medicines for europe
better access. better health.

CMDh & Interested Parties meeting

Medicines for Europe presentations

28 May 2019 Amsterdam


medicines
for europe
better access. better health.
HARP
implementation in
practice

Harmonisation effort

- Domain 2:
  Harmonisation of RMP of same active substances for which MAs have been granted with different RMPs in place
- First set of active substances have been assessed
- First set of active substance ARs have been commented upon
- Publication of harmonised RMP expected during 2019
- What are the next steps ?
  What expectations do you have towards industry ?

Implementation effort

- **For new MAA**, for existing molecules the harmonised RMP should be used
  - How do applicants make clear that a harmonised RMP is used ?
- **For existing MA**, <u>on a voluntary basis</u>
  - What is the process to align existing RMP with harmonised RMP ?
  - Is it possible to include an alignment proposal in another RMP related variation ?
  - Can we assume that we can use an IB by default variation for MAH who wish to align ?
  - Could alignment be done in combination with a renewal submission ?
  - Could alignment be done with any other text variation?

Maintenance effort

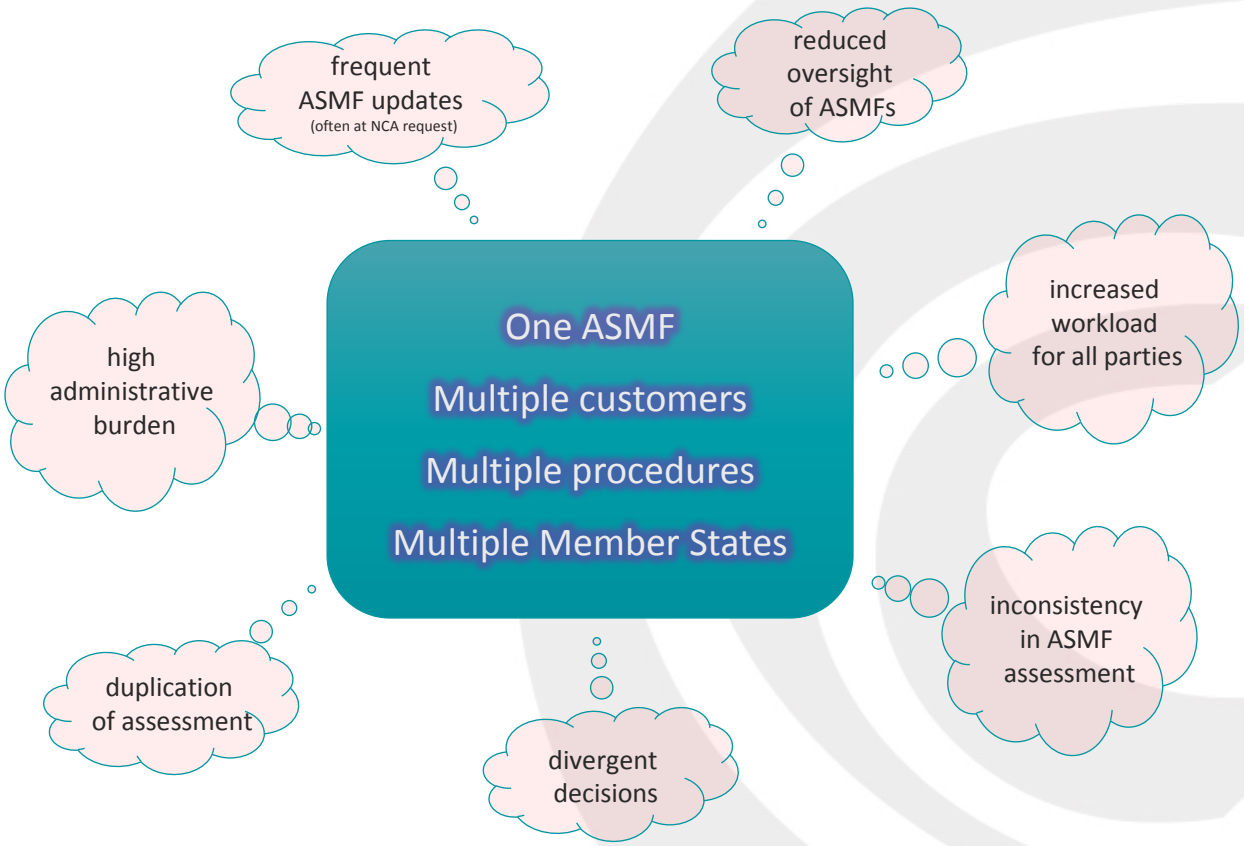
Recent experience

- Some authorities raise questions on the relevance of CMDh list after GVP V Rev 2 was introduced.
  - Forcing MAHs to adjust RMP in accordance with CMDh list even with outdated RMPs, although it is evident that CMDh list is based on GVP V Rev 1
- It would be good if CMDh could guide national authorities not to insist on RMPs based on GVP Rev 1 definitions.
  - However, CMDh list is still “stuck” with newly approved RMPs based on GVP Rev 1

ASMF worksharing

Experience & Improvements

Why workshare?



How it works

- ASMF holder requests EU/ASMF number
- Assessment of new ASMFs composed of 2 to 3 assessment stages
  - ASMF-AR repository uses procedure timetables to identify the “parent” procedure
  - Other procedures are “daughter” procedures
  - RMS of parent procedure drafts assessment report (AR)
  - QA review of the AR by parent CMS or daughter RMS
  - Review of assessment report by parent CMSs
  - **Only Major Objections can be** raised during reviews **!**
  - Parent RMS **updates AR at d105** to include all questions.
- Procedure repeats as above until assessment is complete

Potential advantages

- Reduced workload @ Competent Authorities
