19 December 2018
EMA/854939/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for medicinal products for human use (CHMP)

ORGAM[1] Minutes for the meeting on 5 November 2018

Chair: Harald Enzmann – Vice-Chair: Bruno Sepodes

Health and safety information

In accordance with the Agency's health and safety policy, delegates are to be briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed.

Of note, the minutes are a working document primarily designed for CHMP members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

[1] The CHMP ORGAM is a meeting to discuss CHMP organisational matters. It is a virtual meeting, which usually takes place on Monday before the CHMP Plenary meeting. CHMP members, working party chairs and national experts together with EMA staff are participating in this forum. Depending on the nature of the issue and availability of documents and experts some ORGAM topics can be discussed at the CHMP Plenary. Please note that the ORGAM meeting is not taking place every month.

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1. Agenda and Minutes

1.1. Welcome and declarations of interest of members, alternates and experts

1.2. Adoption of agenda

CHMP ORGAM agenda for 05 November 2018 meeting was adopted.

1.3. Adoption of the minutes

CHMP Orgam Minutes of 05 November 2018 meeting were adopted at the November 2018 CHMP plenary.

2. Working Parties, Committees, SAGs and Drafting Groups

2.1. General

2.1.1. Safety Working Party (SWP)

Chair: Jan Willem Van der Laan

Draft Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1)
Action: For adoption for 7-month public consultation

Laila Sortvik Nilssen presented the guideline. The guideline revision reflects the work of SWP-led Drafting Group including European experts from both environmental and pharmaceutical side.

There were the following substantial changes in the guideline:

- Decision tree approach to identify substances for which a phase I and possibly phase II ERA is required (Figure 2 in GL). Decision tree follows the Directive and requests ERA for all MAAs, independent of the legal basis for the application.
- Broadening of the definition of endocrine active substances (EAS). Current guideline only focuses on potential sexual endocrine disrupting compounds. Proposal is to include all active substances where evidence of effect on development or reproduction can be linked to steroid hormone pharmacology in a weight of evidence approach. Tailored testing strategy based on mechanism of action is described.
- Assessment of potential for secondary poisoning (SP) introduced for substances with log Kow ≥3 and BCF in fish > 100 L/kg. BCF study is requested in the current GL, but without any information on how to use the result. Desktop exercise (calculation)

that does not require additional experimental work compared to current guideline. Can be waived when mammalian toxicity data are not available in the dossier.

- Mandatory OECD 308 (Phase II/Tier A) is replaced with mandatory sediment toxicity testing. Nearly all pharmaceutical products tested meet the criterion for shift to sediment and have to be tested for water sediment effects. OECD 308 is an expensive and resource demanding test. This study is therefore now suggested to only be requested for the PBT evaluation (triggered by log Kow > 4.5), or Phase II/Tier B groundwater assessment.
- Trigger for soil assessment has been changed. The current trigger for soil assessment is Koc > 10.000 L/kg. Proposes to change to a combined trigger considering both sorption and release to waste water flow (PECsw). With this approach, substances with Koc < 10.000, but still being detected at high levels in sewage sludge, can be captured (e.g. carbamazepine).
- Search and evaluation of data. Specific guidance on search, use and evaluation of published data is suggested in the revised guideline.

There were also some structural changes in the guideline: risk assessment and PBT assessment are described separately. Risk assessment described compartment by compartment instead of Phase II Tier A followed by Tier B. The current guideline is brief and often refers to REACH. Therefore, changes were made to increase harmonisation, and facilitate work for applicants and assessors without high level expertise in particular.

The Committee discussed the ERA obligations for generics. The revised guideline should increase the consistency of assessments as it provides much clearer recommendations on how the ERA should be performed for generics. It was noted that discussions were held with EFPIA regarding the obligations for generics.

The CHMP adopted the guideline for 7-month public consultation.

