28 January 2022
EMA/CMDh/32164/2022

Report from the CMDh meeting held on 25-27 January 2022

United Kingdom's withdrawal from the European Union

Following the publication of the Commission Notice (C/2021/524) on the application of the Union's pharmaceutical acquis in markets historically dependent on medicines supply from or through parts of the United Kingdom other than Northern Ireland, and legislative proposals by the European Commission in the end of December 2021, and as announced in the CMDh press release in December 2021, the CMDh has agreed updates to its Practical Guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP and the Practical Guidance on the implementation of the Protocol on Ireland/Northern Ireland for medicinal products for human use approved via MRP/DCP. The updates take into account the information provided in the Commission Notice, among others, that for MR/DC procedures which include the Member States IE, CY, MT or UK(NI), continued use of sites located in the UK for batch control and batch release, MAH, local representative and, for UK(NI) only, QPPV or PSMF, may be permitted under the conditions stated in the Notice.

A further update is foreseen once the legislative proposals are adopted and enter into force.

The updated documents will be published on the CMDh website under "Brexit".

In addition, the CMDh reminds MAHs that still have UK(GB) sites mentioned in the dossier in addition to EU sites, e.g. alternative batch release or batch control sites (except for procedures where IE, CY, MT and/or UK(NI) are CMS and have granted an exemption for their markets), to remove these alternative sites from the MA, using the respective variation procedure type IA, category A.7. This should be done immediately for all procedures not including IE, CY, MT and/or UK(NI) as CMS, as the timeframe for submission of these variations has already expired on 31 December 2021. Further regulatory activity might be possible on a national level in case these variation submissions are further delayed.

CMDh Multi-Annual Workplan (MAWP) to 2025 – for public consultation

Since 2015, the CMDh operates with a multi-annual workplan. The previous MAWP finished in 2020. During 2021, the CMDh has been analysing the actions of the previous MAWP and worked on a new MAWP to 2025, which outlines the priorities of the CMDh for the coming years. The document has been

developed in parallel and is complementary to the HMA MAWP. Any changes to the HMA MAWP made during the finalisation of the document will also be considered in the CMDh MAWP, as appropriate.

The following five main priority areas have been included:

- Availability of essential medicines and coordination during crisis
- Optimisation of procedures
- Innovative projects
- Preparation for legislative changes
- Optimisation of communication/relationship/meetings with interested parties and stakeholders

The draft document will be published for 2 months of public consultation. Comments should be sent to the CMDh Secretariat (H-CMDhSecretariat@ema.europa.eu) by 4 April 2022, coordinated by trade associations where possible.

The document will be published under "About CMDh > CMDh Activities".

Call for review for chemically synthesised and biological medicinal products regarding nitrosamine impurities

The CMDh in collaboration with the EMA agreed an update of the joint EMA/CMDh Questions and Answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. Q&A 10 has been amended to provide guidance on control options when more than one nitrosamine is identified in the same product and to address the calculation of acceptable limits. The updated Q&A document will be published on the EMA website. A link will be provided from the CMDh website under "Advice from CMDh > Nitrosamine impurities".

CMDh positions following PSUSA procedures for nationally authorised products only

The CMDh, having considered the PSURs on the basis of the PRAC recommendations and the PRAC assessment reports, agreed by consensus on the variations of the marketing authorisations of medicinal products containing the following active substances:

- paracetamol (IV formulation)
- lactulose
- levonorgestrel (all indications except emergency contraception)
- pholcodine
- loperamide, loperamide / simeticone
- remifentanil
- benazepril / hydrochlorothiazide

Further information regarding the above mentioned PSUSA procedures, including information on the implementation, will be published on the EMA website.

Medicinal products containing paracetamol

In the framework of the PSUSA on paracetamol (IV formulation), the PRAC noted that paracetamol is also authorised as a single agent via other routes of administration and in fixed dose combinations. The PRAC considered that the risk of high anion gap metabolic acidosis (HAGMA) when paracetamol is administered concomitantly with flucloxacillin would also be relevant to be included in all paracetamol containing medicinal products (monosubstance via other routes of administration and fixed dose combinations of paracetamol). This product information update is needed for MAHs which do not have similar wordings already reflected in the SmPC and PL.

Medicinal products containing pholcodine in fixed dose combination

In the framework of the PSUSA on pholcodine, the PRAC noted that pholcodine is also authorised in fixed dose combination products. The PRAC considered that the warnings regarding the risk of drug abuse and cross-reactivity with NMBAs (Neuromuscular Blocking Agents) would also be relevant to be included in medicinal products containing pholcodine in fixed dose combinations.