- Reduced workload @ ASMF and MAHs
- Harmonised assessment (Parent RMS / Rapporteur)
- Harmonisation of ASMF
- Improved oversight of ASMFs
- Reduced requests for updated ASMFs (by MAHs, CAs, ASMF holders)

Guideline on ASMF Procedure

CHMP/QWP/227/02 Rev 4; November 2018, pg 8/23

Where the same active substance is used in a number of applications for different products in one or more Member States, the ASMF holder should submit identical documentation to every National Competent Authority/EMA. Consequently, the National Competent Authorities/EMA may require that any ASMF updates made in relation to one MA should apply to all. It is the ASMF holder's responsibility to notify the MA holders and National Competent Authorities/EMA concerned about any changes to the AP and/or RP, so that the MA holders can update all affected MAs accordingly. The ASMF holder may consider using an ASMF worksharing procedure[2] (when applicable).

Guideline on ASMF Work Sharing

Daughter procedures should ***only raise additional points that are critical to the quality of the active substance****. Additional points raised by the daughter RMS/Rapporteur should be circulated as a separate document in the Daughter procedure.* ***Where a Daughter CMS/CxMP member raises other concerns, the daughter RMS/Rapporteur should consult with the CMS/CxMP member whether the concerns raised are critical or not. If they are not critical, the concerns should be withdrawn, and the daughter RMS/Rapporteur should notify the ASMF holder and, where relevant, Applicant/MAH that they do not need to be addressed****.*

What is a “Major concern”?

This situation has also been discussed in the ASMF-WG.

It seems there is a misunderstanding on what are considered “additional points that are critical to the quality of the active substance”. For the competent authorities these are not only a potential serious risk to public health but there can also be other concerns when these are considered critical to the quality.

Just for your information, In the guidance for the worksharing procedure on page 10 an example is given on what is not considered critical to the quality of the active substance: *points that do not improve the quality of the active substance, e.g. updating the description of the properties of a well-known active substance, should not be raised*.

- The perspective of the competent authorities will be better explained in a next version of the guidance for the worksharing procedure.

