CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

30 April 2019
EMA/CMDh/204499/2019

Report from the CMDh meeting held on 23-25 April 2019

Brexit preparedness

European Council adopts decision extending the period under 'Article 50'

The European Council agreed to a further extension of the date for the UK's withdrawal from the EU at its meeting on 10-11 April. The extension will last as long as necessary and, in any event, no longer than 31 October 2019. For more information, see:

- European Council decision taken in agreement with the United Kingdom, extending the period under Article 50(3)TEU
- European Commission: Brexit preparedness activities

The UK **remains a Member State** for the duration of the extension, with all the rights and obligations set out in the treaties and under EU law.

All pharmaceutical companies in the EU are reminded to continue their preparedness for the UK's withdrawal.

Based on the European Council decision, the deadline of 29 March 2019 referred to in Brexit related guidance should be understood as referring to 31 October 2019.

If the UK fails to hold European Parliament elections, it will leave the EU on 1 June 2019 and the deadline should be understood as 31 May 2019.

Update on nitrosamine impurities

Following the Art. 31 referral on angiotensin-II-receptor antagonists (sartans) containing a tetrazole group, which concluded on strict legally binding limits for nitrosamine impurities in sartans, the CMDh and national authorities continue to work to ensure manufacturers are taking appropriate measures to avoid or keep impurities below acceptable limits.

Based on experience from the review of sartans, the CMDh is part of an exercise launched by the EMA with experts from across the EU regulatory network including national authorities, the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the European Commission to consider how to prevent such incidents in future and manage them more effectively should they occur.

EMA will publish the outcome of the exercise in due course, including information on any further actions that may be required.

As part of strengthened monitoring of manufacturing, national authorities and EMA are also requesting as precaution that companies using certain reagents to manufacture pioglitazone test their products and check their processes to rule out the presence of nitrosamine impurities, in particular nitrosodimethylamine (NDMA).

The request follows the detection of low levels of NDMA in a few batches of pioglitazone manufactured by Hetero Labs in India, which were within strict limits previously set for sartans and are considered acceptably safe.

Nitrosamines are classified as probable human carcinogens (i.e. substances that could cause cancer). They are present in foods and water, and most people are exposed to them daily in small amounts. However, their presence in medicines is largely avoidable and the relatively low risk they pose to patients does not make them acceptable.

Nitrosamines were first detected in sartan medicines in June 2018. Authorities in the EU took swift action: affected batches were recalled from pharmacies; patients and healthcare professionals were given appropriate advice on alternative treatments; and medicines across the EU were subjected to additional tests to guarantee they did not pose unacceptable risks to patients.

The CMDh and national authorities will continue working closely with the EMA and international partners to ensure that manufacturers are taking appropriate measures with respect to nitrosamines.

Implementation of outcome of Art. 31 referral on angiotensin-II-receptor antagonists (sartans) containing a tetrazole group

Following the publication of information on the implementation of the outcome of the Art. 31 referral on angiotensin-II-receptor antagonists (sartans) containing a tetrazole group in the March CMDh press release, the CMDh wants to provide additional clarification that the conditions to ensure a control strategy and to include the interim limits for NDMA and NDEA in the specifications for the drug substance, as outlined in the Commission Decision, have to be implemented at the time of the Commission Decision. The CMDh agreed that in this case this has to be understood as within 30 days of the publication of the Commission Decision, the respective variations have to be submitted. For the condition to ensure a control strategy a declaration of the MAH that this is in place is regarded as sufficient. This declaration could be added to the scope of the Variation under category C.I.11.a as mentioned below.

The Variation C.I.11.a for inclusion of the conditions on the review and change of the manufacturing process and the final limits for NDMA and NDEA in the specifications for the drug substance into the marketing authorisation have to be submitted within 10 days of the publication of the Commission Decision. The confirmation of inclusion of these conditions in the background and scope of the electronic application form is sufficient for the submission, no additional documentation is needed.

Variations related to the implementation of the Commission Decision can be grouped, as appropriate.

Recommendations on common regulatory approaches for allergen products – Public consultation

In 2016, the CMDh created a drafting group on allergens, which has been working on guidance on regulatory approaches for allergen products. A guidance document "Recommendations on common regulatory approaches for allergen products" has been created and it was agreed to publish the document on the CMDh website for 3 months of public consultation. Interested Parties (e.g.

companies, health care professionals and patients) are invited to provide their comments using the comments template. Comments should be provided via the respective associations, where appropriate.

