GMP News - 1

GMP News
21/01/2015

Print News

CHMP adopts ICH Q3D Guideline as "Scientific Guideline"

After the publication of a final ICH guideline, its implementation into the respective national regulations of the 3 ICH regions Europe, USA and Japan (Step 5 of the ICH process) is usually the next step. The "ICH Guideline for elemental impurities - Q3D" was published on 19 December 2014 as Step 4 document. Four weeks later - on 12 January 2015 - the integration of the Guideline into EMA's set of rules of "Scientific Guidelines" was notified after the CHMP committee had adopted it through a formal act.

As for all the ICH guidelines which are integrated into the collection of "Scientific Guidelines", the corresponding EMA Guideline which is now entitled "ICH guideline Q3D on elemental impurities" is composed of only one table of the document history and the section "scope" identical to that of the original ICH guideline. After that, there is just a direct link to the ICH page containing the "Quality Guidelines" where the Q3D can be easily found.

The table with the document history contains important information for the pharmaceutical and API industry of the EU member states about the coming into force of the ICH Q3D requirements. These regulations will be binding:

- As of **June 2016** for new marketing authorisation applications and
- As of **December 2017** for authorised medicinal products

The time window for the verification of authorised and/ or already marketed medicinal products for compliance with the limits regarding elemental impurities/ acceptable daily doses is now only 3 years.

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Conference Recommendations			
No.	Date	Title	Location
9263	16-18 June 2015	Impurities Forum - all 3 Days	Prague, Czech Republic
9266	9-10 June 2015	6th European GMP Conference - The biennial No. 1 Event in Europe	Heidelberg, Germany
9306	8-10 June 2015	6th European GMP Conference with pre-conference workshop on Quality Metrics	Heidelberg, Germany

Related GMP News	
18/03/2015	New General USP Chapter <1210> on Statistical Tools for Procedure Validation
11/03/2015	Revision of the General USP Chapter <1010>
25/02/2015	Data Integrity: New Inspection Focus of the FDA
18/02/2015	GMP Data Integrity: New MHRA Guideline
28/01/2015	Elemental Impurities: USP announces the Date of Entry into Force of Chapters <232> and <2232>

GMP News 2

GMP News
07/01/2015

Print News

Guideline "ICH Q3D - Elemental Impurities" published as Step 4 Document!

On 19 December 2014, the Guideline "ICH Q3D - Elemental Impurities" was released on the ICH website - nearly one year and a half after the publication of the draft (Step 2b document) on 5 August 2013. The Expert Working Group (EWG) in charge of the guideline has taken more time to find an agreement and a consensus because of the several comments given by diverse associations on the guideline and the final determination of the "permitted daily exposure" (PDE) for the different metals.

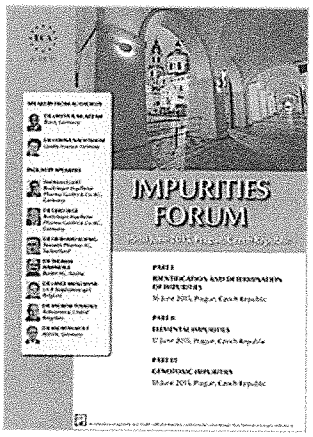
Compared to the draft guideline from August 2013, most of the limits have changed: more stringent PDE values apply for 17 out of the 24 elements! The following table shows the PDE of these elements with regard to the different dosage forms (in brackets the value indicated in the draft guideline from August 2013):

Element	Class	Oral [µg/Day]	Parenteral [µg/Day]	Inhalation [µg/Day]
Cadmium (Cd)	1(1)	5 (5.0)	**2** (6.0)	**2** (3.4)
Mercury (Hg)	1 (1)	**30** (40)	**3** (4.0)	**1** (1.2)
Selenium (Se)	**2B** (2A)	**150** (170)	**80** (85)	**130** (140)
Vanadium (V)	2A (2A)	**100** (120)	**10** (12)	**1** (1.2)
Silver /Ag)	2B (2B)	**150** (170)	**10** (35)	(see Table 2)
Gold (Au)	2A (2A)	**100** (130)	**100** (130)	**1** (1.3)
Iridium (Ir)	2A (2A)	**100** (1000)	10 (10)	**1** (1.4)
Osmium (Os)	2A (2A)	**100** (1000)	10 (10)	**1** (1.4)
Platinum (Pt)	2A (2A)	**100** (1000)	10 (10)	**1** (1.4)
Rhodium (Rh)	2A (2A)	**100** (1000)	10 (10)	**1** (1.4)
Ruthenium (Ru)	2A (2A)	**100** (1000)	10 (10)	**1** (1.4)
Thallium (Tl)	2A (2A)	**8** (8.0)	8 (8,0)	**8** (69)
Barium (Ba)	3 (3)	**1400** (13000)	**700** (13000)	**300** (340)
Lithium (Li)	3 (3)	**550** (780)	**250** (390)	25 (25)
Nickel (Ni)	**2A** (3)	**200** (600)	**20** (60)	**5** (6.0)
Antimony (Sb)	3 (3)	1200 (1200)	**90** (600)	**20** (22)
Tin (Sn)	3 (3)	**6000** (6400)	**600** (640)	**60** (64)

