EDQM & European Pharmacopoeia: State-of-the-art Science for Tomorrow's Medicines

International Conference organised by the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe

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Workshop on Certification

Moderator

Dr Jean-Louis Robert, Chair of the Certification Steering Committee

EU Active Substance Master File (ASMF) work-sharing : viewpoint of a regulator

International Conference on the 'EDQM & European Pharmacopoeia: State-of-the-Art Science for Tomorrow's Medicines'

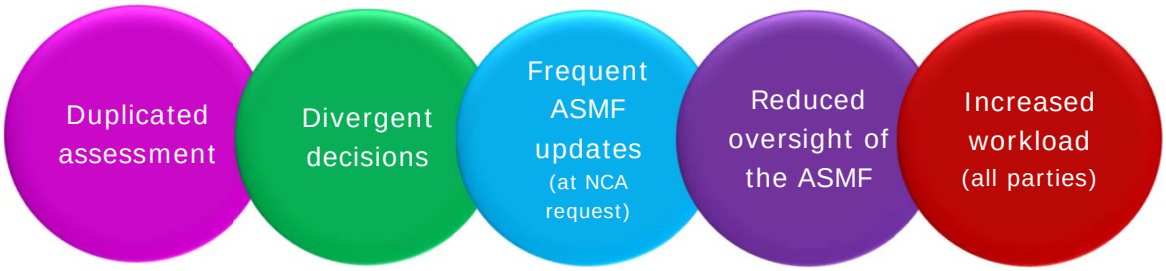
Presented by Nienke Rodenhuis on 20 June 2019

Content

- Introduction
- Status
- Room for improvement
- Future
- Conclusion

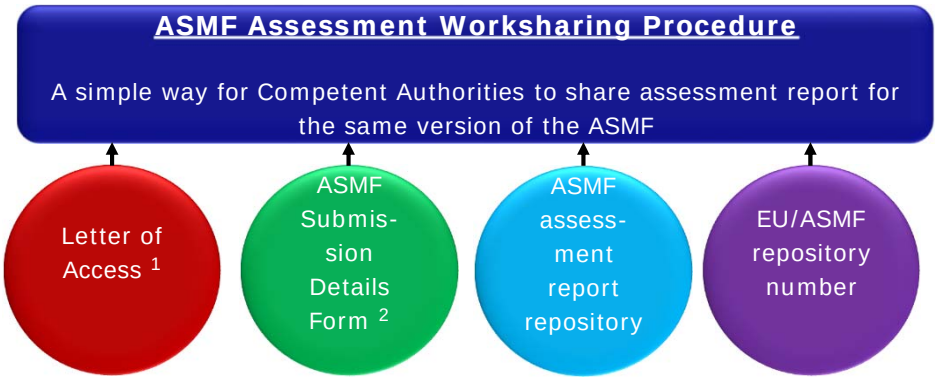
Introduction

- Why do we need a worksharing procedure for ASMF assessments?
  - When the same ASMF is used in multiple procedures and/or Member States, it can lead to…



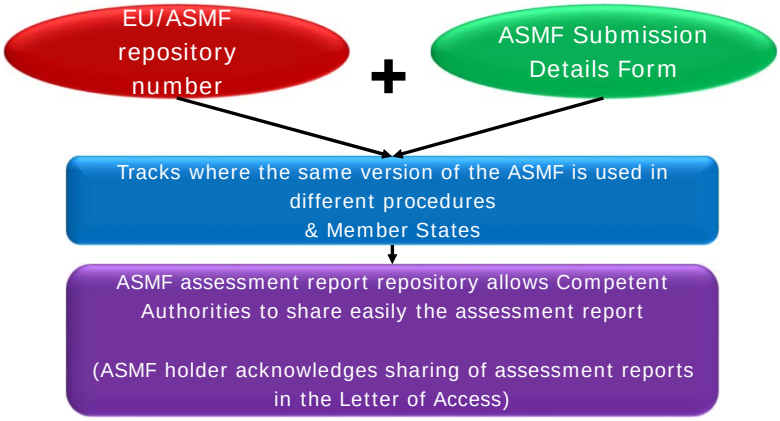
Introduction (2)

- What has been done to solve the challenge?

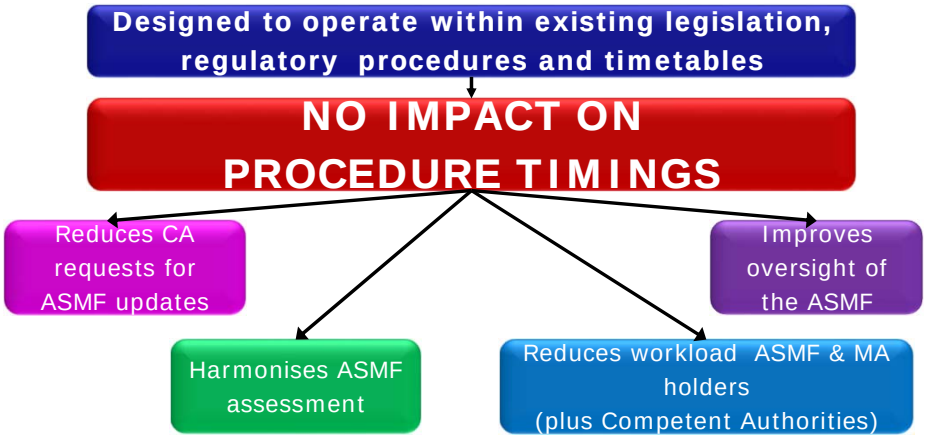


Introduction (3)

- How does the ASMF assessment worksharing procedure work?



Introduction (4)



Status

- Common practice since 2017
- Number of ASMFs for which EU/ASMF has been issued: 254
- Latest version guidance April 2018
  - The Worksharing Procedure for the Assessment of Active Substance Master File (ASMF)
- new ASMFs only, submitted as part of new MAA or variation application through CP or DCP/MRP, where full AR prepared by NCA
  - not previously assessed by NCA in CP, DCP/MRP MAA or variation application
  - may have been assessed as part of national application.
- Variations to accepted ASMFs in WS being submitted

Room for improvement

- Difference in interpretation of “points that are critical to quality of the active substance”
- (Un)familiarity with worksharing procedure
- Understanding of procedure and different steps
- Awareness of ASMF in worksharing procedure at NCA
- ASMF-holder request EU/ASMF-numbers for “existing” ASMFs
- Unclear version numbering of ASMF (updates)
- Unfamiliarity with eCTD submissions

Future

- Updates to the guidance, ongoing process
- Development of Q&A's, where necessary
- Open for "existing" ASMFs
  - Need more experience with new ASMFs and updates to these
  - Describe when possible
    - Which type of variation/update applicable
    - What kind of report
    - Etc.
- From voluntary to mandatory?
- Single assessment of ASMF?

Conclusion

- Effective procedure
- More experience to be gained
- Room for improvement

=> Joint effort authorities and industry

Any questions?

Further information

CMDh Secretariat (H-CMDhSecretariat@ema.europa.eu)
European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
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Send a question via our website http://www.hma.eu/contact.html

ASMF WORKSHARING AND CEPS

Viewpoint of Industry

Martijn Klop MSc.
June 20th, 2019

Synthon

Nice to meet you

~10 Synthon CEPs

~15 Synthon ASMFs in the EU ASMF Worksharing procedure

A lot of additional external CEPs in our portfolio

A lot of additional external EU (WS)-ASMFs in our portfolio

Additional guidance on documents relating to an active substance master file

EMA/CHMP/CVMP/QWP/549010/2012, September 2012, pg 5/10

The same versions of the AP & RP (= ASMF) should be submitted to all NCA/EMA involved in the MA/MAV application. Where the ASMF is used in multiple procedures, the ASMF should be submitted only once, unless otherwise directed by the submission requirements of competent authorities.

Guideline on Active Substance Master File Procedure

CHMP/QWP/227/02 Rev 4; November 2018, pg 8+9/23

In addition to the above, the Applicant/MA holder should include a copy of the AP in the MA dossier (CTD format section 3.2.S or veterinary NtA format part 2.C.1). The version of the AP in the MA dossier should be the most recent and it should be identical to the AP as supplied by the ASMF holder to the National Competent Authority/EMA as part of the ASMF.

Q&A on Active Substance Master File (ASMF)

CMDh/CMDv/280/2012, Rev.10, February 2019, pg 6/12

13. Can one ASMF holder have more than one ASMF for the same active substance but with different synthetic routes, specification, grade, etc.?

An ASMF holder may have more than one ASMF of a same active substance provided that the active substances have, inter alia, substantially different routes of synthesis, which result in changes to important quality characteristics of the active substance or different specifications. In this case, each ASMF should be assigned a different reference number by the ASMF holder; consequently, each ASMF will also require a separate EU/ASMF reference number. Slightly different routes of synthesis that do not result in changes to important quality characteristics should be incorporated into a single ASMF. If the ASMF holder is in doubt, they should contact an appropriate Competent Authority for guidance prior to submission of the ASMF.

ASMF holders are reminded that only one version of an ASMF may be used in marketing authorisation applications and authorisations in Europe.

Guideline on Active Substance Master File Procedure

CHMP/QWP/227/02 Rev 4; November 2018, pg 9/23

Any change to the ASMF should be reported by every MA holder to the relevant National Competent Authority/EMA by means of an appropriate variation procedure. A Submission Letter should be provided (Annex 3).

Q&A on Active Substance Master File (ASMF)

CMDh/CMDv/280/2012, Rev.10, February 2019, pg 9/12

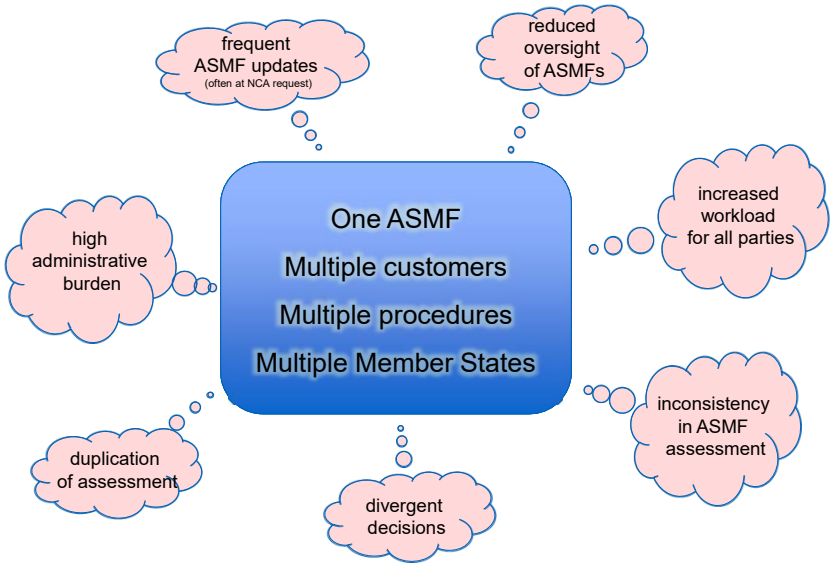
Question 23

Since all changes in new ASMF version are already communicated to the authorities during a marketing authorisation application, can the MAH submit the updated sections of new version in eCTD format outside of scope of variation?