Risks & experience

One ASMF

Multiple customers

Multiple procedures

Multiple Member States

- Individual RMSs / Rapporteur repeating evaluation
- Delays in approval of procedures referring to parent procedures
- Risk of disharmonisation when non critical questions arise during late stage of the procedure
- Risk of variations for non-critical changes to the ASMF

Conclusions

- The ASMF version management in the EU is a problem for both industry and authorities
- There are multiple examples that show how badly we need the ASMF WS!
- The ASMF Working Group did a great job within the boundaries of their possibilities, a very clear guidance document and training are available
- The ASMF WS has incredible potential to make the registration process in the EU more efficient for both ASMF holders as Competent authorities

HOWEVER, the EU ASMF AR WS procedure can only become a success if authorities accept the initial assessment report and daughter procedures stop asking additional questions

The never-ending harmonisation cycle

Suggestions for improvement

Major: Define “critical to the quality of the drug substance”

Other:
Improve awareness
Improve the implementation (mutual recognition) on the authority side
Improve the communication between CA and ASMF holders
Create a contact point regarding ASMF WS questions

Promote the EU Work Sharing -> Stop with national ASMF numbers
Expand to include also ‘approved in marketing authorisation’

Possibility to request EU/ASMF number from EDQM?

medicines for europe
better access. better health.

Medical Devices Regulation

Impact of new EU Medical Device Regulation on Medicinal Products Incorporating a Drug Delivery Device Component

- Question and Answer (Q&A) document EMA/37991/2019 from 27 February 2019
  - The impact on the existing products is not very clear

QA 1.6

" It is not intended to apply retrospectively the requirements of the medical devices Regulation to medicinal products with an integral medical device already authorised or to those MAAs that have been submitted prior to 26 May 2020.

However, if after authorisation there is a substantial change to the design or intended purpose of the device component, or a new device is introduced, any required certificate/declaration of conformity/NB opinion should be submitted as part of the variation/extension application, as appropriate to EMA/NCA (see also Q1.7). Changes to the device component are considered substantial if the changes affect the performance and safety characteristics of the device."

"*Substantial change*" – challenges in the interpretation; any examples/ further clarification could be considered?

