendum to be released for a 3-month public consultation by Q2 2018
Comments  Contribution to development of this guideline.

Guideline on the pharmaceutical quality of inhalation and nasal products (EMA/CHMP/QWP/115777/2017)

Leading group  Quality Working Party (QWP)
Target date  Draft guideline to be released for a 6-month public consultation in Q3 2018
Comments  Draft concept paper on the revision of the guideline published for public consultation (deadline for comments 30 June 2017). The proposed guideline will replace “Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products” (EMEA/CHMP/QWP/49313/2005 Corr). Request for input on identifying a suitable method to evaluate in-vitro data (fine particle dose and/or aerodynamic particle size distribution) expected. This topic is shared between this guideline and the equivalence GL for orally inhaled products (OIP) (CPMP/EWP/4151/00 Rev. 1).
Guideline on quality and equivalence of topical products (H) (EMA/CHMP/QWP/558185/2014)

**Leading group** Quality Working Party (QWP)

**Target date** Draft guideline to be released for a 6-month public consultation Q2 2018

**Comments** Public consultation of the concept paper ended 22 July 2015. The draft reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017) addresses topics relevant for this guideline and BSWP will be consulted for review in Q1 2018.

### 2.2. EU Guidelines under revision

**Action: Lead**

Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017)

**Target date** Final guideline expected to be published in Q2 2018

**Comments** This is a revision from a previous Points to Consider. The guideline was developed in collaboration with the SAWP and the Cardiovascular Working Party (CVSWP). A training of the assessors will be organised via webinar once the guideline has been finalised.

Q&A on data monitoring committees (CHMP/EWP/5872/03)

**Target date** Draft Q&A document expected to be published in Q1 2018

**Comments** The guideline was adopted in 2003. Since then there have been questions on the role and necessity for a Data Monitoring Committee (DMC) in different phases of drug development as well as with regard to the responsibilities for implementing DMC decisions. The Q&A document would provide answers to such questions.

The CVS WP and ONC WP were informed about this Q&A, and the Good Clinical Practice (GCP) Inspections Working Group (IWG) was consulted.

Finalisation of the Q&A after the public consultation period is not expected in 2018.

**Action: Specialised input**

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2)

**Leading group** Cardiovascular Working Party (CVSWP)

**Target date** Draft guideline to be released for public consultation Q1 2018

**Comments** Public consultation of the concept paper ended on 31st October 2016. Contribution to revision of this guideline.
Note on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98 rev.1).

**Leading group**  Cardiovascular Working Party (CVSWP)

**Target date**  Concept paper to be released for public consultation in Q2 2018.

**Comments**  Contribution to revision of this guideline.

Guideline on clinical investigation of medicinal products for the treatment of migraine (CPMP/EWP/788/2001 Rev. 2)

**Leading group**  Central Nervous System Working Party (CNSWP)

**Target date**  Final guideline to be released Q3 2018

**Comments**  Revision to bring the Guideline in line with the recent scientific developments. Contribution to revision of this guideline.

Guideline on clinical investigation of medicinal products in the treatment of depression (CHMP/185423/2010 Rev. 3)

**Leading group**  Central Nervous System Working Party (CNSWP)

**Target date**  Draft guideline to be released for a 6-month public consultation Q4 2018

**Comments**  Revision to bring the Guideline in line with the recent scientific developments. Contribution to revision of this guideline.

Guideline on clinical investigation of medicinal products for the treatment and prevention of bipolar disorder (EMA/CHMP/735080/2015)

**Leading group**  Central Nervous System Working Party (CNSWP)

**Target date**  Draft guideline to be released for a 6-month public consultation Q4 2018

**Comments**  Revision to bring the Guideline in line with the recent scientific developments. Contribution to revision of this guideline.


**Leading group**  Central Nervous System Working Party (CNSWP)

**Target date**  Final guideline to be released Q4 2018

**Comments**  Revision to bring the Guideline in line with the recent scientific developments. Contribution to revision of this guideline.
Guideline on medicinal products for the treatment of Alzheimer's disease and other dementias (CPMP/EWP/553/1995 Rev. 1)

**Leading group**  Central Nervous System Working Party (CNSWP)

**Target date**  Final guideline to be released Q1 2018

**Comments**  Revision to bring the Guideline in line with the recent scientific developments. Contribution to the development of the revised guideline.

Note for Guidance on the Evaluation of anticancer medicinal products in man (CHMP/205/95 Rev. 4)

**Leading group**  Oncology Working Party (ONCWP)

**Target date**  Draft revision 6 to be released for public consultation in Q3 2018

**Comments**  Contribution to the revisions that will focus on new clinical endpoints, biomarkers, interim analysis and data maturation, estimands in oncology. Revisions will take into account BSWP position on methods for treatment switch for time-to-event endpoints in oncology clinical trials.

Revision of the addendum to the guideline on evaluation of anticancer medicinal products in man - paediatric oncology (CPMP/EWP/569/02 Rev. 2)

**Leading group**  Oncology Working Party (ONCWP)

**Target date**  Final document to be released for public consultation by Q3 2018

**Comments**  Contribution to the development of the revised guideline. This document aims to complement the current guideline with specific regulatory requirements related to paediatric oncology.