Draft Guideline on the non-clinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018)
Action: For adoption for 7-month public consultation

Susanne Brendler-Schwaab presented the document. The draft guideline covers radiodiagnostics, radiotherapeutics and non-clinical requirements for clinical trial applications as well as marketing authorisation applications. The proposal is for more targeted and reduced non-clinical programme compared to ICH M3 for the non-radioactive part of a radiopharmaceutical if this was shown not to be pharmacologically active. Possible scenarios could be: the non-radioactive part is well-known, only the radionuclide is changed in the new radiopharmaceutical. A radionuclide is added to a well-known non-radioactive pharmaceutical. A new radiopharmaceutical with an only minimally changed non-radioactive part compared to an already tested non-radioactive part (e.g. change of 1 amino acid). The non-radioactive part is a new molecule, single or multiple dosing with complete wash-out between doses. In all other cases ICH M3 has to be followed.

The CHMP adopted the guideline for 7-month public consultation.

Draft Reflection paper on the qualification of non-genotoxic impurities (EMA/CHMP/SWP/545588/2017)
Action: For adoption for 10-month public consultation

Leon van Aerts presented the document. Draft reflection paper concerns the non-clinical aspects of qualification of non-genotoxic impurities. It does not change the ICH Q3A/B guidance but rather extends on it and provides an alternative approach to qualify non-genotoxic impurities. The reflection paper tries to establish a conceptual framework to facilitate future discussions among stakeholders. The reflection paper may contribute to the ongoing efforts to reduce, refine and replace animal experiments.

The CHMP adopted the reflection paper for 10-month public consultation.

SWP response to CMDh Question concerning “Diethanolamine” and “coconut oil diethanolamine condensate” as excipients (EMA/CHMP/SWP/636821/2018)
Action: For adoption

Sonja Beken presented the SWP response. The CHMP adopted the SWP response.

Final minutes for the SWP meeting held by teleconference on 18 September 2018 (EMA/CHMP/SWP/639112/2018)
Action: For information

The CHMP noted the minutes.

2.1.2. Quality Working Party (QWP)

Chair: Keith Pugh/Blanka Hirschlerova

Nomination of new alternate member: Marina-Fetita Popescu (RO) – replacing Stefania Simionescu
Action: For adoption
The CHMP nominated Marina-Fetita Popescu (RO) as new alternate member.

Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015)
Action: For adoption

- Overview of comments received (EMA/CHMP/CVMP/QWP/366428/2018)
  Action: For information

Keith Pugh presented the guideline. The guideline applies to chemical and biological medicinal products for human and veterinary use but is not applicable to immunological veterinary medicinal products.

It was acknowledged that the recommendations provided for in this guideline may require some adaptation to the specific characteristics of Advanced Therapy Medicinal Products (ATMPs) for human use (e.g. difficulties to differentiate between starting material, active substance and finished product in some cases, scarcity of starting materials/active

substance/finished product (autologous products and matched-donor scenario), small volumes of production). The level of documentation that is expected to be included in marketing authorisation applications for ATMPs may be adapted provided that this is justified under a risk-based approach. For veterinary cell based novel therapies, cross reference is made to EMA/CVMP/ADVENT/751229/2016 Questions and Answers on allogenic stem cell-based products for veterinary use: specific questions on sterility.

Guidance is provided on the choice of sterilisation method, the development data and manufacturing data required to demonstrate the suitability of the selected sterilisation process. The same principles (choice of method of sterilisation, development data and manufacturing data) apply to sterile active substances, excipients and primary containers. Only the information expected in the quality dossier, including information related to Good Manufacturing Practice (GMP) certificates, is described.

The CHMP adopted the guideline and noted the overview of comments.

Letter to EDQM from QWP
Action: For adoption

The CHMP adopted the letter to EDQM.

2.1.3. Scientific Advice Working Party (SAWP)

Chair: Robert Hemmings

Call for nomination of new SAWP delegates
Action: For information

In order to strengthen SAWP capacity in the following expertise areas:

- Statistics, Novel methodologies
- Cardiology, Diabetes
- Central Nervous System, Geriatrics
- Pharmacokinetics, Modelling & Simulation
- Oncology

nominations should be submitted in writing by **9th November 2018**. The appointment of the new SAWP members will take place at the CHMP Plenary November 2018 meeting.