Variations

- National finalisation of variations affecting text elements

Process related to type IB variations

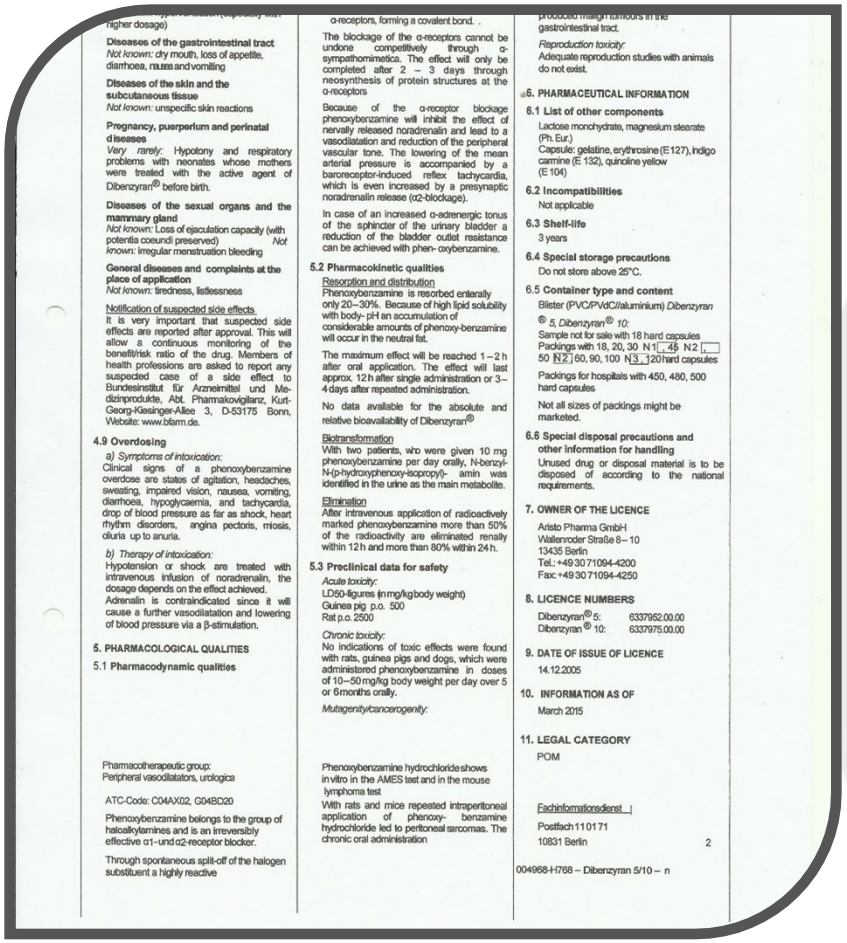
Texts affected

- **Making reference to :**
  CMDh Best Practice Guide for the Processing CMDh/294/2013 Page 3/7 of Type IB Minor Variations

- **2.2 Validation of the application**
  The MAH will submit an application simultaneously to the RMS and CMS containing the elements listed in Annex IV of the Variation Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format:
  - For variations that affect the SmPC, labelling or package leaflet, both the English texts and national translations should be submitted. Mock-ups or specimens should be provided according to Chapter 7 of the NtA, or as discussed with the RMS on a case-by-case basis.

Process related to type IB variations

Texts affected



higher dosage)

Diseases of the gastrointestinal tract
Not known: dry mouth, loss of appetite, diarrhoea, nausea and vomiting

Diseases of the skin and the subcutaneous tissue
Not known: unspecific skin reactions

Pregnancy, puerperium and perinatal diseases
Very rarely: Hypotony and respiratory problems with neonates whose mothers were treated with the active agent of Dibenzyran® before birth.

Diseases of the sexual organs and the mammary gland
Not known: Loss of ejaculation capacity (with potentia coeundi preserved) *Not known:* Irregular menstruation bleeding

General diseases and complaints at the place of application
Not known: tiredness, listlessness

Notification of suspected side effects
It is very important that suspected side effects are reported after approval. This will allow a continuous monitoring of the benefit/risk ratio of the drug. Members of health professions are asked to report any suspected case of a side effect to Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, Website: www.bfarm.de.

4.9 Overdosing

a) Symptoms of intoxication:
Clinical signs of a phenoxybenzamine overdose are states of agitation, headaches, sweating, impaired vision, nausea, vomiting, diarrhoea, hypoglycaemia, and tachycardia, drop of blood pressure as far as shock, heart rhythm disorders, angina pectoris, miosis, diuria up to anuria.

b) Therapy of intoxication:
Hypotension or shock are treated with intravenous infusion of noradrenalin, the dosage depends on the effect achieved. Adrenalin is contraindicated since it will cause a further vasodilatation and lowering of blood pressure via a β-stimulation.

5. PHARMACOLOGICAL QUALITIES

5.1 **Pharmacodynamic qualities**

Pharmacotherapeutic group:
Peripheral vasodilators, urologics

ATC-Code: C04AX02, G04BD20

Phenoxybenzamine belongs to the group of haloalkylamines and is an irreversibly effective α1- und α2-receptor blocker.

Through spontaneous split-off of the halogen substituent a highly reactive

α-receptors, forming a covalent bond. .

The blockage of the α-receptors cannot be undone competitively through α-sympathomimetica. The effect will only be completed after 2 – 3 days through neosynthesis of protein structures at the α-receptors

Because of the α-receptor blockage phenoxybenzamine will inhibit the effect of nervally released noradrenalin and lead to a vasodilatation and reduction of the peripheral vascular tone. The lowering of the mean arterial pressure is accompanied by a baroreceptor-induced reflex tachycardia, which is even increased by a presynaptic noradrenalin release (α2-blockage).

In case of an increased α-adrenergic tonus of the sphincter of the urinary bladder a reduction of the bladder outlet resistance can be achieved with phen- oxybenzamine.

5.2 Pharmacokinetic qualities

Resorption and distribution
Phenoxybenzamine is resorbed enterally only 20–30%. Because of high lipid solubility with body- pH an accumulation of considerable amounts of phenoxy-benzamine will occur in the neutral fat.

The maximum effect will be reached 1 – 2 h after oral application. The effect will last approx. 12 h after single administration or 3 – 4 days after repeated administration.