The document will be published on the CMDh website under "Procedural Guidance, General Information".

Correction of CMDh position on PSUSAs

The CMDh informs MAHs that a correction of the PRAC recommendation and CMDh position of the PSUSA on ciprofloxacin (systemic use) (PSUSA/00000775/201801; CMDh position in October 2018) will shortly be published on the EMA website. Information on the wording to be implemented in the package leaflet was previously partially omitted and has retrospectively been added to the documents. Concerned MAHs that have not yet submitted a variation to implement the outcome should take the updated information into account. MAHs that have already submitted an implementing variation should take the information into account as part of a future update of the product information.

Outcome of PSUR Follow-up procedures (PSUFU)

Abciximab - UK/H/PSUFU/00000014/201711

The CMDh adopted the outcome of the PSUFU procedure for abciximab.

Based on the review of data submitted, the CMDh considers that the risk-benefit balance of medicinal products containing the active substance abciximab remains unchanged. The CMDh, taking into account PRAC recommendations, considers that the product information for abciximab medicinal products should be varied by type IB variation, category C.I.3.z, to update the section 4.4 of the SmPC to add a warning on the monitoring of patients for thrombocytopenia beyond 24 hours from treatment. The Package leaflet does not require further amendment.

The wording to be implemented will be published in the summary assessment report on the CMDh website under "Pharmacovigilance, PSUR, Outcome of PSUFU procedures".

Templates for cover letters for renewal and marketing authorisation applications

The CMDh agreed an update of the templates for cover letters for renewal and marketing authorisation applications. As submission in eCTD format has become mandatory since January 2019, any information related to non-eCTD submissions has been deleted from the templates. This is in line with the update of the cover letter for variation submissions, agreed in January.

The updated templates will be published on the CMDh website under "Templates".

Outcomes of informal PSUR work-sharing procedures

The CMDh has adopted the conclusions of the PSUR assessment for:

- Sterillium (2-Propanol, 1-Propanol, mecetronium ethylsulfate)

which may require changes to the product information or introduction of other risk minimisation measures.

The public summary will be published on the CMDh website under "Pharmacovigilance, PSURs, Outcome of informal PSUR worksharing procedures".

MAHs of the products concerned should implement the outcome of the assessment by the appropriate variation or other procedure (as advised) within 90 days of publication.

EU Work-sharing Articles 45 of the Paediatric Regulation – Public Assessment Reports

The CMDh has agreed on a public assessment report for paediatric studies submitted in accordance with Article 45 of the Paediatric Regulation for:

- flucytosine

which may include recommendations for the text to be included in SmPCs and package leaflets.

Marketing Authorisation Holders of medicinal products with same active substance and pharmaceutical form are requested to include this information in their SmPCs and package leaflets within 90 days of publication of the public assessment reports, in accordance with the Best Practice Guide on Article 45 and 46 - EU work-sharing procedure.

NEW APPLICATIONS

Mutual Recognition Procedure

The CMDh noted that **41** Mutual Recognition Procedures were finalised during March 2019 and **2** Mutual Recognition Procedures were referred to CMDh in this period. **No** Mutual Recognition Procedure was referred to CHMP in this period.

Table 1. The status as of 31 March 2019 of procedures under Mutual Recognition

Year	New applications finalised[1]	Referred to CMDh	Agreement reached in the CMDh For procedures referred in		Withdrawn during CMDh referral For procedures referred in		Applications referred to CHMP For procedures referred to CMDh in	
			2018	2019	2018	2019	2018	2019
2019	101	3	1	0	0	0	0	0

36 Mutual Recognition Procedures (regarding **73** products) started in March 2019. The categories of these procedures are as follows:

- **28** abridged applications (including **16** repeat use procedures);

- **8** known active substance applications (including **5** repeat use procedures);

The Mutual Recognition Procedures started in March 2019 related to the following applications: **1** full dossier, **20** generic, **6** well-established use, **6** hybrid, **2** fixed combination and **1** herbal traditional use.

The procedures consisted of **35** chemical substances and **1** herbal substance;

[1] Due to late database updates cumulative yearly figure differs from the monthly figures. Cumulative yearly figure includes late database updates on finalised procedures not captured in the monthly figures published in press releases. The applications referred to CHMP are included in the 'new applications finalised.'

33 of these procedures related to prescription-only medicinal products and **3** procedures related to non-prescription medicinal products in the reference Member State[2].