Guideline on the investigation of bioequivalence (Appendix 1)

**Leading group**  Pharmacokinetics WP (PKWP) and Quality WP (QWP)

**Target date**  Q4 2018

**Comments**  This is a joint request from the CHMP Pharmacokinetics WP and the Quality WP. Following the publication of the Reflection Paper on statistical methodology for the comparative assessment of quality attributes in drug development, finalise the discussion with PKWP and QWP on the acceptability of the Mahalanobis distance for the similarity of dissolution profiles. The final output may be included in the aforementioned Reflection Paper or may form a Q&A.
Type I error control in two-stage designs in bioequivalence studies

**Leading group**  Pharmacokinetics WP (PKWP)

**Target date**  Q4 2018

**Comments**  Finalise on-going discussion related to type I error in two-stage design bioequivalence studies. The final output will most likely form a Q&A (to be confirmed).

Concept paper on revision of the guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the treatment of asthma in children and adolescents (EMA/CHMP/4151/00 Rev.1)

**Leading group**  Respiratory Drafting Group (RDG)

**Target date**  Draft guideline to be released for a 6-month public consultation in Q3 2018

**Comments**  Potential contribution to revision of the guideline in relation to revision of guideline on the pharmaceutical quality of inhalation and nasal products, EMA/CHMP/QWP/115777/2017.

Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (CHMP/EWP/9147/08)

**Leading group**  Respiratory Drafting Group (RDG) and Infectious Diseases Working Party (IDWP)

**Target date**  Draft guideline to be released for a 6-month public consultation in Q2-Q3 2018

**Comments**  Revision to bring the guideline in line with the current clinical knowledge and developments. Contribution to revision of the guideline.

Guideline on predictive biomarker-based assay development in the context of drug development and life cycle

**Leading group**  Pharmacogenomics working party (PGWP)

**Target date**  Draft guideline to be released for a 6-month public consultation in Q4 2018

**Comments**  Expert meeting with relevant stakeholders envisaged. Contribution to revision of this guideline.
2.3. ICH Guidelines

E9(R1) Addendum to statistical principles for clinical trials on choosing appropriate estimands and defining sensitivity analyses in clinical trials

**Target date**  Step 4 is planned for 2019

**Comments**  Review of comments on draft Addendum to ICH E9. Collaboration with European Commission members of the E9(R1) expert working group (EMA and CHMP).

E11A Paediatric extrapolation

**Target date**  Step 2 is planned in 2020

**Comments**  Support to the expert working group in this work that follows ICH E11(R1), the revised guideline on clinical investigation of medicinal products in the paediatric population and of the EMA Reflection paper on extrapolation of efficacy and safety in paediatric medicine development.

M9 Biopharmaceutics Classification System-based Biowaivers

**Target date**  Step 2 is planned in June 2018

**Comments**  Support to the expert working group in this work is expected in relation to methods for the comparison of dissolution profiles.

3. Medicinal Products-specific activities

3.1. Pre-Authorisation activities

- Contribution to relevant methodological and statistical aspects for the following regulatory systems.
  - Scientific Advice and Protocol Assistance upon request of the SAWP.
  - Paediatric Investigational Plans upon request of PDCO.
  - Innovation Task Force requests upon request of EMA ITF.

- Contribution to briefing meetings on statistical and methodological topics with external parties (pharmaceutical companies, academia, public/private partnership or patients’ associations) through meeting preparation or participation of experts.
3.2. Evaluation and supervision activities

Contribution to relevant methodological and statistical aspects of evaluation activities upon request of CHMP and other committees.

4. Input in European activities

4.1. Training for the network and knowledge building

Organise one or several assessor trainings in 2018 on estimands and, if possible, on other relevant methodology topics such as investigation of multiplicity, subgroups (discuss practical examples) and interim analysis, utilising the European Union Network Training Centre technical facilities.

4.2. Interactions with learned societies and specialised organisations

Organise a meeting with statistical associations.

4.3. Other input into European activities

Action: Lead

Trial integrity in the presence of interim results in on-going clinical trials

Target date Draft a regulatory position by Q3 2018

Comments Discuss methodological issues of trial integrity when interim analysis results of an ongoing trial become available and are assessed for marketing authorisation assessments. This should consider sponsor involvement, acceptability of methods to maintain integrity such as 'firewalls', and publication of results, by sponsor or by regulator (in relation to EMA Policy 0070 on the publication of clinical data for medicinal products for human use). If additional guidance is proposed, BSWP will discuss whether existing guidance documents are most appropriate to include the different aspects, or if these aspects call for the development of new guidance documents.

Collaboration with CVS WP. Other working parties of relevance for this subject, such as ONC WP, will be consulted.

Type I error control in umbrella trials

Target date Draft a position paper by Q2 2018

Comments This work stems from a number of Scientific Advice proposals. Discuss the position paper with SAWP.
Analysis of Individual Patient Data for evaluation and surveillance of medicinal products

**Target date**  
Draft a regulatory position by Q2 2018

**Comments**  
Identify areas where scientific assessment can be extended to visualisation or analysis of IPD.  
Investigate mechanisms that can leverage current analytical capabilities in the network, and ways to develop it in the future.  
Collaboration with other working parties as appropriate.

*Action: Specialised input*

Clinical aspects of biosimilarity

**Leading group**  
Biosimilar Medicinal Products Working Party (BMWP)

**Comments**  
Discussion on methodological elements related to clinical aspects of biosimilarity.

5. **Input in International activities (beyond ICH guidelines)**

5.1. **Activities with other regulators**

**Meetings with FDA**

Organise a meeting twice a year during BSWP face-to-face meetings via teleconference with FDA statisticians to discuss methodological issues. The objective is to foster methodological interaction on topical subjects (e.g. related to guidelines under development).

6. **Contribution to dialogue and engagement with stakeholders and external parties**

6.1. **Workshops**


This workshop will discuss comments received during the public consultation and will have an impact on the finalisation of the document.

*In addition to the actions identified above, the working party can be involved in any other activities foreseen in its mandate:*