No data available for the absolute and relative bioavailability of Dibenzyran®

Biotransformation
With two patients, who were given 10 mg phenoxybenzamine per day orally, N-benzyl-N-(p-hydroxyphenoxy-isopropyl)- amin was identified in the urine as the main metabolite.

Elimination
After intravenous application of radioactively marked phenoxybenzamine more than 50% of the radioactivity are eliminated renally within 12 h and more than 80% within 24 h.

5.3 Preclinical data for safety

Acute toxicity:
LD50-figures (in mg/kg body weight)
Guinea pig p.o. 500
Rat p.o. 2500

Chronic toxicity:
No indications of toxic effects were found with rats, guinea pigs and dogs, which were administered phenoxybenzamine in doses of 10–50 mg/kg body weight per day over 5 or 6 months orally.

Mutagenity/cancerogenity:

Phenoxybenzamine hydrochloride shows in vitro in the AMES test and in the mouse lymphoma test
With rats and mice repeated intraperitoneal application of phenoxy- benzamine hydrochloride led to peritoneal sarcomas. The chronic oral administration

produced malign tumours in the gastrointestinal tract.

Reproduction toxicity:
Adequate reproduction studies with animals do not exist.

6. PHARMACEUTICAL INFORMATION

6.1 List of other components
Lactose monchydrate, magnesium stearate (Ph. Eur.)
Capsule: gelatine, erythrosine (E 127), indigo carmine (E 132), quinoline yellow (E 104)

6.2 Incompatibilities
Not applicable

6.3 Shelf-life
3 years

6.4 Special storage precautions
Do not store above 25°C.

6.5 Container type and content
Blister (PVC/PVdC/aluminium) *Dibenzyran® 5, Dibenzyran® 10:*
Sample not for sale with 18 hard capsules
Packings with 18, 20, 30 N1, 45 N2, 50 N2 60, 90, 100 N3, 120 hard capsules

Packings for hospitals with 450, 480, 500 hard capsules

Not all sizes of packings might be marketed.

6.6 Special disposal precautions and other information for handling
Unused drug or disposal material is to be disposed of according to the national requirements.

7. OWNER OF THE LICENCE
Aristo Pharma GmbH
Wallenroder Straße 8 – 10
13435 Berlin
Tel.: +49 30 71094-4200
Fax: +49 30 71094-4250

8. LICENCE NUMBERS
Dibenzyran® 5: 6337952.00.00
Dibenzyran® 10: 6337975.00.00

9. DATE OF ISSUE OF LICENCE
14.12.2005

10. INFORMATION AS OF
March 2015

11. LEGAL CATEGORY
POM

Fachinformationsdienst
Postfach 110171
10831 Berlin

2

004968-H768 – Dibenzyran 5/10 – n

- **2.4 The Evaluation Process (Day 0 to Day 30)**
- If the product information is concerned by the change applied for, the national translations have to be evaluated and may be commented on by the CMS until Day 27.
- MAH are reminded that if the product information is concerned by the change applied for, national translations, updated in accordance with requests for amendment raised in the Notification with Grounds, have to be submitted in the amended notification in order to be validated during this second 30-day period.

Process related to type IB variations

Texts affected

- **2.5 Outcome of the notification process**
- The RMS will make the decision as to whether the notification is accepted or rejected. The following actions will be taken on or before Day 30/New Day 30:
- **Approval:** The RMS will inform the MAH that the variation application is approvable, together with the date of approval. The CMS are informed of the outcome by means of the updated CTS record.
- **Competent authorities should implement the decision nationally within six months from the end of the procedure; however, the MAH can implement the changes prior to the marketing authorisation being updated by the national competent authority, i.e. immediately after the RMS has informed the holder that it has accepted the notification or after the notification has been deemed accepted**

What are we struggling with ?

- There are countries that ask MAH after variation closure to submit the national translation again, either directly or via a portal in text fragments.
- These countries seem to be assessing the translation only then.
- MAH are very reluctant to already start implementing the text in the day 30 status
- What should the expectation be ? Can this be detailed per country ? This information is relevant for proper implementation processes.