Answer:

A "baseline" ASMF in eCTD format can be submitted outside a marketing authorisation application or variation, providing it is identical to that already accepted for use in a medicinal product. This should be clearly stated in the Submission Details Form and confirmed by the Quality Expert. Any changes to the ASMF, other than formatting and typographical corrections, will require a new marketing authorisation application or variation.

The problem of the decentralized assessment of EU ASMFs:



How CEPs work

EUROPEAN PHARMACOPOEIA 6.5 — Tamsulosin hydrochloride

01/2008:2131 corrected 6.5

TAMSULOSIN HYDROCHLORIDE

Tamsulosini hydrochloridum

$C_{20}H_{28}ClN_2O_5S$ [106463-17-6] M_r 445.0

DEFINITION

5-[(2*R*)-2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: slightly soluble in water, freely soluble in formic acid, slightly soluble in anhydrous ethanol.

mp: about 230 °C.

IDENTIFICATION

Carry out either tests A, C, D or tests A, B, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison: tamsulosin hydrochloride CRS.

B. Specific optical rotation (2.2.7): − 12.5 to − 20.5 (dried substance).

Dissolve with heating 0.15 g in *water R* and dilute to 20.0 ml with the same solvent.

C. Enantiomeric purity (see Tests).

D. Dissolve with heating 0.75 g in *water R* and dilute to 100.0 ml with the same solvent. Take 5 ml of the solution and cool in an ice-bath. Add 3 ml of *dilute nitric acid R* and shake. Allow to stand at room temperature for 30 min and filter. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances.

A. Impurities eluting before tamsulosin. Liquid chromatography (2.2.29).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (b). Dissolve 4 mg of tamsulosin *impurity D CRS* and 4 mg of the substance to be examined in the mobile phase and dilute to 20.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 20.0 ml with the mobile phase.

Reference solution (c). Dissolve 4 mg of tamsulosin *impurity H CRS* and 4 mg of the substance to be examined in the mobile phase and dilute to 20.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 20.0 ml with the mobile phase.

Column:

– *size:* *l* = 0.15 m, Ø = 4.6 mm;

– *stationary phase:* octadecylsilyl silica gel for chromatography *R* (5 µm);

– *temperature:* 40 °C.

Mobile phase: dissolve 3.0 g of sodium heptanesulfonate *R* in a mixture of 8.7 ml of perchloric acid *R* and 1.9 litres of *water R*; adjust to pH 2.0 with *0.5 M sodium hydroxide* and dilute to 2 litres with *water R*; to 1.4 litres of this solution, add 600 ml of *acetonitrile R*.

Flow rate: 1.3 ml/min.

Detection: spectrophotometer at 225 nm.

Injection: 10 µl of the test solution and reference solutions (a) and (b).

Run time: 1.5 times the retention time of tamsulosin (retention time = about 6 min).

System suitability: reference solution (b):

– *resolution:* minimum 6 between the peaks due to impurity D and tamsulosin.

Limits:

– *unspecified impurities:* for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

– *disregard limit:* 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

B. Impurities eluting after tamsulosin. Liquid chromatography (2.2.29) as described in test A with the following modifications.

Mobile phase: dissolve 3.0 g of sodium heptanesulfonate *R* in a mixture of 8.7 ml of perchloric acid *R* and 1.9 litres of *water R*; adjust to pH 2.0 with *0.5 M sodium hydroxide* and dilute to 2 litres with *water R*; add 2 litres of *acetonitrile R*.

Flow rate: 1.0 ml/min.

Injection: 10 µl of the test solution and reference solutions (a) and (c).

Run time: 3 times the retention time of tamsulosin (retention time = about 2.5 min).

System suitability: reference solution (c):

– *resolution:* minimum 2 between the peaks due to tamsulosin and impurity B.

Limits:

– *unspecified impurities:* for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

– *sum of impurities eluting before tamsulosin in test A and after tamsulosin in test B:* not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *disregard limit:* 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Enantiomeric purity. Liquid chromatography (2.2.29).

Test solution. Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 25.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with *methanol R*. Dilute 1.0 ml of this solution to 10.0 ml with *methanol R*.

Reference solution (b). Dissolve 5.0 mg of tamsulosin racemate *CRS* in *methanol R* and dilute to 25.0 ml with the same solvent. Dilute 2.0 ml of this solution to 10.0 ml with *methanol R*.

Monographs

General Notices (1) apply to all monographs and other texts 4969

When a drug substance manufacturer can demonstrate that the quality of his drug substance can be controlled using the monograph in the European Pharmacopoeia, a CEP application at the EDQM is possible.

Certificate of Suitability to the monograph of the Ph. Eur.

edqm — European Directorate for the Quality of Medicines & HealthCare

Certification of Substances Division

Certificate of suitability
No. R0-CEP 2010-204-Rev 01

Name of the substance:
TAMSULOSIN HYDROCHLORIDE

Name of holder:
SYNTHON BV
Microweg 22
The Netherlands-6545 CM Nijmegen

Site(s) of production:
SYNTHON S.R.O. BLANSKO
Brnenska 32
Czech Republic-678 17 Blansko

SYNTHON ARGENTINA S.A.
Ruta 11 km 325
Argentina-2200 San Lorenzo, Provincia de Santa Fe

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2010-204-REV 00

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production mentioned above, we certify that the quality of the substance is suitably controlled by the current version of the monograph **TAMSULOSIN HYDROCHLORIDE** no. 2121 of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

– Test for residual solvents by gas chromatography (Annex 1)
Methanol not more than 2000 ppm

The re-test period of the substance is 5 years if stored in double polyethylene bags in a polyethylene container.

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (93) 5 as amended] for a period of five years starting from **12 October 2011**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has one annex of 5 pages.
This certificate has
lines.

On behalf of the
Director of EDQM

Strasbourg, 4 January 2012

DECLARATION OF ACCESS (to be filled in by the certificate holder under their own responsibility)

Synthon BV, as holder of the certificate of suitability
R0-CEP 2010-204-Rev 01 for TAMSULOSIN HYDROCHLORIDE
hereby authorises _____
(name of the pharmaceutical company)
to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (name of product(s) and marketing number(s), if known)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (of the CEP holder)

CEP = **EU approval of the ASMF !!**

The 2-page certificate + annexes will *replace* the ASMF in regulatory filings for CEP accepting countries.

Advantages of the CEP

CEPs save time
- ✓ **Less and cheaper variations**
- ✓ Less to review for authorities
- ✓ Addition of new API supplier with CEP takes ~1 month (vs ASMF ~1 year)

CEPs provide freedom to operate / room for improvement
- ✓ **Less and cheaper variations**
- ✓ Less variation costs increases improvement cost/benefit

CEPs attract customers
- ✓ **Less and cheaper variations**
- ✓ Introducing API suppliers with CEP is fast and relatively cheap
- ✓ CEPs represent European Quality drug substance
- ✓ CEPs are publicly listed on EDQM's website/database

CEPs save money
- ✓ **Less and cheaper variations**

However CEPs are not always an option!
- × **Availability of Ph. Eur. monograph!**

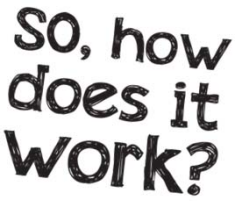
What is ASMF Worksharing?

ASMF Worksharing (ASMF WS) is simply authorities sharing the work related to ASMF assessments. When 10 authorities receive 10 ASMFs, instead of every authority assessing all 10 ASMFs (resulting in 100 ASMF Assessment Reports (ASMF ARs)), 1 authority will be in the lead per ASMF to create the AR, and the other authorities will use the same assessment.

CEP procedure can only be used for compendial drug substances, the ASMF WS procedure can also be used for non-compendial drug substances. Unfortunately, the ASMF WS procedure is currently only available for new ASMFs submitted in DCP and CP applications. ASMFs that have been previously assessed or are undergoing assessment in a DCP/MRP/CP are (currently) excluded from participation.

Also based on mutual recognition, (similar to the CEP procedure), however in this case all authorities still receive the ASMF.

How ASMF WS works (*absurdly simplified version*)



- 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 CMSes
  - **Only critical points / major concerns can be** raised during reviews **!**
- Procedure repeats as above until assessment is complete

The worksharing procedure for the assessment of Active Substance Master File (ASMF)

EMA/CMDh/CMDv/308/2013, Rev. 2, April 2018, pg 10+11/24

3.3.2.3.2. Parent CMS/CxMP members comments on the First Stage ASMF-AR

Parent CMS/CxMP member should only raise additional points that are critical to the quality of the active substance using the appropriate comments template. The comments will be added onto the ASMF-AR to improve transparency of the assessment procedure and avoid Daughter procedures from raising the same or similar points. It is acknowledged that this will not avoid raising duplicate comments when the Daughter Procedures are running less than 30 days behind the Parent procedure.

3.3.2.3.3. Circulation of the First Stage ASMF-AR in the daughter procedures

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.

Q&A on Active Substance Master File (ASMF)

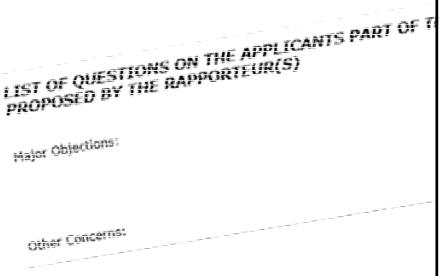
CMDh/CMDv/280/2012, Rev.10, February 2019, pg 7/12

18. If an ASMF is used in multiple procedures, when do we send the response to deficiency questions, including any updates to the ASMF?

