Implementation of ICH Q3D in the Certification Procedure

PQRI/USP Workshop on ICH Q3D Elemental Impurities Requirements – Recent Experience and Plans for Full Implementation in 2018

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EU policy for component approach

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/QWP/115498/2017
Committee for Medicinal Products for Human use (CHMP)

Implementation strategy of ICH Q3D guideline

Adopted by CHMP	December 2016

EDQM Policy document

- **PA/PH/CEP (16) 23, published in August 2016**

https://www.edqm.eu/sites/default/files/implementation_of_ich_q3d_in_the_certification_procedure_august_2016.pdf

- In force for CEPs granted (new, renewals, some revisions) since 01/09/2016
- Applicable to substances used in products within the scope of Q3D

(e.g. not implemented for vet. only, herbals, etc.)

Concepts

- No mandatory implementation of ICH Q3D at the level of pharmaceutical substances
- Same basic principles for ASMF & CEPs
- Define an appropriate quality for APIs and excipients
- Serve the Component Approach of ICH Q3D:
  - Provide necessary information to MAH for their Risk Assessment on the Drug Product
  - Be useful for substances manufacturers and MAH and keep the benefits of the centralised assessment

Concepts (2)

Applicant for a CEP has the choice between two possible approaches:

1. Provide a Risk Management Summary (RMS) performed at the level of the drug substance ("component approach" as per ICH Q3D). This is the **preferred scenario.**
2. No Risk Management is done on elemental impurities (EI).

The approach taken is independent of the use or non-use of EI in the manufacturing process.

Scenario 1: RMS provided

- It should be apparent that the component approach is followed.
- The route of administration should be indicated: (associated risks and thresholds)
  - ➢ oral, parenteral or inhalation
  - ➢ ICH Q3D option 1 (10 g drug product/d) should normally be used as reference
- A RMS should be provided:
  - ➢ Why are impurities considered/not considered?
  - ➢ Justification of control strategy

⇨ Screening alone is not a RMS

Scenario 1: RMS provided (2)

Which EI should be included in the risk assessment?

- Class 1 and Class 2A elements
- EI's which might reach the control threshold, for example EI's:
  - introduced close to the final substance
  - originated from multiple sources
  - with low PDE and/or
  - introduced as contaminants by raw materials at highly variable levels
  - present in packaging material (for non-solid APIs/excipients).

No routine screening for all 24 EI's is expected.

Scenario 1: RMS provided (3)

Analytical methods:

- For screening
  - Specify analytical methodology (i.e. ICP-MS/AES / AAS; no full method description needed) + specificity and sensitivity
- In specification of the final substance
  - Detailed method description + full validation

Scenario 1: Assessment of RMS

Assessors will look at:

- Completeness and relevance of the risk assessment
- Content of the RMS
- Control strategy and method validation if necessary

RMS provided: on the CEP

CEP:

A risk management summary for elemental impurities has been provided.	(Annex 2)

and if applicable

– Test for elemental impurities by ICP-MS Palladium not more than 10 ppm	(Annex 3)

Scenario 2: no RMS provided

- All intentionally introduced EI should be declared (catalysts, reagents)

2. Particulars for Intentionally Added Element(s)

Any element intentionally added during the manufacturing must be included in the description of the drug substance manufacturing process in the marketing authorization dossier, an ASMF or a CEP application, as well as its fate and the need for any controls (for instance the use of a metal catalyst in the last step of the synthesis). This obligation of description is independent of whether the substance is made in-house, relies on an ASMF or on a CEP.

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- Carry-over data should be provided

Scenario 2: no RMS provided (2)

Analytical methods

- For EI not specified in the final substance
  - Mention analytical methodology (i.e ICP-MS/AES / AAS; no full method description needed) + specificity and sensitivity
- In specification of the final substance
  - Detailed method description + full validation

Scenario 2: Assessment of data

Assessors will look at:

- Presence of EI in the final substance
- Control strategy and method validation if necessary

No RMS provided: on the CEP

CEP:

The following elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance: Palladium

or

No elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance.

Regardless of levels found

Specification

For both scenarios:

- EI intentionally introduced in last synthetic step

⇨ A limit in the final substance is normally expected, unless levels below 30% of option 1 limit (for the claimed/known route of administration)

- EI intentionally introduced (absent or not)

⇨ Specification accepted as proposed by applicant

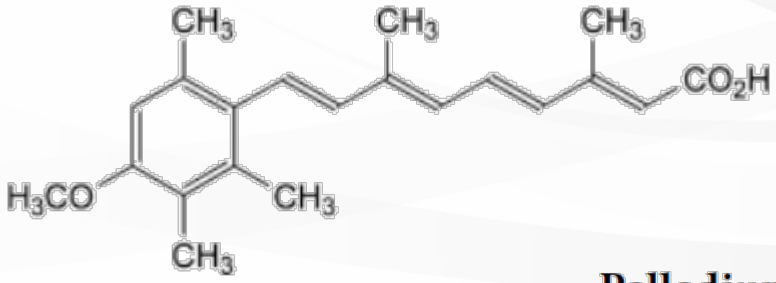
How to set limits

Limit unrealistic?