The same timelines as for the present PSUSA would apply in accordance with the CMDh guidance on implementing variations.

Medicinal products containing sildenafil

In the framework of the PSUSA on Revatio (sildenafil; indication: pulmonary hypertension), the PRAC noted that sildenafil is also authorised in medicinal products indicated for erectile dysfunction. The PRAC considered that the risk of increase in hypotension in case of concomitant use of sildenafil and Entresto (sacubitril/valsartan) would also be relevant to be included in products containing sildenafil indicated for erectile dysfunction, as data from one PK/PD study are available (Hsiao et al.), in which 28 male patients with hypertension received sildenafil as add-on to sacubitril/valsartan at steady state.

The same timelines as for the present PSUSA would apply in accordance with the guidance on implementing variations.

Working Party on Pharmacovigilance Procedures Work Sharing

The CMDh adopted an update of the mandate of the Working Party on Pharmacovigilance Procedures Work Sharing. The mandate has been reviewed to reflect the changing tasks of the Working Party over time.

The updated document will be published on the CMDh website under "CMD Working Parties/Working Groups > Working Party on Pharmacovigilance Procedures Work Sharing".

CTS Working Group

The CMDh is pleased to announce that Mr Dino Soumpasis (DE) has been re-elected as Chair of the CTS Working Group.

Update of the End of Procedure template for DCP

Following the agreement on the new template for the End of Procedure for MRP/RUP in November 2021, the CMDh has also reviewed its template for the End of Procedure for DCP. The templates have been aligned as much as possible.

The updated template will be published on the CMDh website under "Templates > Assessment Reports > DCP".

Requirements on Submissions for New Marketing Authorisation Applications within MRP, DCP and National Procedures and for Variations and Renewals within MRP and National Procedures

The CMDh agreed an update of its guidance documents on Requirements on submissions for new MAAs and for variations and renewals. The format of the documents has been revised to be clearer on the national requirements with regard to signatures. Member States were encouraged to review and reduce national requirements as appropriate.

The updated documents will be published on the CMDh website under "Procedural Guidance > eSubmissions".

MRP/DCP statistics in 2021

Statistics regarding new applications in MRP and DCP in 2021 according to the 5-levels of classification of the MRP/DCP Communication Tracking System database will be published on the CMDh website.

The statistics also include information on variation worksharing procedures, referrals to the CMDh and rapporteurships in paediatric worksharing procedures according to Art. 45 and 46 of the Paediatric Regulation.

NEW APPLICATIONS

Mutual Recognition Procedure

Table 1. New applications in Mutual Recognition procedure started in December 2021

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	1	3
Belgium		6
Bulgaria		5
Croatia		
Cyprus		1
Czech Republic	2	5
Denmark	4	5
Estonia	1	1
Finland	1	4
France		3

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Germany	8	4
Greece		3
Hungary		3
Iceland	1	4
Ireland		1
Italy		6
Latvia		1
Liechtenstein		
Lithuania		1
Luxembourg		3
Malta		6
Netherlands	10	3
Norway		7
Poland		11
Portugal	4	4
Romania		5
Slovak Republic		7
Slovenia	2	
Spain	1	6
Sweden	4	7
United Kingdom (Northern Ireland)		

Decentralised Procedure

Table 2. New applications in Decentralised procedure started in December 2021

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	5	14
Belgium		8
Bulgaria		16
Croatia	1	13
Cyprus		10
Czech Republic	4	12
Denmark	12	17
Estonia		13
Finland	1	13
France		25
Germany	25	28
Greece		14
Hungary	8	10
Iceland	9	5
Ireland	1	10
Italy	1	29
Latvia	2	14

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Liechtenstein		
Lithuania		15
Luxembourg		14
Malta	3	8
Netherlands	8	15
Norway	2	21
Poland	2	14
Portugal	12	9
Romania		13
Slovak Republic	3	10
Slovenia		8
Spain		25
Sweden	7	21
United Kingdom (Northern Ireland)		3

Information on the above-mentioned issues can be obtained:

Chair of the CMDh
Mrs Kora Doorduyn-van der Stoep
Medicines Evaluation Board
P.O Box 8275
3503 Utrecht RG
The Netherlands

CMDh Secretariat
Or you could visit the CMDh website at:
E-mail: H-CMDhSecretariat@ema.europa.eu
http://www.hma.eu/cmdh.html