Responses should only be sent after the List of Questions has been finalised, that is, e.g. Day 120 for Centralised Procedure, Day 105 for Decentralised Procedure and Day 59 for type II variations and Day 30 for type IB variations. As the ASMF assessment report is being shared between Member States, it is not expected that the list of questions will be different between procedures, unless major concerns are raised in the context of one of the daughter procedures.

EU ASMF assessment report contains two groups of comments:

- **Major objections** and
- **other concerns**.



If the 2nd group is "Other **concern**", the 1st group are also concerns?

Does this mean that "Major *objection*" = "Major *concern*" ?

EU/ASMFs "Non-critical (?) CMS Questions"

EU/ASMF "A" (2014)	d100 HR, PL
EU/ASMF "B" (2014)	daughter RO RUP, daughter PT N, daughter AT N
EU/ASMF "C" (2014)	d100 IE, RO, PT, PL; d145 PT, IE
EU/ASMF "D" (2014)	d100 PT
EU/ASMF "E" (2015)	d100 DE; d145 DE
EU/ASMF "F" (2016)	daughter RMS DE, daughter CP
EU/ASMF "G" (2016)	d100 RO, DE
EU/ASMF "H" (2016)	☺
EU/ASMF "I" (2017)	d100 RO
EU/ASMF "J" (2017)	d100 PL, UK, RO
EU/ASMF "K" (2018)	daughter RMS AT, daughter RMS LV

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 potential serious risk to public health but 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.

Example of a "critical" question

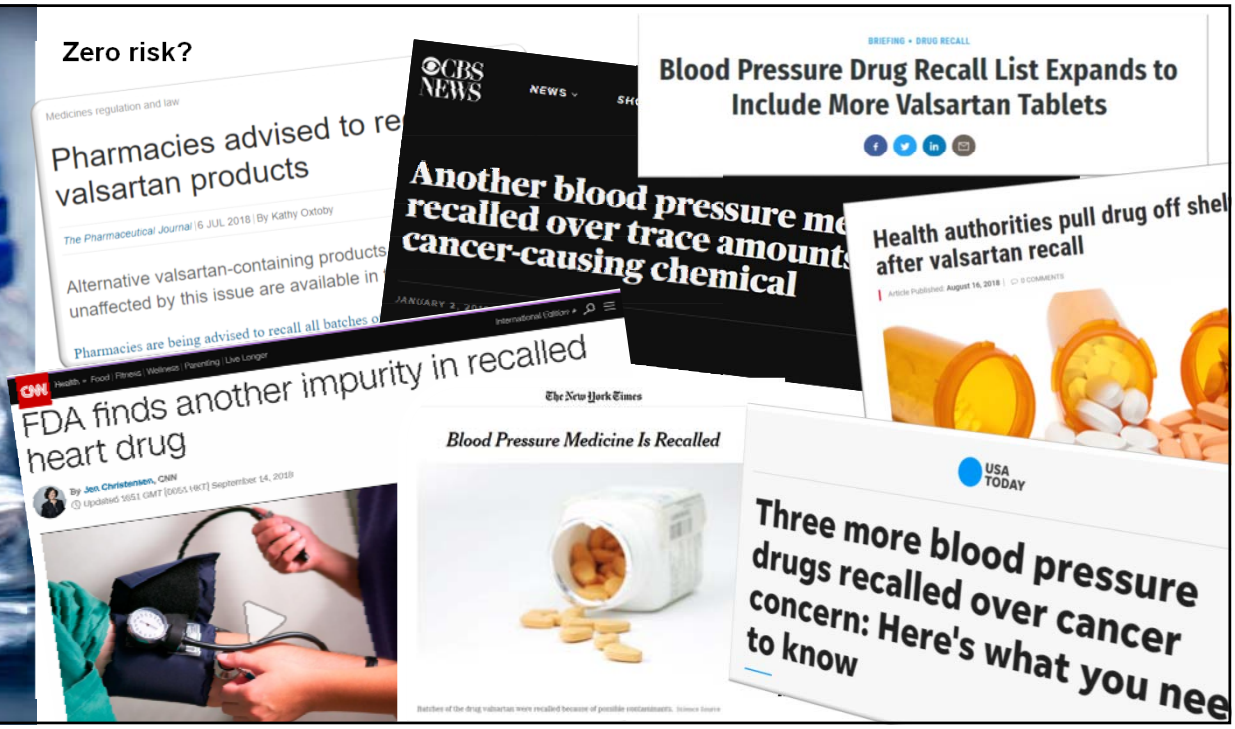
"*The batch size range should be stated in the open part, as this information should be available to the applicant*"

> "We [the RMS] have consulted the CMS to check whether they regarded their comment as critical. The CMS confirmed that the quested is considered to be critical. Therefore, we would like to ask you answer the question of the CMS."

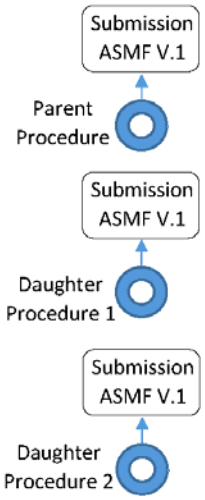
A very relevant question?

Which one does not belong here?

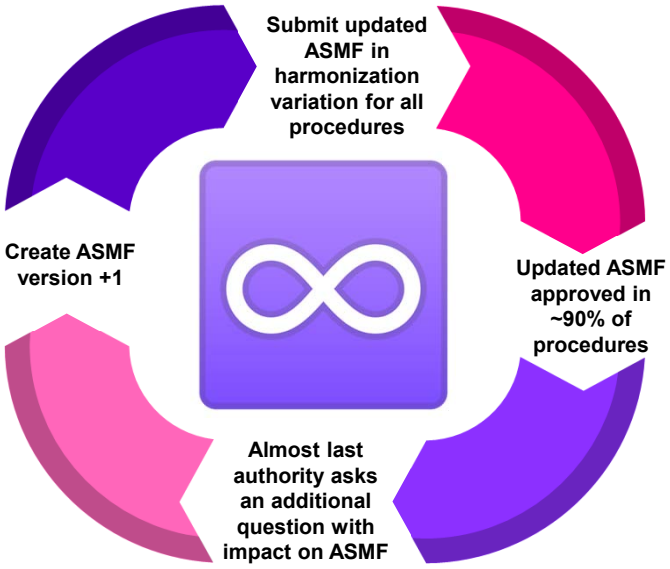
Zero risk?



Impact of differences in assessment timing on ASMF version



The never-ending harmonization cycle



Examples from real life!

Examples from real life (pt. 2)

Parent DCP RMS UK.

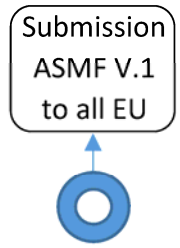
6 Daughter DCPs RMS UK

1 Daughter CP

Market open (!)

DCP 1	DCP 2	DCP 3	DCP 4	DCP 5	DCP 6	DCP 7	CP
UK	UK	UK	UK	UK	UK	UK	28 MS
1 CMS	1 CMS	1 CMS	4 CMS	18 CMS	1 CMS (DE)	2 CMS (DE)	IS, NO, LI
ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1

EU/ASMF “F”



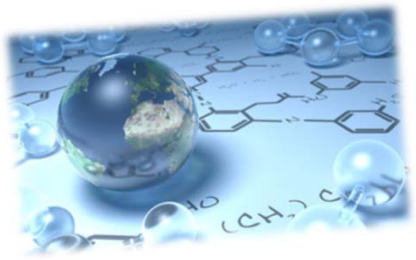
EU/ASMF “F”

	DCP 1	DCP 2	DCP 3	DCP 4	DCP 5	DCP 6	DCP 7
	UK	UK	UK	UK	UK	UK	UK
	1 CMS	1 CMS	1 CMS	4 CMS	18 CMS	1 CMS (DE)	2 CMS (DE)
d0	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1
d70	9/9	9/9	9/9	9/9	9/9	9/9	9/9
d100	-	-	-	-	-	DE 23/12	DE 23/12
d105	ASMF 2	ASMF 2	**ASMF 3**	**ASMF 3**	**ASMF 3**	**ASMF 3**	**ASMF 3**

EU/ASMF "F"

CP d120 Applicant's quality LoQ stated the following:

"The reference is made of the EU ASMF worksharing procedure (EU/ASMF/"E"). The revised LoQ on the drug substance has been harmonised with the Day 70 WS AR with the few additional issues raised"



EU/ASMF "F"

UK D70		DE D100			CP D80		
Q1	~~Q6~~	~~Q1~~	~~Q6~~	~~Q11~~	Q1	Q6	Q11
Q2+2A	Q7	~~Q2~~	~~Q7~~	~~Q12~~	~~Q2~~	~~Q7~~	Q12
Q3	Q8	~~Q3~~	~~Q8~~		Q3	Q8	~~Q13~~
~~Q4~~	Q9	~~Q4~~	~~Q9~~		Q4	~~Q9~~	
~~Q5~~		~~Q5~~	~~Q10~~		~~Q5~~	~~Q10~~	

CP d120 RP LoQ					
Q1	UK Q1	Q7	UK Q9	Q13	CP Q12
Q2	CP Q1	Q8	CP Q4	Q14	UK Q7
Q3	UK Q2	Q9	UK Q3		
Q4	UK Q2A	Q10	CP Q6		
Q5	CP Q3	Q11	CP Q8		
Q6	UK Q8	Q12	CP Q11		

EU/ASMF "F"

UK D70		DE D100					CP D80		
Q1	~~Q6~~	~~Q1~~	~~Q6~~	Q11	~~Q16~~	~~Q21~~	Q1	~~Q6~~	~~Q11~~
~~Q2~~	Q7	~~Q2~~	~~Q7~~	Q12	~~Q17~~	~~Q22~~	~~Q2~~	~~Q7~~	~~Q12~~
~~Q3~~	Q8	~~Q3~~	Q8	~~Q13~~	~~Q18~~	~~Q23~~	~~Q3~~	~~Q8~~	~~Q13~~
Q4	~~Q9~~	~~Q4~~	Q9	~~Q14~~	~~Q19~~		~~Q4~~	Q9	Q14
Q5		~~Q5~~	Q10	~~Q15~~	~~Q20~~		Q5	Q10	

CP d120 OP LoQ					
Q1	CP Q1	Q6	NEW	Q11	CP Q10
Q2	UK Q1	Q7	DE Q8,9,10	Q12	UK Q7
Q3	UK Q5	Q8	DE Q11	Q13	UK Q8
Q4	UK Q4	Q9	CP Q9	Q14	CP Q14
Q5	CP Q5	Q10	DE Q12		

