2017 – The GMP Regulations Report

This summary review of GMP documents published in 2017 helps you to maintain an overview of developments in the most important international legislation and regulations.

By Sabine Rabus

EMA: Draft Q&A on Health Based Exposure Limits, January 2017

- The focus is on setting health-based exposure limits for risk identification and the risk-based prevention of cross-contamination.
- 14 questions and answers relating to the *"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"*, which was published in November 2014 and has been in force since June 2015.
- **The core message:** HBELs should be established for all products (Question 1). A distinction is made between highly hazardous products (Question 2) and products that do not fall into this category (Question 4). Besides the definition five categories of highly hazardous products are listed. For those products, a complete toxicological profile according to the PDE-guideline should be established. The HBELs of all other products can be based on clinical data.
- If a product is well established and has a favourable therapeutic index, HBELs based on the 1/1000th minimum therapeutic dose approach would be considered as sufficiently conservative and could be utilised for risk assessment and cleaning purposes.
- LD50 is not an adequate point of departure to determine an HBEL (Question 5).

Especially notable: Question 6, regarding cleaning validation, brings traditional cleaning limits back into play. Originally seen in connection with the new approach of Annex 15 and the PDE-guideline, those were regarded as obsolete. According to the answer to Question 6 cleaning limits should not only be established by means of PDE-values but also by a risk based approach and additional safety margins. Traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product, may accomplish this for non-highly hazardous products.

Newest development:

Publication of the final version in May 2018.

- GMP News summary
- final Q&A

PIC/S: GMP Guide PE 009-13, January 2017

The following chapters of the PIC/S GMP Guide have been revised based on the equivalent chapters of the EU GMP Guide:

- Chapter 1 on “Quality Management” (which has become “Pharmaceutical Quality Systems”)
- Chapter 2 on “Personnel”
- Chapter 6 on “Quality Control”
- Chapter 7 on “Contract Manufacture and Analysis” (which has become “Outsourced Activities”).

The revised GMP Guide (PE 009-13) entered into force on 1st January 2017.

- GMP News summary
- Official guide

FDA: Final Guidance on cGMP for Combination Products, January 2017

The 59-page final *guidance on the CGMP requirements for combination products* describes and explains specific provisions from 21 CFR Part 4. It

- applies to all combination products
- provides a definition of “combination product” according to FDA
- gives an overview of 21 CFR Part 4
- describes the role of the lead center and other Agency centers (e.g. CDER, CBER, CDRH)
- addresses certain general considerations for CGMP compliance for combination products
- presents the purpose and content of specific CGMP requirements addressed in 21 CFR Part 4
- analyzes hypothetical scenarios that illustrate how to comply with certain requirements for specific types of combination products (for a prefilled syringe, drug-eluting stent and drug-coated mesh)
- refers to a “CGMP operating system” meaning the operating system within an establishment designed and implemented to address and meet the CGMP requirements for manufacturing a combination product
- clarifies how to deal with constituent parts of cross-labeled combination products
- explains the two ways to demonstrate compliance: a streamlined approach and a CGMP/QS approach
- addresses the documentation needed for a CGMP approach.

- GMP News summary
- Official guidance

EMA: Concept Paper for Drug-device Combination Products, February 2017

The *“Concept paper on developing a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product”* considers the need for a guideline on dossier requirements for medical devices (MD). Addressed are MDs that are supplied along with medicinal products where a device is necessary for administration or localization of the medicinal product.

- The scope of the guideline will only include human medicinal products.
- It will not specifically address issues related to integral device as part of combined ATMPs, but it is expected that the same principles will apply.

- Quality issues related to devices when used for a delivery function in combined advanced therapy medicinal products (ATMPs) will be covered.
- There is no intention on duplication of assessment performed during assignment of CE mark for the medical device.

↳ GMP News summary

↳ Concept Paper

EMA: Implementation strategy of ICH Q3D guideline, March 2017

- Final guideline supports medicinal product manufacturers regarding the implementation of the ICH Q3D "*Guideline on Elemental Impurities*".
- Provides guidance for Applicants/MAHs, drug product, drug substance and excipient manufacturers, as well as regulators and also applies to existing authorised medicinal products.

↳ Official Guideline

EMA: Concept Paper on the Revision of Note on Quality of Water for Pharmaceutical Use, March 2017

- Addresses the need for revision of the *note for guidance on quality of WPU (H+V)* which originally went into effect on 1st June 2002.
- A revision of the *monograph for WFI* finally allows the use of non-distillation technologies for WFI production such as reverse osmosis, coupled with appropriate techniques.

↳ GMP News summary

↳ Official Concept Paper

↳ Expert commentary on the revision

EC: New Regulation on Medical Devices, April 2017

On 5 April 2017, two new Regulations on Medical Devices were adopted. They entered into force on 25 May 2017 and replace the existing Directives.

- **Regulation (EU) 2017/745** of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and **repealing Council Directives 90/385/EEC and 93/42/EEC**
- **Regulation (EU) 2017/746** of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and **repealing Directive 98/79/EC and Commission Decision 2010/227/EU**

The new rules will only apply after a transitional period:

- 3 years after entry into force for the Regulation on medical devices (spring 2020) and
- 5 years after entry into force (spring 2022) for the Regulation on in vitro diagnostic medical devices.