01/2017:1385

ACITRETIN

Acitretinum



Palladium: maximum 10 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

MDD 75 mg; ⇨ 1333 ppm toxicologically acceptable

Implement Ph.Eur. test and limit (unless not relevant for the synthesis!)

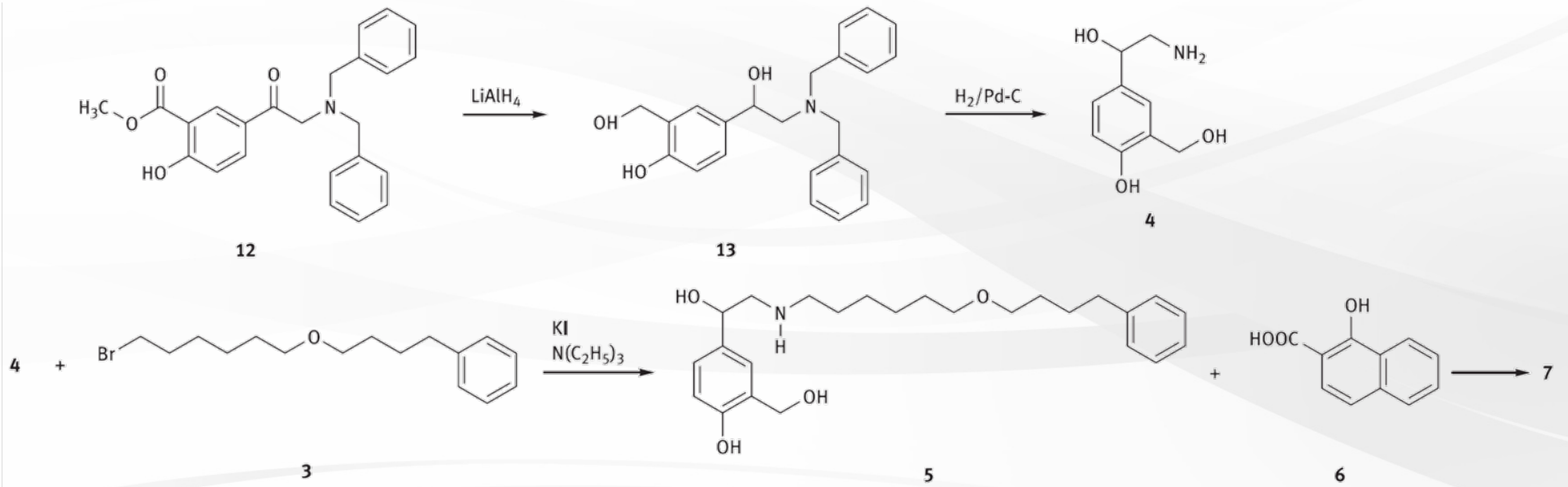
How to set limits (2)

Applicant does not apply ICH Q3D option 1 limits but absence may be concluded

04/2014:1765

SALMETEROL XINAFOATE

Salmeteroli xinafoas



mdd 200 µg; inhalation ⇨ excipients likewise << 10 g

reproduced from Arzneibuch-Kommentar

How to set limits (3)

Maximum Daily Dose > 10 g

- Colestyramine 36 g/d
- Sodium phenylbutyrate 20 g/d (lifetime)
- Contrast agents
- Iohexol, gadobutrol monohydrate,... >> 10 g (single administration)
- Lactulose 120 g

RMS:
No conclusion on absence (based on option 1) possible.
Applicants should report actual levels

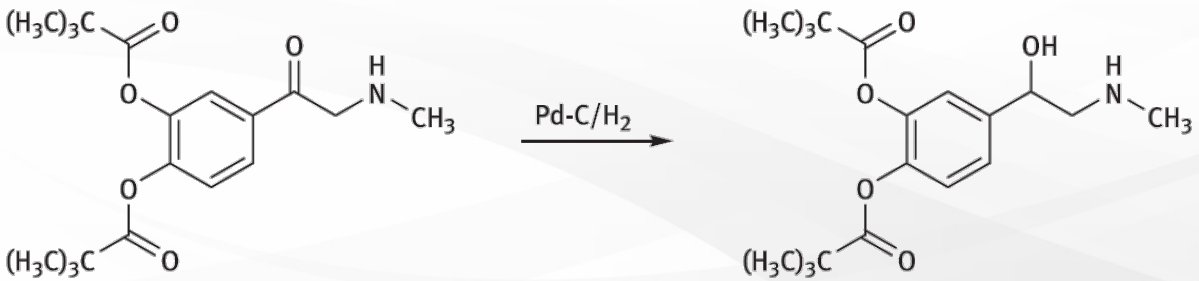
How to set limits (4)

Ophthalmic (or dermal,...) use only

01/2008:1719
corrected 7.0

DIPIVEFRINE HYDROCHLORIDE

Dipivefrini hydrochloridum



4 (E) 5

No PDE in ICH Q3D (oral PDE can provide the basis of a route-specific safety assessment). No safety assessment at the stage of component possible.