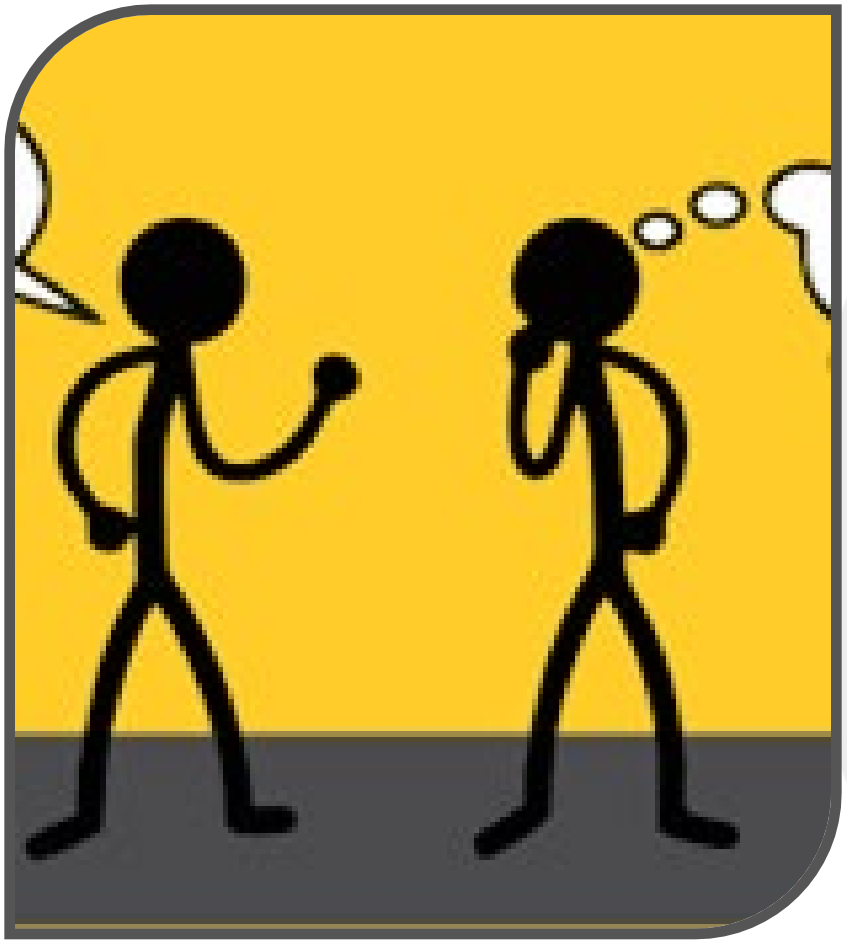
Variations

Listing supply chain in 3.2.p.3.1

M 3.2.P.3.1 standard wording

- M 3.2.P.3.1
  Typically lists actors in the FDF supply chain, whereas also the eAF (M 1.2) lists the actors in the FDF supply chain applied for
- Looking at IT developments, being proactive
  - Assuming we will be able to make applications for changes in the FDF supply chain actors, based on data, making reference to SPOR/ISO IDMP database
  - Avoiding having to submit documents in a setting where only data could be exchanged
  - Facilitating making use of IT tools not just for new data, but also partly for legacy products

M 3.2.P.3.1 standard wording



- Our ask is
  - Allowing the applicant to refer in M 3.2.P.3.1 for the FDF supply chain set up to actual data in the eAF via a standard statement, such as
    - For manufacturers please refer to eAF or M1.2
  - Making submission of an updated M 3.2.P.3.1 (which is a document and not a data set) redundant for variations affecting FDF supply chain set up.


medicines
for europe
better access. better health.
PSUSA submission

Question raised

"Should the PSUR be part of the dossier, or would it be better to have a standalone life cycle, linked to the Active Substance?"