EU/ASMF "F"

	DCP 1	DCP 2	DCP 3	DCP 4	DCP 5	DCP 6	DCP 7	CP
	UK	UK	UK	UK	UK	UK	UK	28 MS
	1 CMS	1 CMS	18 CMS	4 CMS	1 CMS	1 CMS (DE)	2 CMS (DE)	IS, NO, LI
d0	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1	ASMF 1
d70/80	9/9	9/9	9/9	9/9	9/9	9/9	9/9	CP 14/13
d100/120	-	-	-	-	-	DE 23/12	DE 23/12	CP 14/14
d105/121	ASMF 2	ASMF 2	ASMF 3	ASMF 3	ASMF 3	ASMF 3	ASMF 3	ASMF 4

EU/ASMF “F”

	DCP 1	DCP 2	DCP 3	DCP 4	DCP 5	DCP 6	DCP 7	CP
	UK	UK	UK	UK	UK	UK	UK	28 MS
	1 CMS	1 CMS	18 CMS	4 CMS	1 CMS	1 CMS (DE)	2 CMS (DE)	IS, NO, LI
d105	ASMF 2	ASMF 2	ASMF 3	ASMF 3	ASMF 3	ASMF 3	ASMF 3	CP 14/13
d120	No AR	No AR	No AR	No AR	No AR	No AR	No AR	CP 14/14
d160	ASMF 2 approved	ASMF 2 approved	approve ASMF 3?	approve ASMF 3?	approve ASMF 3?	ASMF 5	ASMF 5	ASMF 4
approval	ASMF 2	ASMF 2	ASMF 6	ASMF 6	ASMF 6	ASMF 6	ASMF 6	ASMF 6

Assessment of the Company´s response

The clarifications provided have been accepted to be in line with in EU worksharing ASMF assessment.

Conclusion

Point resolved

Q&A on Active Substance Master File (ASMF)

CMDh/CMDv/280/2012, Rev.10, February 2019, pg 7/12

18. If an ASMF is used in multiple procedures, when do we send the response to deficiency questions, including any updates to the ASMF?

Responses should only be sent after the List of Questions has been finalised, that is, e.g. Day 120 for Centralised Procedure, Day 105 for Decentralised Procedure and Day 59 for type II variations and Day 30 for type IB variations. As the ASMF assessment report is being shared between Member States, it is not expected that the list of questions will be different between procedures, unless major concerns are raised in the context of one of the daughter procedures.

CEP vs EU ASMF WS

CEP	EU-ASMF WS
Based on (mutual) recognition.	Based on mutual recognition.
Centralized procedure with 1 authority and always only 1 current + active file, no risk for diverging ASMF versions. No time/money/capacity wasting harmonization variations.	Decentralized procedure with 31 authorities and 31 active files, high risk for diverging versions. A lot of time/money/capacity wasting harmonization variations.
Efficient use of reviewer capacity, review by 2 assessors (reviewers can be EU and non-EU).	Inefficient use of reviewer capacity, review by at least 2, but >31 assessors possible (only EU reviewers).
Assessment fully recognized within EU and even in some countries outside EU.	Assessment not even fully recognized within EU.
Chronological assessment WF, all questions at the beginning of the procedure.	Non-chronological assessment WF, ASMF nearly approved in procedure A, but lot of additional questions at that moment in time in procedure B.
ASMF holder in the lead for ASMF lifecycle management. ASMF holder paying for own ASMF changes. These changes are paid and reviewed only once. Administrative fee to update dossier payed by MAH.	Lifecycle management of ASMF nearly impossible. Timing for change implementation unclear. MAH to pay for ASMF changes. Each ASMF change paid and reviewed multiple times.

Conclusions

- The ASMF version management in the EU is a problem for both industry and authorities.
- CEPs are the best tool in the ASMF toolbox. Use it where possible! Their 25 year anniversary is absolutely a good reason for a party!
- The examples 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 an 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.**

My suggestions for improvement EU ASMF WS

- Create the possibility to request EU/ASMF number from EDQM.
  They are in some cases the authority to perform the first review of the ASMF.
- Define “critical to the quality of the drug substance”.
- Implement a fixed rapporteur/co-rapporteur
  This opens up the possibility to add National procedures.
- Expand to include also ‘approved in marketing authorization’ ASMFs with risk of reassessment.
- Make it mandatory and stop with national ASMF numbers. Will increase overview.

- Improve the recognition of assessment reports at the authority side.
  Without acceptance of the AR there is no ASMF WS!
- **Make it a Centralised stand alone procedure – paying for own changes.**
  A “CEP-like” option for non-compendial drug substances.

Thank you for your attention!

Questions?

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The Netherlands
www.synthon.com

Sources:

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- *CMDh – Active Substance Master File Working Group*
  http://www.hma.eu/306.html
- *CMDh – Agenda and Meeting Minutes*
  http://www.hma.eu/457.html

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IPRP
International Pharmaceutical Regulators Programme

Overview of the International Pharmaceutical Regulators Programme (IPRP)

and the

IPRP Quality Working Group for Generics

Gary Condran, Health Canada

EDQM and the Ph.Eur.: State-of-the-art Science for Tomorrow's Medicines

Strasbourg, France

20 June 2019

IPRP

Outline

Overview of IPRP:

- Concept – who we are
- History – origin of IPRP
- Mission – what we want to achieve
- Scope
- Strategic Priorities 2018 – 2020
- IPRP versus ICH – where is the difference?
- Governance
- Operating Principles
- IPRP Members and Observers
- Activities – our working groups
- Reflections on IPRP
- Looking ahead – next steps

IPRP Quality Working Group for Generics:

- Origins
- Mandate
- Scope
- Objectives
- Barriers
- Approach
- Competed Projects
- Ongoing Projects

IPRP

Concept – Who we are

THE regulatory «hub» for regulatory authorities and organisations

- To share information
- To discuss issues of common concern, especially emerging scientific areas/new technologies
- To work towards regulatory convergence

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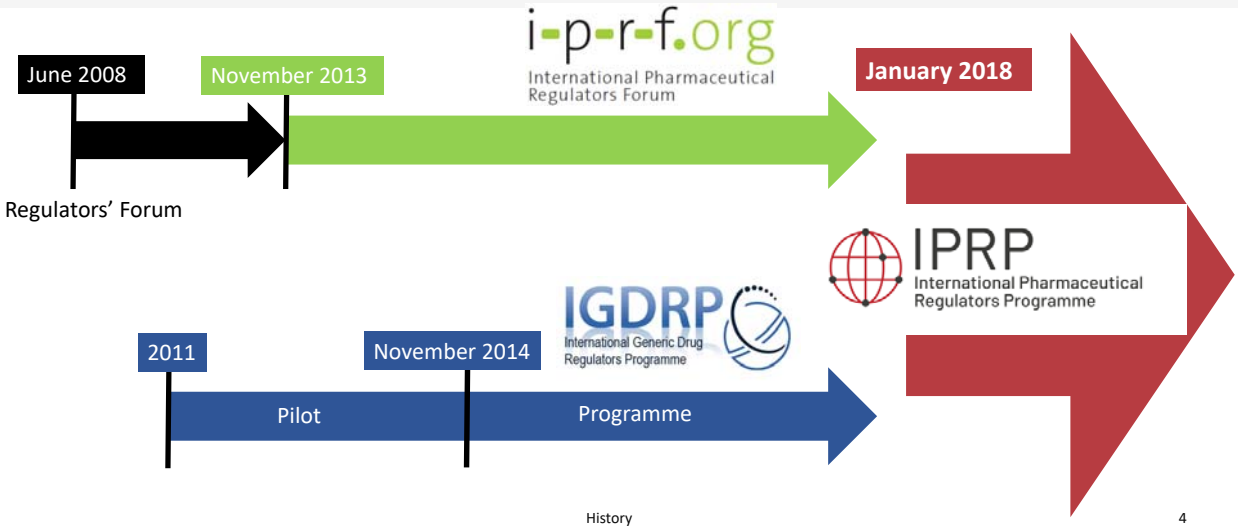
Where we come from



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Drivers for the consolidation of IPRF and IGDRP

- A shared vision
- Creating “the” regulatory hub for pharmaceuticals
- Coherent membership and level of engagement
- Maximise synergies and avoid duplication of efforts
- Avoidance of the misperception of differences between innovative and generic medicines
- Improving governance, increasing support, saving human and financial resources of involved regulators
- Single management committee
- Permanent secretariat
- Single website, infrastructure and platform for sharing information

IPRP

Mission

Promotion of regulatory convergence by means of practical and operational information exchange which fosters trust and a mutual understanding of the range of challenges and contexts facing each regulatory authority.

This is done in order to enhance the health of our populations by the most efficient means possible.

IPRP

Scope

Medicinal products for human use ("pharmaceuticals") including but not limited to:

- innovator pharmaceuticals,
- cell and gene therapies,
- biologics,
- biosimilars,
- generic pharmaceuticals, and
- nanomedicines

IPRP

Strategic Priorities 2018 - 2020

1. Create a discussion forum for regulatory authorities and regulatory organisations to identify and address emerging issues of shared interest and discuss approaches
2. Establish a collaborative environment to share regulatory perspectives on ICH work, discuss challenges and promote consistent implementation of ICH guidelines
3. Promote greater convergence in regulatory approaches based on international standards and best practices
4. Create conditions to facilitate greater inter-agency collaboration, enhance communications and support capacity building (e.g. training)

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IPRP versus ICH – where is the difference?