It is remarkable that the metal nickel has now moved to a class 2A - a class with stricter requirements/ greater toxicity. Elements listed in this class require a risk assessment of the finished product as - according to the synthetic route and/ or the manufacturing process - there is a substantial likelihood of accumulation in the final product. Class 3 - the former class of nickel - contains the elements which show a relatively low toxicity for oral use. The reclassification of nickel and the associated lower limits (one third of the value set in Q3D Step 2!) means for certain products higher control efforts as nickel is frequently used as catalyst in the API synthesis and is present as supplement in metallic materials in many parts of the production equipment. The PDE for thallium has also been considerably reduced with regard to inhalation and sank from 69 to 8 µg per day! Further (partly drastic) tightening concern the elements iridium, osmium, rhenium, ruthenium, and platinum whose current PDE for oral administration is roughly one-tenth of the value indicated in Q3D Step 2. Some of these metals are also used as catalysts in chemical syntheses.

In the present guideline, some limits have been eased compared to the draft from 2013. The following 6 elements have now higher PDE values:

Element	Class	Oral [µg/Day]	Parenteral [µg/Day]	Inhalation [µg/Day]
Arsenic (As)	1(1)	15 (15)	15 (15)	**2** (1.9)
Cobalt (Co)	2A (2A)	50 (50)	5 (5.0)	**3** (2.9)
Silver (Ag)	2B (2B)	(see Table 1)	(see Table 1)	**7** (6.9)
Molybdenum (Mo)	**3** (2A)	**3000** (180)	**1500** (180)	**10** (7.6)
Chromium (Cr)	3 (3)	11000 (11000)	1100 (1100)	**3** (2.9)



GMP News by Topics
Analytical QC
APIs and Excipients
Blood and Biologics
Computer Validation
Counterfeit Medicines
Good Distribution Practices
GMP Inspections/Audits
Pharma Technology
Quality Assurance
Sterile / Aseptic / Microbiology
Validation
Medical Devices
Pharmaceutical/Clinical Development
Regulatory Affairs

Copper (Cu)	3 (3)	**3000** (1300)	**300** (130)	**30** (13)

Only the values for lead (Pb) and Palladium (Pd) have remained the same as in the Draft Consensus Guideline.

This guideline constitutes a milestone in the risk assessment and analysis of new medicinal products that have not yet been authorised. It is partly complex and will pose a considerable challenge to the chemical and pharmaceutical industry - particularly of already authorised medicinal products. A **transposition period of 3 years** has been granted for the application of the requirements set in the guideline. *(Last sentence in Chapter 2 Scope: "Application of Q3D to existing products is not expected prior to 36 months after publication of the guideline by ICH".).*

You can find the final ICH Q3D Guideline here.

Note: You will get up-to-date information about the implementation of ICH Q3D at the "ECA Impurities Forum" from 16 to 18 June 2015.

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Related GMP News	
15/01/2015	Draft: New Clinical Trial Rules in India
15/01/2015	EMA publishes Report on GCP Inspections
10/12/2014	ICH Working Group Elaborates Training Materials on ICH Q3D
19/11/2014	EMA Guideline on similar Biological Medicinal Products adopted
30/09/2014	ICH endorses new Working Groups on Clinical Trials

GMP News - 3

GMP News
06/05/2015

Print News

Elemental impurities - A database to facilitate the risk assessment of active ingredients and excipients

Released in December 2014, the ICH Q3D Guideline on Elemental Impurities contains extensive specifications for the control of a total of 24 elements (21 metals, 3 metalloids) that can be present as impurities in pharmaceutical products. Main sources can be

- Active ingredients
- Excipients (including water)
- Processing auxiliaries and catalysts
- Production equipment
- Container and closure systems

The Guideline ICH Q3D calls for a risk assessment with regard to the presence of metallic impurities in various dosage forms, taking into account the respective limit values. The main factors of influence are to be included (see fishbone diagram on p. 6 of the Guideline). The risks identified in a comprehensive analysis have then to be categorized in a meaningful and justifiable manner.

The data for the content of metallic impurities, e.g. in excipients (for this purpose there is a study conducted by the FDA) or of migratable impurities in container / closure systems (there exists a Literature review in the PDA journal of pharmaceutical science and technology) is rather thin. And the sources of information can only be found through extensive research. The greatest treasure of information is located in the databases of several pharmaceutical and API manufacturers which have carried out analytical studies already.