Applicant may propose oral route or parenteral route (higher safety factor, more EI covered). Suitability has to be assessed at the stage of DP.

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Analytical methods

Ph. Eur. General Method 2.4.8. Heavy metals

			Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn			As	Se		
					Mo		Ru	Rh	Pd	Ag	Cd		Sn	Sb			
					W				Pt	Au	Hg	Tl	Pb	Bi			

not detectable

colour not comparable to lead

Pharmeuropa Sep.-Dec. 1989 Vol. I

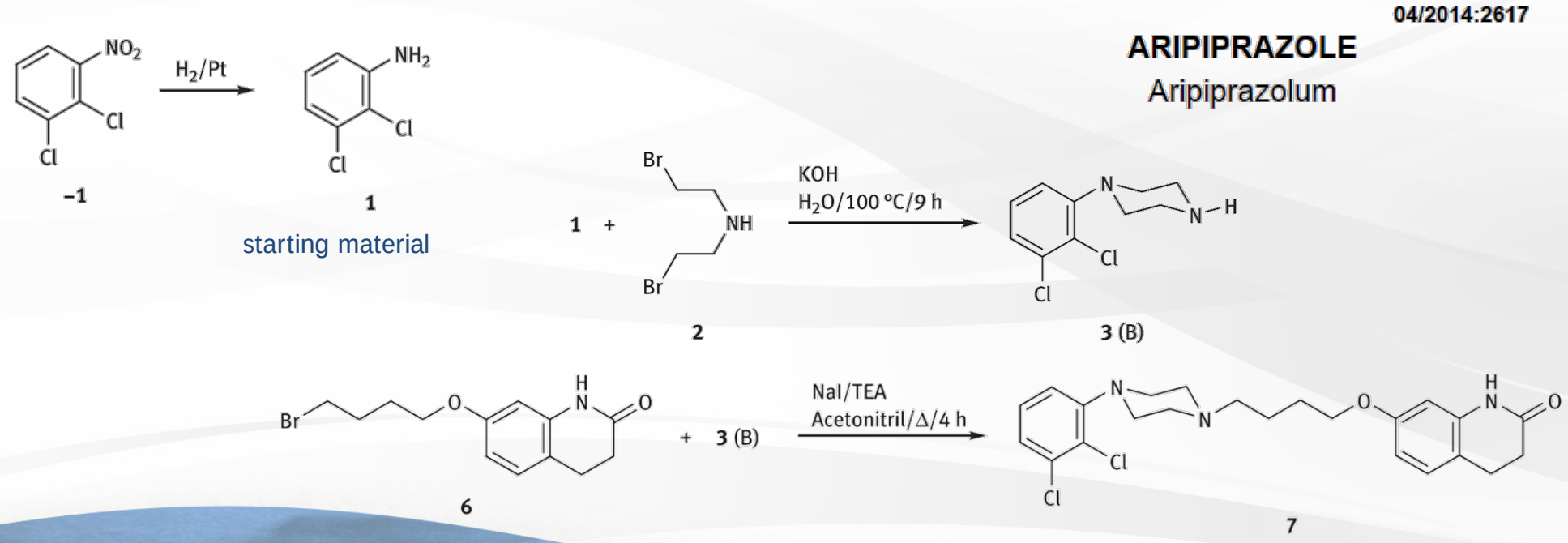
(rare metals not verified in this study)

⇨ Specific methods should be used

Assessment

Catalyst in synthesis of SM

considered as contaminant and not intentionally introduced ⇨ use of catalyst not mentioned on CEP



modified from Arzneibuch-Kommentar

Revision/Renewal

What to do for existing CEPs?

- **Renewal:** Dossiers are systematically reviewed against the principles of the policy
  - Opportunity to introduce a RMS and/or to update control strategy
- **Revisions:**
  - Policy considered when the changes relate to controls for EI, changes in the mfg process involving addition/removal of EI
  - Or possibility to introduce a RMS

Revisions/Renewals

Deletion of reference to Ph. Eur. General Method 2.4.8

- No or little impact - CEP holders/applicants have not been contacted
- Update of specification under responsibility of manufacturer's QA system
- If no analytical control is necessary, deletion of heavy metals test may be included in next submission for revision (for filing; no assessment)
- Introduction of alternative tests should be done according to EDQM "Guideline on Requirements for Revision/renewal" (PA/PH/CEP (04) 2)

Conclusion:

This is still a new policy for everybody but experience so far is positive

Acknowledgements

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EDQM working group

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Questions?

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or

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