The CHMP noted the call. New members, who are appointed, will be expected to attend the December SAWP meeting. It was clarified that also single individuals can be proposed and not only pairs from NCAs.

2.1.4. European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP)

Co-chair: Kaisa Immonen

Agenda for the PCWP meeting of 25 September 2018 (EMA/610994/2018)
Action: For information

The CHMP noted the agenda.

Agenda for the Joint PCWP/HCPWP meeting of 25 September 2018 (EMA/610994/2018)
Action: For information

The CHMP noted the agenda.

2.1.5. European Medicines Agency Human Scientific Committees' Working Party with Healthcare Professionals' Organisations (HCPWP)

Co-chair: Gonzalo Calvo

Agenda for the HCPWP meeting of 26 September 2018 (EMA/610994/2018)
Action: For information

The CHMP noted the agenda.

See 2.1.4

2.1.6. Geriatric Expert Group (GEG)

Chair: Katarina Vučić

No items

2.1.7. Committees

Area of expertise for CHMP Co-opted member

In light of the expiry of the mandate of co-opted member Koenraad Norga on 24 January 2019 the CHMP should discuss and agree on the required area of expertise at the November CHMP Plenary.

The area of expertise of Koenraad Norga is Pharmacology.
Action: For discussion

The CHMP Members were reminded and asked to come up with proposals for the plenary next week, but some areas were already brought forward.

It was agreed to have a maximum of 3 areas. The proposals were:

- Pharmacokinetics;

- Pharmacoepidemiology – Pharmacovigilance (PhV was not supported by all members as covered by PRAC);

- Methodology/Biostatistics;

The current co-opted membership Koen's role cross linking to the PDCO was also acknowledged and considered valuable.

Final discussion is expected to take place during the November Plenary.

CHMP 2019 Work Plan, draft

Action: For discussion

The members were reminded to send comments.

Overview of comments on 'Guideline on Clinical Development of Fixed Combination Medicinal Products'

To be presented by Peter Mol, the lead author from the ad hoc drafting group
Action: For information

Peter Mol presented the overview of comments from several different stakeholders. Comments related to legal basis description and to the wording of the indication were noted. It was clarified that the guideline itself has already been published. The CHMP noted the overview of comments.

2.1.8. International Council on Harmonisation (ICH)

No items

2.1.9. Joint CVMP/CHMP ad-hoc expert group on the application of the 3Rs (replacement, reduction and refinement) in the regulatory testing of medicinal products (J 3RsWG)

Chair: Ellen-Margrethe Vestergaard, CoChair: Susanne Brendler-Schwaab

No items

2.1.10. Joint CHMP/CVMP/CMDh/CMDv Working Group on Active Substance Master File Procedures (ASMF WG)

Chair: Nienke Rodenhuis

No items

2.1.11. Joint CVMP-CHMP antimicrobial advice ad hoc expert group (AMEG)

Chair: Gérard Moulin

No items

2.1.12. Modelling and Simulation Working Party (MSWP)

Chair: Kristin Karlsson/Flora Musuamba Tshinanu

No items

2.2. Biologicals

2.2.1. Biosimilar Medicinal Product Working Party (BMWP)

Chair: Elena Wolff-Holz/Niklas Ekman

No items

2.2.2. Biologicals Working Party (BWP)

Chair: Sol Ruiz/Nanna Aaby Kruse

Final minutes from September face-to-face meeting held 10-12 September 2018 (EMA/CHMP/BWP/618392/2018)
Action: For information

The CHMP noted the minutes.

Draft agenda for BWP face-to-face meeting to be held 5-7 November 2018 (EMA/CHMP/BWP/635558/2018)
Action: For information

The CHMP noted the agenda.

Update on Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies) – 26 November 2018

- Workshop agenda (EMA/188075/2018)
- Presentation

Action: For discussion

Workshop on Quality support to early access approaches (PRIME & Breakthrough) will be held on 26th November 2018. The CHMP was updated on the agenda after last presentation given in July 2018 ORGAM.