To merge these data and information and to make them available to all interested companies in the form of a database, representatives of eight major companies have joined forces to an "Elemental Impurities Pharma Consortium". This group was formed in October 2013, after a Conference on "Elemental Impurities" conducted by the Joint Pharmaceutical Analysis Group (JPAG).

The database that is currently established under the auspices of the EI Pharma Consortium, now comprises analytical data on elemental impurities from over 100 different materials (pharmaceutical excipients, dyes, etc.), which were provided by other companies. These data are anonymized, so that interested users of the database can not recognize the specific origin of the information.

The benefit for the user increases to the same extent as the database grows, which basically means for the companies that have to implement one of the main requirements of the ICH Q3 Guideline - to carry out a risk assessment. The timeframe for this is tight: for medicinal products still to be approved the provisions of ICH Q3D need to be fulfilled by June 2016. Already approved products have to comply from December 2017 (see also our news "Industry Coalition" gives practical advice for the control of elemental impurities in active substances and excipients).

Note : At the Impurities Forum from 16-18 June 2015 in Prague you will receive more information about this topic. Andrew Teasdale, one of the initiators of the Consortium, will report about the database and the possibilities to use it.

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GMP News by Topics

Analytical QC
APIs and Excipients
Blood and Biologics
Computer Validation
Counterfeit Medicines
Good Distribution Practices
GMP Inspections/Audits
Pharma Technology
Quality Assurance
Sterile / Aseptic / Microbiology
Validation
Medical Devices
Pharmaceutical/Clinical Development
Regulatory Affairs

Conference Recommendations

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9263	16-18 June 2015	Impurities Forum - all 3 Days	Prague, Czech Republic
9300	4-6 November 2015	18th APIC/CEFIC European Conference on Active Pharmaceutical Ingredients (All 3 Conference Days)	Amsterdam, The Netherlands

Related GMP News	
06/05/2015	Data Integrity - Indian Government puts EU under pressure
29/04/2015	Update of the USP Requirements for Packaging Materials made of Plastics
22/04/2015	The "Industry Coalition" gives practical advice for the control of elemental impurities in active substances and excipients
15/04/2015	Recommendations of the EMA for the risk assessment of metallic impurities in approved drugs
15/04/2015	EU Medicines Agencies: Strategy for the next five Years

GMP News - 4

GMP News
22/04/2015

Print News

The "Industry Coalition" gives practical advice for the control of elemental impurities in active substances and excipients

The requirements of the "Guideline for Elemental Impurities ICH Q3D" published in December of last year mean a considerable expense for the affected pharmaceutical companies and drug manufacturers in terms of laboratory and personnel upgrading (see also our news about "ICH Q3D - Elemental Impurities" of 07 January 2015). In addition, the deadlines for the implementation of this guideline are quite tight. (June 2016 for newly approved drugs and December 2017 for already approved drugs, see our news "CHMP adopts ICH Q3D Guideline as "Scientific Guideline" of 21 January 2015).

In the March issue of "Pharmaceutical Technology Europe", an article of the "Industry Coalition" has been published with the title "Implementation of ICH Q3D Elemental Impurities Guideline: Challenges and Opportunities", which is intended to support the efffected companies with a number of pragmatic pieces of advice in the implementation of these requirements.

The "Industry Coalition" (exact name: "Coalition for Rational Implementation of Elemental Impurities Requirements") is a consortium of economic/industrial associations (members include IPEC Europe, IPEC Americas, The Generic Pharmaceutical Association GPhA, etc.) and has been in existence since 2011. The aim of the coalition is to provide information regarding elemental impurities. To this end, the Coalition has developed a standardised procedure (standardised information request) according to which specific information can be requested through the use of a form. More information about the "Industry Coalition", their goals and projects can be found in a Position Paper which appeared in "Pharmaceutical Technology Europe" in November 2012.

The Guideline ICH Q3D calls upon drug manufacturer to conduct a risk assessment as part of a strategy for the control of element impurities, but without specifying which aspects need to be considered in such an assessment. Here, the article of the "Industry Coalition" provides helpful hints; it is described how, for example, production equipment (various types of steel), processing aids (activated carbon, silica gel, etc.), inorganic reagents, solvents, packaging materials and closure systems are to be included in the risk assessment. A detailed section is dedicated to the subject of excipients, regarding which the assessment of risks is often particularly difficult in terms of element impurities, due to the unclear origin or the complex composition of the excipients.

The approaches described by the "Coalition" may be useful for many companies in their efforts to meet the requirements of the Guideline ICH Q3D. In this context, the document which has recently been published by the EMA entitled "Elemental impurities in marketed products. Recommendations for implementation" should also be considered.

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