IPRP

- Regulators-only forum
- Identifying and addressing emerging regulatory issues of shared interest
- Discussing of potential approaches towards convergence resulting in reflection papers, common templates, articles in journals, …
- **NO t**echnical Guideline development

Once «mature», a topic can be handed over to ICH

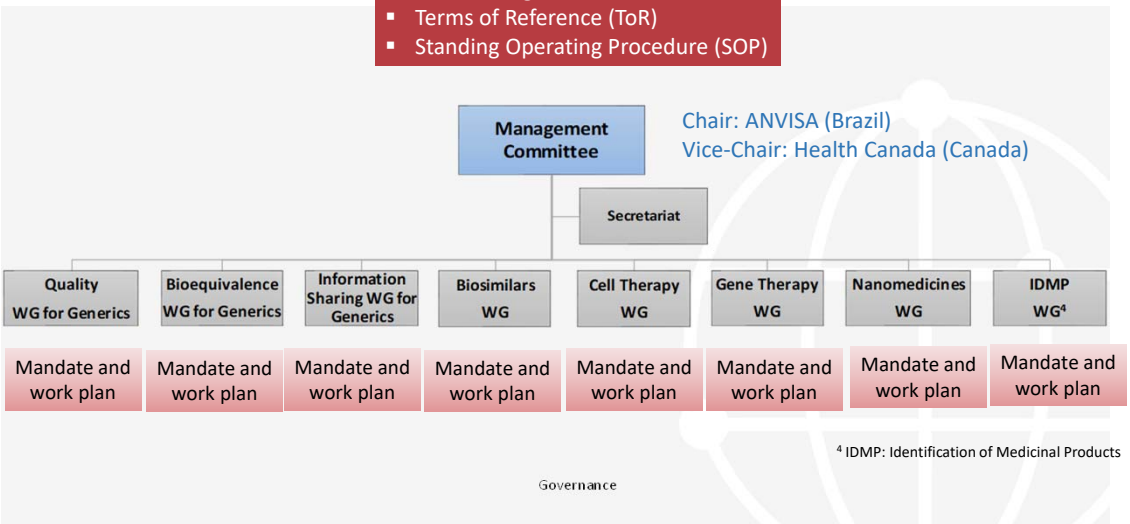
ICH

- Non-Profit Association under Swiss law between Regulators, Industry and other Organisations
- Harmonisation of technical requirements in the area of quality, safety, efficacy and multidisciplinary topics
- **Outcome:** harmonised technical Guidelines

IPRP

Governance

- IPRP Strategic Vision 2018 – 2020
- Terms of Reference (ToR)
- Standing Operating Procedure (SOP)



[4] IDMP: Identification of Medicinal Products

IPRP

Operating principles

- Voluntary network of members and observers with possibility to “opt-out”
- Management Committee (MC) as decision making body and laying out the strategic vision
  - ☞ decision making is consensus driven (no voting)
  - ☞ meets face-to-face twice a year within the margins of ICH
  - ☞ comprised of up to three (3) official representatives from each participating member and observer
  - ☞ Chair and Vice-Chair for the term of one year (can be renewed for up to three times)
- MC is supported by a permanent secretariat
  - ☞ IPRP Secretariat function is provided by ICH Secretariat based upon an MoU between IPRP and ICH
- Financing:
  Contributions on a voluntary basis by its members through funding mechanisms that are consistent with the laws regulating the activities of each member
- Currently 8 Working Groups (WGs) reporting to MC

IPRP

Membership / Observership

Representatives from

- Pharmaceutical regulatory authorities
- Organisations with responsibilities relating to the regulation of medicinal products for human use
- Regional Harmonisation Initiatives (RHIs)

Principal rules:

☞ No differences in expectations and level of participation between members and observers.

☞ Inclusive membership

IPRP

IPRP Members and Observers – 1 of 3 (as of October 2018)

- Agência Nacional de Vigilância Sanitária (ANVISA) (Brazil)
- Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED) (Cuba)
- European Commission (EC) / European Medicines Agency (EMA) (Europe)
- European Directorate for the Quality of Medicines and Healthcare (EDQM) (Observer)
- Federal Commission for the Protection against Sanitary Risk (COFEPRIS) (Mexico)
- Federal Service for Surveillance in Healthcare and Social Development (Roszdravnadzor) (Russia)
- Health Canada (HC) (Canada)
- Health Sciences Authority (HSA) (Singapore)
- Medicines and Medical Devices Safety Authority (MEDSAFE) (New Zealand)

IPRP

IPRP Members and Observers – 2 of 3 (as of October 2018)

- Ministry of Food and Drug Safety (MFDS) (South Korea)
- Ministry of Health, Labour and Welfare (MHLW) / Pharmaceuticals and Medical Devices Agency (PMDA) (Japan)
- National Center for Expertise (Kazakhstan)
- South African Health Products Regulatory Authority (SAHPRA) (South Africa)
- Swissmedic, Swiss Agency for Therapeutic Products (Switzerland)
- Taiwan Food and Drug Administration (TFDA) (Chinese Taipei)
- Therapeutic Goods Administration (TGA) (Australia)
- United States Food and Drug Administration (FDA) (US)
- World Health Organization (WHO) (Observer)

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IPRP Members and Observers – 3 of 3 (as of October 2018)

Regional Harmonisation Initiatives

- APEC (Asia-Pacific Economic Cooperation)
- ASEAN (The Association of Southeast Asian Nations)
- EAC (East African Community)
- GHC (Gulf Health Council)
- PAHO/PANDRH (Pan American Network for Drug Regulatory Harmonization)
- SADC (Southern African Development Community)

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Activities – Our Working Groups

IPRP

Quality Working Group for Generics

Co-Chairs	WHO and EDQM
Mandate	▪ Establish a framework and mechanisms for information sharing and work sharing of Quality information ▪ This is with a view to greater collaboration and potentially regulatory convergence in the assessment of ASMFs/DMFs and applications for generic drug products
Main Achievements	▪ Lexicon of Quality Terms ▪ Common ASMF/DMF Submission Form ▪ Quality Assessment Report (QAR) template for ASMFs/DMFs ▪ Gap Analysis on ASMF/DMF frameworks and procedures ▪ Criteria for when a separate ASMF/DMF should be submitted ▪ Guidance for Quality Assessors-Drug Substance

IPRP

Bioequivalence Working Group for Generics

Co-Chairs	HSA (Singapore) and WHO
Mandate	▪ Promote collaboration and regulatory convergence relating to the assessment of bioequivalence for generic drug products ▪ Develop tools (e.g., assessment templates, guidance for assessors) to aid in assessment of bioequivalence
Main Achievements	▪ Biopharmaceutics Classification System (BCS) Biowaivers Assessment Report template (published on the IPRP website) ▪ Survey of the Regulatory Requirements for BCS-Based Biowaivers for Solid Oral Dosage Forms by Participating Regulators and Organisations of the International Generic Drug Regulators Programme: https://journals.library.ualberta.ca/jpps/index.php/JPPS/article/view/29579

IPRP

Information Sharing Working Group for Generics

Chair	EC/EMA (Europe)
Mandate	▪ Sharing assessment reports in real-time with non-EU regulatory agencies ▪ Participating IPRP members: Health Canada, Swissmedic, Taiwan FDA, Therapeutic Goods Administration
Main Achievements	▪ EU Decentralised Procedure (DCP) pilot (launched July 2014) ▪ EU Centralised Procedure (CP) pilot (launched January 2015)

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Biosimilars Working Group

Co-Chairs	MFDS (South Korea) and Health Canada (Canada)
Mandate	▪ Promote convergence of review and regulation of biosimilar products ▪ Contribute to provide meaningful outcome to promote public health through more affordable biosimilar products
Main Achievements	▪ Public Assessment Summary Information for Biosimilars (PASIB) ▪ Reflection Paper on Extrapolation of Indications in Authorisation of Biosimilar Products

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Cell Therapy Working Group

Chair	Rotating Chair among members; FDA (US) serves as secretariat
Mandate	▪ Open discussion and sharing of best practices for the regulation of cell and tissue-based therapies ▪ Support harmonization initiatives such as APEC ▪ Refer topics to appropriate organizations such as ICH, PIC/S, PANDRH, WHO
Main Achievements	▪ Reflection paper «General Principles to Address the Nature and Duration of Follow-up for Subjects of Clinical Trials Using Cell Therapy Products»

IPRP

Gene Therapy Working Group

Chair	Rotating Chair among members; FDA (US) serves as secretariat
Mandate	▪ Open discussion and sharing of best practices for the regulation of gene therapy products ▪ Focused discussion of topics that are potentially suitable for regulatory convergence, and producing reflection documents ▪ Support harmonization initiatives such as APEC and PANDRH ▪ Refer topics to appropriate organizations such as ICH, PIC/S, WHO
Main Achievements	▪ Reflection Paper «Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products»

IPRP

Nanomedicines Working Group

Co-Chair	Health Canada (Canada), TGA (Australia)
Mandate	▪ Non-confidential information sharing, regulatory harmonization or convergence focused on nanomedicines / nanomaterial in drug products and borderline and combination products ▪ Regulatory cooperation, including work-sharing, in specific areas of nanomedicines / nanomaterial in drug products with other related international bodies ▪ Collaboration of training organization between international regulators ▪ Promotion of potential consensus finding on standards
Main Achievements	▪ Joint Research Centre (JRC) Technical Reports: Identification of regulatory needs for nanomedicines ▪ Summary of liposomal survey and terminology poster ▪ Information sharing and mapping

IPRP

Identification of Medicinal Products (IDMP) Working Group

Chair	Health Canada (Canada)
Mandate	▪ Ensure the awareness and understanding of the IDMP standards more globally by pharmaceutical regulators ▪ Clarify how and why these standards can add value to regulator business processes to improve the quality and effectiveness of shared regulatory functions ▪ Share strategies and experiences for their successful and consistent implementation
Main Achievements	▪ IDMP Frequently Asked Questions *(to be published on IPRP website)*

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Reflections on IPRP

- Clear Mission & Vision is key to ensure there is no overlap with other international initiatives
- Close linkages and communication with other international initiatives are important
  - ☞ updates at each MC meeting
- Transition phase/implementation of the consolidation:
  No impact on WGs activities
  - ☞ All WGs maintained the activities proposed in their workplans
  - ☞ Momentum was not lost
- Transparent communication through dedicated website is essential to raise awareness of what IPRP is and what its objectives are
  - ☞ Press Release after each MC f2f meeting
  - ☞ Publication of working group results/achievements

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Next steps

- How to approach Stakeholder Engagement?
  - ☞ Stakeholder Engagement Plan under discussion
- Reflection on mature topics that might be proposed to ICH for consideration by the Assembly
  - ☞ Upon proposal by respective Working Group when reporting back to MC
- Reflection on new topics to be addressed under IPRP
  - ☞ Standing item on MC meeting agenda

IPRP MC meeting: 2 – 3 June 2019 in Amsterdam, the Netherlands

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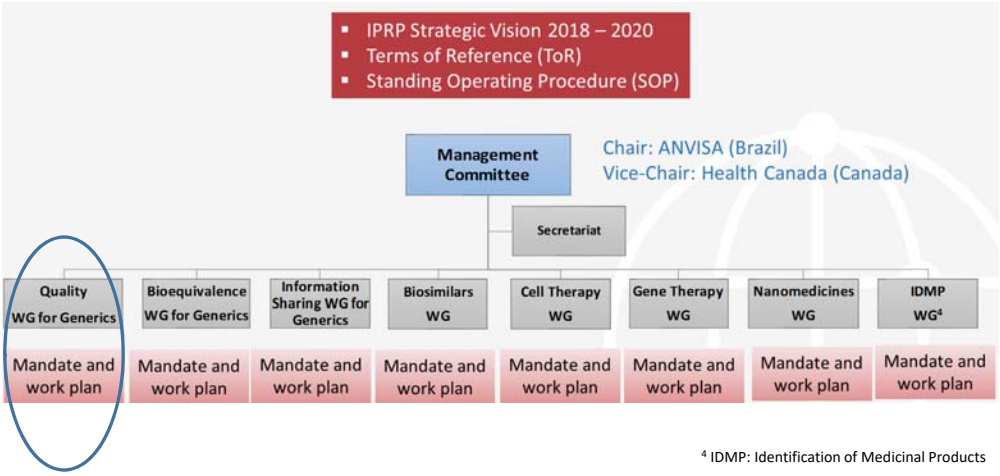
IPRP Quality Working Group for Generics (QWGG)

IPRP

Quality WG for Generics

Governance



[4] IDMP: Identification of Medicinal Products

IPRP

Quality WG for Generics

Origins

In 2013, the working group's first incarnation was as the **ASMF/DMF Working Group** of the International Generic Drug Regulators Pilot (IGDRP).