Problem statement & aims will be discussed in the workshop. Other agenda points are Process validation, Control strategy, GMP compliance.

There will be 2 afternoon parallel sessions - Biological (Process validation & control strategy, comparability, stability) and Chemical (Process validation & control strategy, & stability) session. Regulatory tools will also be discussed.

Topic areas of scientific advice requests for PRIME designated products received were analysed.

The event will be broadcasted and Sol Ruiz will be chairing the meeting. Meeting report will be published 2-3 months after the workshop.

The CHMP noted the update on Workshop. It was suggested to consider making the conclusions from the workshop available to a broader audience within a Peer review publication.

2.2.3. Vaccines Working Party (VWP)

Chair: Mair Powell/Svein Rune Andersen

No items

2.2.4. Blood Products Working Party (BPWP)

Chair: Jacqueline Kerr

Nomination of new core member Mirco Mueller-Olling to replace Anneliese Hilger

- CV
- Current membership list

Action: For adoption

The CHMP nominated a new core member Mirco Mueller-Olling.

Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009 rev. 2)

Action: For adoption for public consultation

The guideline was presented by Mirco Mueller-Olling. This guideline describes the information to be documented when an application for a marketing authorisation for recombinant or human plasma-derived factor IX products is made for use in treatment and prevention of bleeding in patients with haemophilia B. The guideline covers clinical investigations to be conducted pre- and post-marketing authorisation. Guidance is also provided for authorised products where a significant change in the manufacturing process has been made.

It was decided to reorganise the guidance to have separate documents: The Guideline on clinical investigation of recombinant and plasma derived factor VIII products (EMA/CHMP/BPWP/144533/2009) and the Guideline on clinical investigation of recombinant and plasma derived factor IX products (EMA/CHMP/BPWP/144552/2009). EMA/CHMP/BPWP/144552/2009 came into effect on 1 February 2012. Revision 1 is was a rapid revision following the 2013 EMA/EDQM workshop on potency assays. In July 2015 an EMA workshop exploring on registries in hemophilia came to the recommendation that the clinical trial concept requiring PUP studies for FVIII IX products needs to be reconsidered. In light of increasing scientific knowledge. The number of suitable patients especially previously untreated patients (PUPs) to be enrolled in clinical trials is problematic. Hence,

the conduct of sufficiently informative clinical trials in PUPs to estimate important characteristics of single products is considered difficult. Therefore the obligation to perform clinical trials in PUPs for marketing authorisation purposes has been deleted. Furthermore, a core parameter set for registry data collection in haemophilia is introduced.

The CHMP adopted the guideline for public consultation as suggested by GCG.

Guideline on core SmPC for human plasma derived and recombinant coagulation factor IX products (EMA/CHMP/BPWP/1625/1999 rev. 3)

Action: For adoption

The guideline was presented by Mirco Mueller-Olling. The CHMP adopted the guideline.

2.2.5. Pharmacogenomics Working Party (PGWP)

Chair: Krishna Prasad/Markus Paulmichl

No items

2.3. Therapeutics

2.3.1. Cardiovascular Working Party (CVSWP)

Chair: Kristina Dunder/Alar Irs

No items

2.3.2. Central Nervous System Working Party (CNSWP)

Chair: Karl Broich/André Elferink

No items

2.3.3. Infectious Diseases Working Party (IDWP)

Chair: Maria Jesus Fernandez Cortizo

No items

2.3.4. Oncology Working Party

Chair: Pierre Demolis/Paolo Foggi

Final minutes of the ONCWP meeting held by Adobe on 12 September 2018 (EMA/619778/2018)
Action: For information

The CHMP noted the minutes.

Final minutes of the ONCWP meeting held F2F 20-21 September 2018 (EMA652244/2018)
Action: For information

The CHMP noted the minutes.

2.3.5. Pharmacokinetics Working Party (PKWP)

Chair: Jan Welink/Henrike Potthast

Q&A - Ferric citrate coordination complex 1g film-coated tablets - product specific equivalence guidance (EMA/CHMP/246806/2018)

Rapporteur: Sotiris Michaleas
Action: For adoption

The document was presented by Sotiris Michaleas. This document takes into account the LALA (locally applied, locally acting) guideline adopted at the October 2018 Plenary.