Situation – Optimised Process from 2016

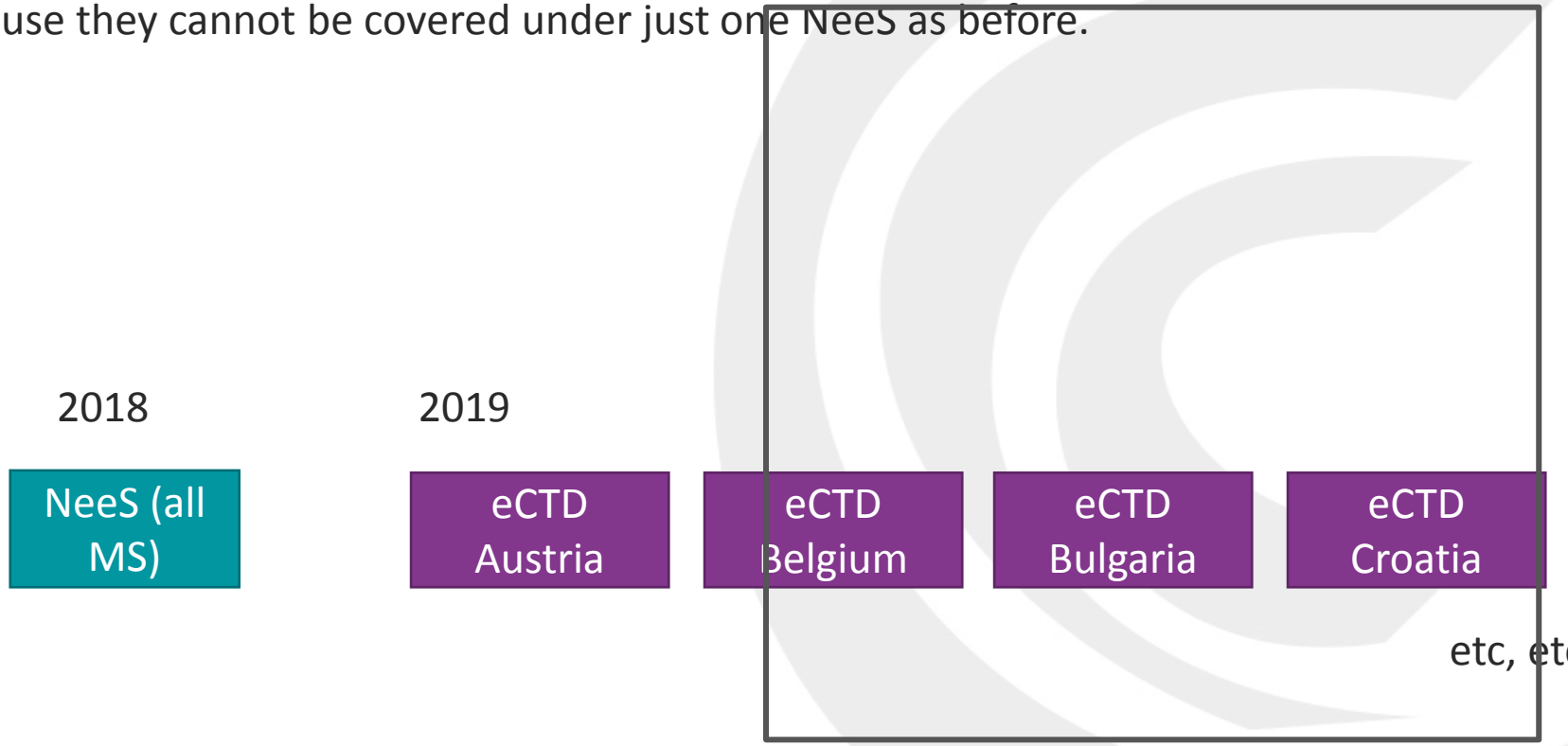
PSUR Single Assessment Procedure (PSUSA)

- 23 June 2016 - EMA/401580/2016 – **all PSUR submissions must be submitted to Central EMA Repository**
  - Not permitted to be sent directly to applicable NCAs
  - One assessment on behalf of all EEA Network
  - Applies to APIs governed by the EURD list, and also to pure NAP procedures where the API(s) are outside of the EURD list.