Table 2. New applications in Mutual Recognition procedure started in March 2019

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	3	1
Belgium		
Bulgaria		
Croatia		1
Cyprus		
Czech Republic	1	1
Denmark		4
Estonia	1	3
Finland		
France		
Germany		
Greece		3
Hungary	1	
Iceland		2
Ireland	1	
Italy		1
Latvia	1	2
Liechtenstein		
Lithuania		1
Luxembourg		
Malta		18
Netherlands	5	1
Norway		3
Poland		3
Portugal	1	
Romania		3
Slovak Republic		
Slovenia		
Spain	1	
Sweden	4	4
United Kingdom	17	4

Decentralised Procedure

The CMDh noted that **88** Decentralised procedures with positive outcome and **4** procedures with negative outcome were finalised during March 2019. **9** Decentralised procedures were withdrawn after day 120 in this period. **1** Decentralised Procedure was referred to the CMDh in this period. **No** Decentralised Procedure was referred to the CHMP in this period.

[2] In this category products are classified as prescription-only or Non-prescription (OTC) products as applied for in the RMS, although the legal status is not part of the Decentralised Procedure.

Table 3. The status as of 31 March 2019 of procedures under Decentralised Procedure

Year	New applications finalised[3]	New applications Withdrawn[3] (After day 120)	Referred to CMDh	Agreement reached in the CMDh For procedures referred in		Withdrawn during CMDh referral For procedures referred in		Applications referred to CHMP For procedures referred to CMDh in	
				2018	2019	2018	2019	2018	2019
2019	327	26	2	0	0	0	0	0	0

93 Decentralised Procedures (regarding **165** products) started in March 2019. The categories of these procedures are as follows:

- **68** abridged applications (including **7** multiple applications);
- **23** known active substance applications (including **4** multiple applications);
- **2** extension applications;

The new Decentralised Procedures started in March 2019 related to the following applications: **4** full dossier, **60** generic, **6** well-established use, **18** hybrid and **5** fixed combination.

The procedures consisted of **91** chemical substances, **1** vaccine and **1** herbal.

84 of these procedures related to prescription-only medicinal products and **9** procedures related to non-prescription medicinal products in the reference Member State[4].

Table 4. New applications in Decentralised procedure started in March 2019

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	5	17
Belgium	1	12
Bulgaria		12
Croatia		10
Cyprus		3
Czech Republic	4	13
Denmark	4	14
Estonia	1	8
Finland		12
France		28
Germany	30	20
Greece		16
Hungary	1	15
Iceland		5
Ireland	3	10

[3] Due to late database updates cumulative yearly figure differs from the monthly figures. Cumulative yearly figure includes late database updates on finalised procedures not captured in the monthly figures published in press releases. The applications referred to CHMP are included in the 'new applications finalised.

[4] In this category products are classified as prescription-only or Non-prescription (OTC) products as applied for in the RMS, although the legal status is not part of the Decentralised Procedure.

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Italy		28
Latvia	2	10
Liechtenstein		
Lithuania		12
Luxembourg		16
Malta	2	4
Netherlands	15	15
Norway		12
Poland	1	21
Portugal	12	15
Romania		14
Slovak Republic	4	14
Slovenia		9
Spain	5	30
Sweden	1	16
United Kingdom	2	22

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMDh noted that **747** type IA variations, **567** type IB variations, **95** type II variations and **81** renewals were finalised during March 2019. **No** Type II variations, variations worksharing, or renewal procedures were referred to the CMDh in this period. **No** variation worksharing procedure was referred to the CHMP in this period.

Table 5. The status as of 31 March 2019 of variations and renewals under Mutual Recognition[3]

Year	Type IA variations finalised	Type IB variations finalised	Type II variations finalised	Variation work-sharing[5] finalised	Renewals finalised
2019	2125	1589	252	87	209

2019	Referred to CMDh	Agreement reached in the CMDh (For procedures referred in)		Withdrawn during CMDh referral	Applications referred to CHMP (For procedures referred to CMDh in)	
		2018	2019		2018	2019
Type II	0	0	0	0	0	0
Worksharing	0	0	0	0	0	0

[5] Finalised work sharing do not include work sharing involving centrally approved products coordinated by EMA

Year	Type IA variations finalised	Type IB variations finalised	Type II variations finalised	Variation work-sharing[5] finalised	Renewals finalised
Renewal	0	0	0	0	0	0

Information on the above mentioned issues can be obtained:

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Or you could visit the CMDh website at: *http://www.hma.eu/cmdh.html*