The CHMP adopted the document.

Final minutes of the PKWP meeting held by Adobe on 15 June 2018 (EMA/418256/2018)
Action: For information

The CHMP noted the minutes.

2.3.6. Biostatistics Working Party (BSWP)

Chair: Anja Schiel/Jörg Zinserling

No items

2.3.7. Rheumatology/Immunology Working Party (RIWP)

Chair: Jan Mueller-Berghaus/Romaldas Mačiulaitis

Call for nomination of a new core member

Action: For information

Nominations should be sent by **30 November 2018.**

The CHMP noted the call for nomination.

2.3.8. Scientific Advisory Groups (SAGs)

No items

2.3.9. Drafting Groups (DGs)

2.3.9.1. Gastroenterology Drafting Group (GDG)

Chair: Mark Ainsworth

Draft reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)

Rapporteur: Elmer Schabel
Action: For adoption for 9-month public consultation

Elmer Schabel presented the document. As a reflection paper, this guidance document provides a high level description of the requirements for drug development in the field. For all three disease entities dealt with in the paper, the regulatory experience with the licensing of new medicinal product is limited. Therefore, this paper aims at a preliminary definition of development strategies only, which, in the case of several successful MAAs occurring in the future, will have to be refined, and may finally be superseded by full guidance documents.

Furthermore, safety considerations are discussed in the document and chapter dedicated to children is included. The Stakeholder meeting will be held after the document is published. GCG comments were received and will be taken into account.

The CHMP adopted the reflection paper for 9-month public consultation.

2.3.9.2. Respiratory Drafting Group (RDG)

Chair: Karolina Törneke

No items

2.3.9.3. Radiopharmaceutical Drafting Group (RadDG)

Chair: Anabel Cortes

No items

2.3.9.4. Excipients Drafting Group

Chair: Dominique Masset

No items

2.3.10. Additional agenda points

2.3.10.1. Innovation Task Force

ITF Briefing Meeting

Meeting date: 4th December 2018

Action: For discussion and agreement

The meeting was presented.

The CHMP agreed to the meeting.

ITF Briefing Meeting
Meeting date: 27 November 2018

Action: For discussion and agreement

The meeting was presented.

The CHMP agreed to the meeting.

Minutes of ITF meeting
Action: For information

The CHMP noted the minutes.

Minutes of ITF meeting
Action: For information

The CHMP noted the minutes.

Minutes of ITF meeting
Action: For information

The CHMP noted the minutes.

Minutes of ITF
Action: For information

The CHMP noted the minutes.

2.3.10.2. Guideline Consistency Group (GCG)

Chair: Aranzazu Sancho-Lopez

No items

2.3.10.3. IPRF Nano Working Group

Chair: Harald Enzmann

No items

3. List of participants

CHMP Chair:

Harald Enzmann

CHMP members:

Agnes Gyurasics

Andrea Laslop

Bruno Sepodes (Vice-Chair)

Concepcion Prieto Yerro

Ewa Balkowiec Iskra

Greg Markey

Jan Mueller-Berghaus

Johann Lodewijk Hillege

Koenraad Norga

Kristina Dunder

Outi Mäki-Ikola

Robert James Hemmings

Simona Badoi

Sinan B. Sarac

Svein Rune Andersen

CHMP alternate members:

Christophe Focke

Nithyanandan Nagercoil

Fátima Ventura

Milena Stain

Experts:

Elmer Schabel

Jan Willem van der Laan

Keith Pugh

Laila Sortvik Nilssen

Leon van Aerts

Maria Escudero Galindo

Mette Toftegaard Madsen

Milena Peraita Ezcurra

Mirco Juergen Mueller Olling

Sabine Mayrhofer

Sonja Beken

Sotiris Michaleas

Susanne Brendler-Schwaab

The meeting was run with support from the relevant EMA staff