- **Multiple products based on the same API from the same MAH**
  - All products must be listed in the cover letter.
  - It should also be clarified in the cover letter that the content of each sequence/submission is identical
  - EMA uses the above list to extrapolate from XEVMPD and then charge MAHs a fee for PSUR assessment.

Impact of Mandatory eCTD in NAT

From January 2019, when national approved products are mandated to be maintained in eCTD format, the number of submissions to the PSUR repository can multiply considerably because they cannot be covered under just one NeeS as before.



Medicines for Europe

Year	Number of eCTD submissions if provided in MAA*	Number eCTD submissions if provided once per EURD**	Number of companies that provided data
2019	559	135	5 companies
2020	547	83	4 companies
2021	383	99	4 companies
2022	365	94	4 companies
TOTAL	1854	411	-

* i.e. the total number of eCTD sequences that would need to be published and submitted if the PSUR remains part of the eCTD lifecycle and a sequence needs to be submitted for each individual eCTD dossier.

** i.e. if PSUR submissions are separated from the product dossier lifecycle, hence only one sequence is required per EURD.

Revised Proposal (HHG March 2019)

PROPOSAL:

1. For products impacted by issue of multiple copies, submit **just one copy of the PSUR in eCTD format through the Gateway in a new PSUR specific eCTD application**

2. List **other products where the PSUR is relevant in the cover letter** (and delivery file, would need a change to the PSUR delivery file)

3. For products with limited impact of countries/strengths/dosage forms – **process as today**

Minimum Aim: to avoid multiple, separate submission of eCTD sequences containing the same PSUR to the PSUR Repository

Investigated possible solutions

1. One submission from a marketing authorisation holder including all products within the scope of the given PSUSA procedure into **one of the eCTD lifecycles only**
2. Remove PSURs from the eCTD application life-cycle. PSURs would be submitted separately as **one submission in PDF format** (not NeeS or eCTD) on behalf of all applicable MAAs, to the PSUR Repository
3. Submit just **one PSUR in NeeS** format through the Gateway as today (do not mandate eCTD for PSURs)
4. Submit **just one PSUR in eCTD format through the Gateway** and commit to submitting the others as catch-ups next time there is a life-cycle activity or within 12 months, whichever is earlier
5. Consider the **PMS TOM** as a solution
6. A **standalone life cycle**, linked to the **Active Substance**

Medicines for Europe position

PSUR - a standalone life cycle, linked to the Active Substance

- For submission of RUP applications, the PSUR as submitted to the Single Repository should be included in the dossier.

medicines for europe
better access. better health.

Reporting on Shortages

EMA/ HMA Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)

- CMDh has been consulted on the guideline
- Main issues identified by the industry:
  - Scope of reporting: “all cases”
    - High risk of overloading the system
    - No detection of the most impactful cases/ Lost of focus on critical cases
    - Still a significant national component in reporting/ deviation from the harmonised approach- further comparison quite challenging
  - Applicability of Matrix to multisourced products anticompetitive
    - Scope of data to be provided/ analysed
  - Industry suggestion: to start with the pilot first before moving to massive reporting
- What is the status of the Guideline and what are the next steps?
  - Another consultation round?
  - When is the guideline planned for release?


medicines
for europe
better access. better health.
Warning emollient products- MHRA request

Request

- MHRA requests the introduction of specific warnings for so-called “emollient products”
- Warnings to be introduced into the labelling, product information, and instructions for use via a Variation Type IB.
- No scientific data available, nor experimental data has been requested nor generated to justify the product-specific risk
- Topic has been discussed in CMDh: majority of EU authorities seem not to share MHRA’s view.
- No Referral procedure has been started to ensure a harmonised approach across Europe.

Problem statement and proposal

Problem statement:

- UK included in EU procedures that fall within scope of the MHRA initiative
- For these EU procedures: disharmonisation across MAH and markets
- Competition disadvantages for MAH having UK as CMS in a larger MRP/DCP

Proposal:

- To include specific warnings in UK PIL and packaging only, no variation procedure for products registered via EU procedure