In 2016, the title and mandate of the working group was expanded to the **Quality Working Group**.

In 2018, the title was changed to the **Quality Working Group for Generics (QWGG)** as part of the IPRP.

The focus still primarily remains on ASMF/DMF issues.

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Quality WG for Generics

Membership

- Agencia Nacional de Vigilancia Sanitaria (ANVISA)
- European Commission (EC) / European Medicines Agency (EMA)
- European Directorate for the Quality of Medicines and Healthcare (EDQM) - Observer
- Federal Commission for the Protection against Sanitary Risk (COFEPRIS)
- Food and Drug Administration, US (FDA, US)
- Health Canada
- Health Sciences Authority (HSA)
- Ministry of Food and Drug Safety (MFDS)
- Ministry of Health, Labour and Welfare (MHLW) & Pharmaceuticals and Medical Devices Agency (PMDA)
- South African Health Products Regulatory Authority (SAHPRA)
- Swissmedic
- Taiwan Food and Drug Administration (TFDA)
- Therapeutic Goods Administration (TGA)
- World Health Organization (WHO) - Observer

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Quality WG for Generics

Mandate

To establish a framework and mechanisms for information sharing of Quality-related information. This is with a view to greater collaboration and potentially regulatory convergence in the assessment of ASMFs/DMFs and applications for Generic Drug Products, taking into account established international initiatives, best practices and ongoing developments.

Scope

The projects of the QWGG focus on technical requirements, procedures and tools for the assessment of Quality information related to ASMFs/DMFs and Generic Drug Products.

Current Co-Chairs: WHO and EDQM

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Quality WG for Generics

Objectives

- To develop tools for ASMF/DMF assessment
- Sharing best practices, technical requirements, issues of interest
- Strengthen ASMF/DMF assessment processes
- Potentially share Quality Assessment Reports for ASMF/DMF
- Share information about API sources of concern, facilitate identification of alternatives (eg. In case of shortages)
- To develop tools for generic Drug Products assessment
- Sharing best practices, technical requirements, issues of interest
- Potentially share Quality Assessment Reports for Generic Drug products applications (where enabled by information sharing agreements)

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Quality WG for Generics

In brief … the ultimate goal

- Reduction in efforts to review ASMFs/DMFs and Generics
- Increased consistency in the style and information captured during assessment of ASMFs/DMFs and Generic Drug Products
- Increased consistency in assessment outcomes of ASMFs/DMFs and Generic Drug Products

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Quality WG for Generics

Barriers

Information sharing

- Restrictions on sharing of Confidential business information
- Willingness of industry to participate
- Submissions in multiple jurisdictions

Barriers to usefulness

- Language/terminology
- Assessment approaches
- Assessment documentation
- Identification of common applications

Regulatory

- Different assessment procedures
- Different timelines
- Different approaches to post-approval changes

Quality WG for Generics

Approach

- Familiarisation among regulators (TCs, face-to-face meetings, points of contact)

  (Getting to know the relevant people in agencies)

- Understanding regulatory processes and requirements
- Establishing a common language
- Establishing a common approach/model documentation
- Identifying common ASMFs/DMFs
- Sharing of information

Quality WG for Generics

Understanding processes & requirements

- Gap Analysis on ASMF/DMF frameworks and procedures
  - *J Pharm Pharm Sci.* 2016 Apr-Jun; 19(2):290-300
  - Author: Pharmaceuticals and Medical Devices Agency (PMDA)
  - http://www.iprp.global/page/gap-analysis-asmfdmf-frameworks-and-procedures
- Survey and comparison of ASMF/DMF procedures, submission requirements, assessment processes, technical requirements for active pharmaceutical ingredients (APIs), generation of assessment reports, Good Manufacturing Practice (GMP) inspection/certification of API manufacturers, etc
- Contains key considerations in order to facilitate the filing of ASMFs/DMFs globally and to establish a framework for sharing and utilising information related to ASMFs/DMFs among QWGG members.

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Quality WG for Generics

Completed projects

Tools for the assessment of ASMFs/DMFs:

- *These are model documents and information. Not mandatory for adoption, but members are committed to their implementation when possible.*

- ASMF/DMF lexicon of quality terms.
- Common ASMF/DMF information fields that should be recorded at the time of submission.
  - includes a list of agencies/jurisdictions where the same ASMF/DMF has been submitted
- Criteria for when a separate ASMF/DMF should be provided.
- ASMF/DMF common Quality Assessment Report template.
- Guidance for Quality Assessors – Drug Substance.

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Quality WG for Generics

On-going projects (1)

- Repository of Technical Issues of Interest (ROTII) for ASMF/DMF:
  - Members share issues of common interest (e.g., which format is required, is a test for microbial contamination routinely required, is a GMP inspection of the manufacturer required, etc)
  - Updated on a regular basis and discussed
- Survey on administrative procedures and terminologies for quality variations/post-approval changes:
  - Publication of a summary foreseen in the near future
- ASMF/DMF Quality Information Summary:
  - Establishment of a common Quality Information Summary template, to facilitate information sharing and identification of similar ASMF/DMF among agencies
- Repository of key Quality Guidance (ASMF/DMF & Drug products):
  - Collection of links to key guidance (technical requirements and procedures) available in the different agencies

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Quality WG for Generics

On-going projects (2)

- Expansion of the ROTII to issues related to generic Drug Products
- Common Quality Assessment Report template for generic Drug Products
- Guidance for Quality Assessors – Drug Product

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Quality WG for Generics

On-going : Pilot ASMF/DMF Database (1)

- Objective:
  - Explore the feasibility and requirements for a common ASMF/DMF database to facilitate information sharing
  - Identification of commonly held ASMF/DMFs, to allow requests of another agency's Assessment Report when assessing the ASMF/DMF
- Initial scoping:
  - High-level descriptive information regarding an ASMF/DMF to be included in the database
  - Selection of a number of drug substances of interest (~20-30)
- Participation is on voluntary basis
- Pilot for 2 years ➔ Oct 2020

IPRP

Quality WG for Generics

On-going : Pilot ASMF/DMF Database (2)

The ASMF/DMF Database:

- Contains high-level descriptive information regarding an ASMF/DMF:
  - Drug substance name, quality standard, ASMF/DMF version number (AP/RP), Holder details, final manufacturing site(s) details, receiving agency, date of receipt, etc
- Not intended to hold assessment reports nor ASMF/DMF files
- Held within a secure IT environment (EDQM)

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Quality WG for Generics

On-going : Pilot ASMF/DMF Database (3)

The process:

- At receipt of an ASMF/DMF, the participating agency identifies if it is a potential candidate for the project (e.g. based on list of APIs and common submission elements)
- ASMF/DMF holder is approached by the receiving agency to get permission to record the data into the database
- Data are recorded after permission is obtained
- ASMF/DMF holder is approached by the agency to get permission to share assessment report with a project member in case it is identified that the same documentation has been submitted to another agency

Quality WG for Generics

On-going : Pilot ASMF/DMF Database (4)

- Industry engagement:
  - Initial feedback from Industry representatives gathered in 2017, on the database and on ASMF/DMF reports sharing
  - Letter sent to Industry associations and some companies submitting globally (Brazil, China, Europe, IGBA, India, Taiwan)
  - On perceived benefits and concerns for the database, on possibility to share assessment reports and on possibility to get permission to share reports at the same time as permission to record ASMF/DMF into the database
  - Few replies received – feedback not so positive

Quality WG for Generics

On-going : Pilot ASMF/DMF Database (5)

- Status today:
  - About 100 entries in the database (all ASMF/DMF holders gave permission) – 5 agencies
  - A couple of common ASMF
  - Use to be combined with confidence building exercise for assessment of ASMF/DMF.
- Industry participation and feedback is critical!

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THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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Recent developments of the CEP procedure

EDQM international conference, 19-20 June 2019

Hélène BRUGUERA, Head of the Certification Department, EDQM

Content

- Recent EDQM guidelines and policies
- Nitrosamines in sartans
- Optimising use of CEPs

Recent EDQM guidelines

Issued in 2018:

- New gdl "How to read a CEP"
  - explains information reported on CEPs related to assessment carried out at EDQM and links to the Ph. Eur. monograph
- Revised gdl "Content of the dossier for TSE risk"
- Revised gdl on Elemental Impurities
  - Based on experience gained since initial implementation in 2016
- Revised gdl on Revisions/renewals of CEPs
  - Has triggered revision of several EDQM gdls:
    - Content of the dossier for chemical purity
    - Management of applications for CEPs
    - Sister File procedure

Revised EDQM guideline for Revisions / Renewal of CEPs

- Published in September 2018, implementation on **1 January 2019**
- A number of changes in order to:
  - Align with EU and EU ASMF Worksharing policy
  - Facilitate lifecycle management of CEP applications
  - Facilitate use of CEPs by stakeholders: traceability of processes, sites etc

  - More situations where a revision of the current CEP is no longer possible and a separate CEP application is required (➔ Sister File procedure):
    - "Substantially different route of synthesis" (addition or replacement)
    - New site for the final substance not belonging to the original group

    ➔**1 process, 1 company = 1 CEP**

- No major implementation issues

Use of material of animal/human origin

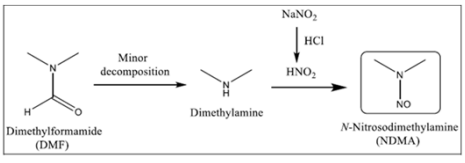
- For substances covered by CEPs
- When material of animal/human origin is used in during production
  - Concerns mainly fermentation products, amino-acids, etc
  - In such situations, assessors confirm:
    - absence of risk of viral contamination (no need for viral safety assessment) OR
    - Need for viral safety assessment in the context of the marketing application
- Outcome reported on the CEP
- Implementation on new applications and renewals

  ➔ Centralisation of decision & transparency

Nitrosamines in sartans

Nitrosamines in sartans

- Background:
  - June 2018: information that Valsartan manufactured by Zhejiang Huahai Pharmaceutical (ZHP) was contaminated with NDMA (N-Nitrosodimethylamine)
  - Source covered by a CEP (suspended immediately)
  - NDMA likely to be present in batches since 2012, when a change of process was made ➔ via a revision of the CEP application
  - NDMA was unexpected and therefore not controlled
  - Origin: reaction of sodium nitrite + amine, acidic conditions



Nitrosamines in sartans (2)

- The review of process conditions suggested quickly that other dossiers for valsartan and for other sartans may be affected, and that other nitrosamines may be generated ➔ This has been confirmed since then
  - NDEA, NMBA, NDBA, NDIPA, EIPNA etc
  - And possibly other active substances beyond sartans…

- Nitrosamines are part of ICH M7 "cohort of concern"
  - Very low acceptable amounts – require sensitive analytical methods
- Many API manufacturers and Finished Products manufacturers affected
- Worldwide issue – eg. Australia, Brazil, Canada, China, Japan, Korea, Russian Federation, Singapore, Taiwan, USA, etc
- EU initiated referral (Article 31) on Valsartan. Extended to other sartans having a tetrazole ring

Nitrosamines in sartans (3) – Actions taken

- Actions taken by EDQM:
  - Review and update of CEP applications
  - Sampling and testing (OMCLs)
  - GMP inspections
  - International collaboration (exchange of information)
  - Update of Ph. Eur

Nitrosamines in sartans (4)

- Review of CEP applications:
  - About 125 applications concerned (incl. history)
  - A number of sources of nitrosamines :
    - Reaction conditions (reagents, solvents, their quality, degradation of materials)
    - Cross-contaminations between processes (running on same line)
    - Recovery of solvents (contamination at 3rd party)
  - 11 CEPs suspended due to contamination
    - Valsartan sources contaminated with NDMA, NDEA, NDIPA
    - Irbesartan contaminated with NDEA
    - Losartan K contaminated with NDEA, NMBA
  - Exercise almost completed
    - Letters of approval or revised CEPs granted
    - CEPs restored

Nitrosamines in sartans (5)

- Sampling & testing:
  - EDQM coordinating network of European Official Medicines Control Laboratories (OMCLs) – 13 labs involved
    - Methods developed by several labs
    - Detection of NDMA, NDEA or both, in APIs and/or drug products ➔# 2000 Drug Products and 600 APIs batches tested for NDMA and/or NDEA
  - A number of methods published on the EDQM website (GC/MS, HPLC-UV, LC/MS/MS, GC/MS/MS):

    https://www.edqm.eu/en/ad-hoc-projects-omcl-network
  - OMCLs provide official results:
    - to confirm patient exposure for products on the market
    - for samples taken from the GMP inspections
    - to verify data given by manufacturers
    - Market surveillance for various sartans

Nitrosamines in sartans (6)

- GMP inspections:
  - EDQM/EMA of Zh. Huahai, September 2018 and March 2019
  - EDQM/EMA of Zh. Tianyu
  - EDQM (with CH) of Lantech Pharma
  - EU inspection of Hetero Labs, March 2019
  - Other manufacturers by international partners

- International cooperation:
  - The issue has fostered international cooperation and exchange of information worldwide
  - Under confidentiality agreements, sharing test results from OMCLs & data from manufacturers with many authorities
  - Harmonisation of policies, decisions (eg. Limits etc)

Nitrosamines in sartans (7) – Ph. Eur

- Impact on the Ph. Eur:
  - Revision of the Ph. Eur monographs for 5 sartans with tetrazole ring: addition of a Production section + Test section. Published in Ph. Eur 10th ed and implementation in January 2020

TESTS

Nitrosamines. Carry out the test by a suitable method (4)

Ref. to EDQM website where methods dev. by OMCL are available

The substance to be examined does not contain either NDMA or NDEA above the limits provided below or both impurities at whatever level:

- *N-nitrosodimethylamine (NDMA)*: maximum 0.300 ppm;
- *N-nitrosodiethylamine (NDEA)*: maximum 0.082 ppm.

  - Elaboration of a General Chapter on control of nitrosamines (NDMA, NDEA)
  - Revision of General Monograph « Substances for pharmaceutical use » foresee in the future

Nitrosamines in sartans (8) – Next steps

- Next steps
  - EU decision following Article 31 referral 2 April 2019:
    - All sartan (with tetrazole ring) batches to be tested for NDEA, NDMA before release (API + DP)
    - Transition period of 2 years with limits for NDEA, NDMA in specification of the drug substance & only 1 nitrosamine allowed
    - After the transition period, "no measurable level" (< 0.03 ppm)
  - Some CEP applications to be updated to align with revised Ph. Eur monographs
  - New updates foreseen within 2 years (changes of process and controls) ➔ revisions to be submitted by CEP holders
  - Lessons learnt exercise on-going
- Consider other substances !

Optimising use of CEPs

ASMFs & CEPs in Europe

- European National regulatory authorities and EDQM learn regularly about duplicate submissions of ASMF/CEP
- Optimisation ASMFs & CEPs
  - To reduce duplication of assessments
  - For ASMF submitted before the CEP application
    - Use of ASMF Assessment Report (AR) to support CEP assessment
    - Conditions: after October 2012, in EU via CP, DCP, MRP
  - Parallel submissions ASMF/CEP
    - Exchange of information between EDQM and regulatory authority, use of AR if available to support assessment
  - Applicants can help by identifying these submissions in the respective application forms

Use of CEPs in MAA lifecycle

- CMDh/EDQM project to optimise use of CEPs in variations to marketing authorisations applications (MAA) in EU
  - Rationale: Type IA variations:
    - Most variations to marketing authorisations involving CEPs are Type IA
    - Overall 20-25% of Type IA concern CEP updates
  - CEP revisions outcomes:
    - Approval without revision of the CEP # 30% (600/year)
    - Revised CEP with content changed # 54% (1080/year)
    - Revised CEP with content unchanged # 16% (320/year)

- Need to improve communication between CEP holder and DP manufacturer / MAH

Use of CEPs in MAA lifecycle (2)

- Possible actions:
  - Reduce number of revised CEPs (eg. more situations which do not lead to a revised CEP)
  - Authorities to consider which variations involving CEPs are needed
  - Use of databases to report administrative information currently on CEPs (eg. companies details)
  - Promote better sharing of information between CEP holder & MAH
    - Adapt design and content of the CEP or tools to force information sharing
- Status:
  - On-going, initial discussions started
  - Consultation of stakeholders needed

Modernising CEPs in the future

- Over 25 years, the content of CEPs has evolved slightly with regulatory environment and needs
- Time to start reflecting on modernisation of CEPs
- Wide consultation of various stakeholders
  - Gather feedback on how to better fit with needs ➔ 2019-2020
  - Long term project…

Thank you for your attention

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Update on Quality Guidelines for the Control of Active Substances

Olaf Ludek, Icelandic Medicines Agency

Strasbourg June 20th, 2019

Top 10 Deficiencies in Certification*

1. Control of mutagenic impurities
2. Carry-over of impurities from starting materials to API
3. Inadequate description of the manufacturing process
4. Redefinition of starting materials
5. Quality of starting materials
6. Quality of raw materials
7. Carry-over of elemental impurities to API
8. Quality of intermediates
9. Carry-over of impurities from intermediates to API
10. Information on manufacture of starting materials

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* Top Ten Deficiencies - PA/PH/CEP (16) 58

Top 10 Deficiencies in Certification*

1.	Control of mutagenic impurities	**ICH M7**
4.	Redefinition of starting materials	Control strategy of API manufacturing process **ICH Q11**
2.	Carry-over of impurities from starting materials to API	
9.	Carry-over of impurities from intermediates to API	
3.	Inadequate description of the manufacturing process	Level of detail **GL on the Chemistry of AS**
5.	Quality of starting materials	
6.	Quality of raw materials	
8.	Quality of intermediates	
10.	Information on manufacture of starting materials	
7.	Carry-over of elemental impurities to API	**ICH Q3D**

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Control of Mutagenic Impurities

Situation prior to publishing of ICH M7 (January 2016)

- Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/QWP/251344/2006)
- Q&A on the Guideline on the Limits of Genotoxic Impurities (EMA/CHMP/SWP/431994/2007)
- Q&A on Setting Specifications for Genotoxic Impurities (EMA Q&A on Quality – Part 1)

Situation post January 2016

- Only one Guideline: ⟶ **ICH M7**
- Harmonized approach by all ICH members
- Many of the principles stated in the EU documents were included in the ICH GL, however some new features were introduced:

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Impurities Classification

- Actual and potential impurities that are likely to arise during the synthesis and storage of a new drug substance (and drug product) should be evaluated with respect to their mutagenic potential ⟶ **5 classes of impurities**

Class	Definition	Proposed Action for Control
Class 1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
Class 2	Known mutagens with unknown carcinogenic potential	Control at or below acceptable limits (appropriate TTC)
Class 3	Alerting structure, unrelated to API, no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct mutagenicity assay: Non-mutagenic = Class 5 Mutagenic = Class 2
Class 4	Alerting structure, related to API	Treat as non-mutagenic impurity
Class 5	No structural alerts or data available demonstrating non-carcinogenicity	Treat as non-mutagenic impurity

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Control Strategies for Mutagenic Impurities

- For impurities of Classes 1, 2, or 3, a control strategy assuring levels of the respective impurity in the drug substance below the acceptable limit needs to be developed:
  → **4 Options**

Control	Definition
Option 1	Include a test in the **drug substance specification** with acceptance criterion at or below the acceptable limit.
Option 2	Include a test in the specification for a **raw material**, **starting material** or **intermediate**, or as an **in-process control**, with acceptance criterion *at or below* the acceptable limit.
Option 3	Include a test in the specification for a **raw material**, **starting material** or **intermediate**, or as an **in-process control**, with acceptance criterion *above* the acceptable limit. → If levels of impurity are consistently below 30% of the acceptable limit in API
Option 4	Understand the process with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity. → Analytical data to support this control approach may be requested

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Control Strategies for Mutagenic Impurities

- The Option 4 control strategy (no additional control of mutagenic impurities) leaves room for interpretation and different approaches are accepted in the different ICH regions

→ Currently, an ICH Q&A document on M7 is developed

- Clarification on control strategies (i.e. use of Option 4)
- Expectation with respect to purge factor calculations

→ Aimed for publication in 2020

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Compound-Specific Acceptable Intakes

- Compound-specific risk assessments to derive acceptable intakes should be applied instead of the TTC-based acceptable intakes where sufficient carcinogenicity data exist.

Name	AI or PDE (µg/day)
Acrylonitrile	6
Benzyl chloride	41
Bis(chloromethyl)ether	0.004
1-Chloro-4-nitrobenzene	117
p-Cresidine	45
Dimethylcarbamoyl chloride	5
Ethyl chloride	1810

Name	AI or PDE (µg/day)
Glycidol	4
Hydrazine	39 (0.2 inhalation)
Methyl chloride	1361
Aniline (HCl)	720
Hydrogen peroxide	68,000 or 0.5%, whichever is lover
p-Chloroaniline (HCl)	34
Dimethyl sulfate	1.5 (TTC)

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→ Further compounds will be added to the list with future revisions of the document

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Control strategy of API manufacturing process
ICH Q11

Level of detail
GL on the Chemistry of AS

7. Carry-over of elemental impurities to API

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Selection of Starting Materials

Situation prior to publishing of ICH Q11 (November 2012)

- Chemistry of Active Substances (3AQ5a)
- Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96)
- Policy Note on Starting Materials (PA/PH/CEP(10)19)

Situation post November 2012

- Only one Guideline: ⟹ **ICH Q11**
- In the guideline, the principles on which starting materials should be selected are stated
- High-level document, leaving room for interpretation

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Selection of Starting Materials

Clarification on EU-side regarding ICH Q11 (starting materials)

- Reflection Paper on the Requirements for Selection and Justification of Starting Materials for the Manufacture of Chemical Active Substances (EMA/CHMP/CVMP/QWP/826771/2016 - Corr. 1)
- Adopted by CHMP/CVMP September 2014

⟹ **Document no longer valid**

Clarification on ICH-level regarding ICH Q11 (starting materials)

- ICH Guideline Q11 on Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological / Biological Entities) – Questions and Answers (EMA/CHMP/ICH/809509/2016)
- Effective since February 2018

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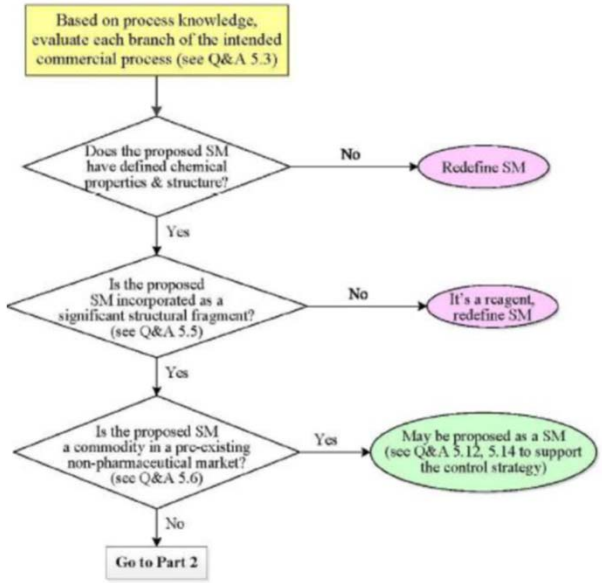
Selection of Starting Materials

Part 1



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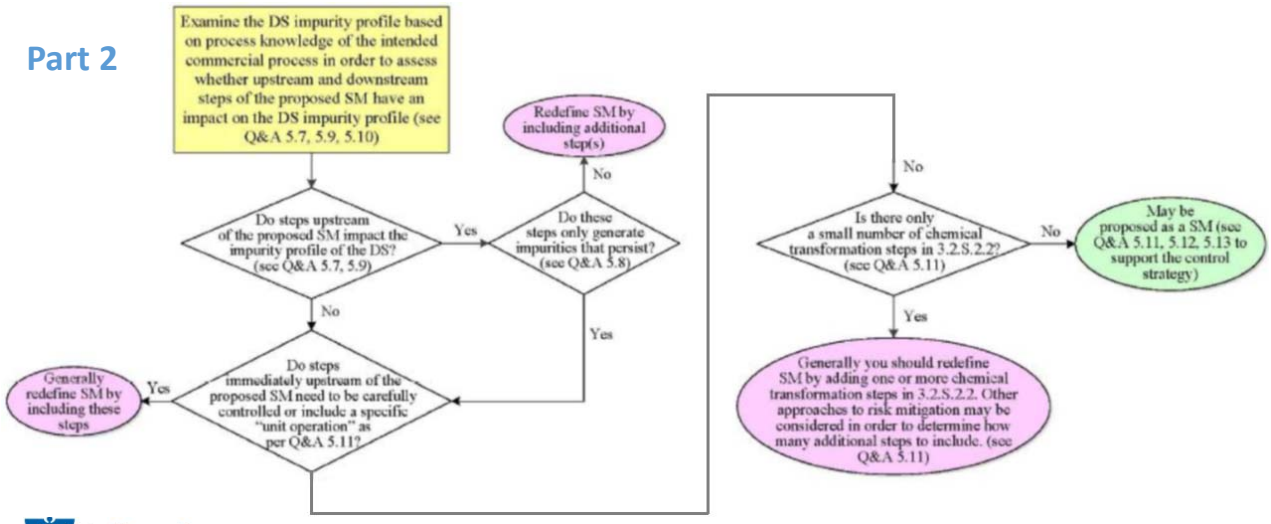
Selection of Starting Materials

Part 2



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Control strategy of API manufacturing process
ICH Q11

Level of detail
GL on the Chemistry of AS

7. Carry-over of elemental impurities to API

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New Guideline on the Chemistry of Active Substances

Chemistry of Active Substances (3AQ5a)
1987

Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96)
2004

2017

Guideline on the Chemistry of Active Substances (EMA/454576/2016)

- No new requirements were introduced
- The list of references was updated
- The GL also covers starting materials isolated from plant materials

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Top 10 Deficiencies in Certification

1. Control of mutagenic impurities
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3. Inadequate description of the manufacturing process
5. Quality of starting materials
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8. Quality of intermediates
10. Information on manufacture of starting materials
7. Carry-over of elemental impurities to API **ICH Q3D**

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Control of Elemental Impurities

Situation prior to implementation of ICH Q3D (June 2016)

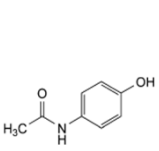
- Note for Guidance on Specification Limits for Residues of Metal Catalysts (CPMP/SWP/QWP/4446/00)
- Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents (EMEA/CHMP/SWP/4446/2000)
- Q&A on Setting Specifications for Heavy-Metal-Catalyst Residues (EMA Q&A on Quality – Part 1)

➡ **Focus was on drug substance**

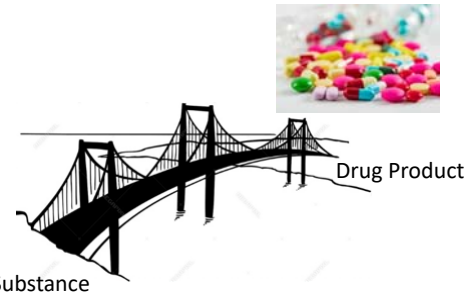
Situation post June 2016

- Only one Guideline:

➡ **Focus is on drug product**



Drug Substance



Drug Product

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Implementation of ICH Q3D

- Bridge information between API and finished product:
  - ➡ Implementation Strategy of ICH Q3D Guideline (EMA/CHMP/QWP/115498/2017)
  - ➡ Implementation of ICH Q3D in the Certification Procedure (PA/PH/CEP(16)23)
- A risk assessment on the need to control elemental impurities (EIs) in the drug product is expected from the drug product manufacturer.
- In order to perform the risk assessment, any element intentionally added during the drug substance manufacturing process must be included in the description of the process.
- For intentionally added EIs, a limit in the drug substance specification, or an in-process control, applied by the drug substance manufacturer needs to be implemented, if the EI is consistently found above 30% of the Option 1 PDE for the intended route of administration.
- No control of the intentionally added EI is needed, if the EI is consistently purged to levels below the control threshold (<30% of the Option 1 PDE for that route of administration).

Lyfjastofnun Icelandic Medicines Agency ➡ Data on carry-over on EIs is expected in the dossier

Implementation of ICH Q3D

- It is also recommended that the drug substance manufacturer provides a summary of a risk assessment/ management that also covers elemental impurities that are not intentionally added to inform the drug product manufacturer on the overall risk assessment including any mitigation steps necessary.

Intended route of administration / Use of the substance: ..Oral / Parenteral / Inhalation

Element	Class	Intentionally added?	Considered in risk management?	Conclusion
Cd	1	Yes/No	Yes	Absent / max level: x ppm
Pb	1	Yes/No	Yes	Absent / max level: x ppm
As	1	Yes/No	Yes	Absent / max level: x ppm
Hg	1	Yes/No	Yes	Absent / max level: x ppm
Co	2A	Yes/No	Yes	Absent / max level: x ppm
V	2A	Yes/No	Yes	Absent / max level: x ppm
Ni	2A	Yes/No	Yes	Absent / max level: x ppm

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Outlook

- **Continuous Manufacturing of Drug Substances and Drug Products (ICH Q13)**
  - CM-related definitions and regulatory concepts
  - Key scientific approaches for CM
  - CM-related regulatory expectations
- **Analytical Procedure Development (ICH Q14)**
  - Include analytical methods other than HPLC (e.g. NIR, Raman, NMR, MS..)
  - Potentially merge with ICH Q2
  - Intended to complement ICH Q8 to Q12 (analytical Quality by Design)

Publication for public consultation 2020

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