Some key changes are:

- stricter ex-ante control for high-risk devices
- reinforcement of the criteria for designation and processes for oversight of Notified Bodies
- the introduction of a new risk classification system for in vitro diagnostic medical devices improved transparency through the establishment of a comprehensive EU database on medical devices and of a device traceability system based on Unique Device Identification

- the strengthening of post-market surveillance requirements for manufacturers

↳ Regulation (EU) 2017/745 and Regulation (EU) 2017/46

EC: Commission Delegated Regulation (EU) 2017/1569, May 2017

The Delegated Regulation specifies principles of and guidelines for GMP for Investigational Medicinal Products (IMPs) for human use and their arrangements for inspections and aims at assuring conformity of GMP and GCP. It is divided in three Chapters

- Chapter I General Provisions
- Chapter II Good Manufacturing Practice (similar structure as the EU GMP Guide)
- Chapter III Inspections

and shall apply as of 1 April 2018. The document is listed under the EudraLex, Volume 4 “Introduction”.

↳ Delegated Regulation (EU) 2017/1569

EMA: Regulatory Guidance on Brexit for the Pharmaceutical Industry Q&A, June 2017-January 2018

Following a Notice to MAHs based in the UK the European Medicines Agency EMA and the European Commission released the *Q&A document regarding the withdrawal of the UK from the European Union*. It should help the pharmaceutical industry to prepare for the upcoming changes.

The Q&As include information related to the location of the establishment of a company in the context of centralised procedures and certain activities, including the location of orphan designation holders, qualified persons for pharmacovigilance (QPPVs) and companies’ manufacturing and batch release sites.

↳ GMP News summary

↳ Official Guidance

FDA: Draft Q&A to Electronic Records and Signatures in Clinical Investigations – 21 CFR 11, June 2017

The Q&A document on 21 CFR Part 11 *“Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers”*

- includes 28 questions and aims at encouraging and facilitating the use of electronic records and systems to improve the quality and efficiency of clinical investigations
- aids sponsors, clinical investigators, institutional review boards and contract research organisations (CROs).

↳ GMP News summary

↳ Official Q&A Draft

FDA: Draft on cGMP for Medical Gases, June 2017

- The draft shall supersede the original guidance already issued in 2003 and help manufacturers of medical gases in meeting the GMP requirements of 21 CFR 210 and 211.
- The regulatory compliance burden should be reduced by providing clear, up-to-date, detailed

recommendations regarding cGMP issues that have been the subject of industry questions.
- The text volume has been reduced significantly from 45 to 28 pages.

↳ GMP News summary

↳ Official Draft

European Pharmacopoeia: Draft of the Monography to Purified Water, June 2017

- Includes a new section on Elemental Impurities which reads:
"*Elemental impurities: If purified water in bulk does not meet the requirement for conductivity prescribed for Water for injections (0169) in bulk, a risk assessment according to general chapter 5.20 Elemental impurities is carried out. The risk assessment should consider the role of water in the manufacturing process, in particular when water is used in a process but is no longer present in the final product*."
- In line with the Ph. Eur. implementation strategy for the ICH Q3D guideline for Elemental Impurities, the test for heavy metals (2.4.8) has been deleted.

↳ GMP News summary

↳ Logfile by Fritz Röder

EC: Safety Features for Medicinal Products for Human Use, Q&A Version 7, July 2017

The European Commission published Version 7 of the Q&A document about safety features. Eight new questions and answers were added and six were revised. In total the document contains 65 Q&As.

Newly added are Q&As 1.15, 1.16, 2.14, 2.15, 2.16, 5.4, 5.5 and 7.12
Revised were Q&As 1.8, 3.4, 4.3, 5.3, 7.11 and 8.1

↳ Official Q&A document

WHO: Technical Report Series 1003, 51st report, July 2017

Chapter 7 *Quality Assurance – Good Manufacturing Practices* of TRS No. 1003 sums up all updates in the area of GMP. The main focus lies on the guidance on validation and its appendices:

- Appendix 1: **Validation of heating, ventilation and air-conditioning systems** - will be replaced by cross reference to WHO Guidelines on GMP for HVAC systems for considerations in qualification of HVAC systems.
- Appendix 2: **Validation of water systems for pharmaceutical use** - will be replaced by cross-reference to WHO Guidelines on water for pharmaceutical use for consideration in qualification of water purification systems
- Appendix 3**: Cleaning validation** – consensus to retain, will be republished
- Appendix 4: **Analytical method validation** – adoption of revised main text with amendments, publication is pending
- Appendix 5: **Validation of computerized systems** – adoption of revised main text with amendments, publication is pending

- Appendix 6: **Qualification of systems and equipment** – adoption of revised main text with amendments

- Appendix 7: **Non-sterile process validation** –update published as Annex 3, WHO Technical Report Series, No. 992, 2015 – will be republished.

A complete guidance package on validation can be expected by the end of 2017.

- GMP News summary
- Official TRS

EMA: Q&As on Production of Water for Injections by Non-distillation Methods – Reverse Osmosis and Biofilms and Control Strategy, August 2017

The Q&A paper comprises of two parts:

- In the first part, emphasis is very strongly on reverse osmosis, which represents the barrier to germs. Additional control mechanisms such as measurement of the total organic carbon (TOC) at multiple points during preparation or membrane autopsy ("destructive analysis") are mentioned. The information about the autopsy is new, as is the establishment of maximum hold times for reverse osmosis membranes.
- The second part deals with "biofilms" and controlling them. A flexible sanitisation concept which allows for the use of multiple procedures is recommended. This includes hot water sanitisation and chemical procedures using ozone, hydrogen peroxide, sodium hydroxide or other chemicals. The appropriate sanitisation method should be used, depending on the type of a possible infestation. This also requires the system components to be resistant to the procedure.

- Logfile by Fritz Röder
- Q&As

EMA: Final Guideline on the Manufacture of the Finished Dosage Form, August 2017

- Clarification on the type and level of information that should be included in the common technical document module 3 of the marketing authorisation application dossier is provided.
- CGMP in terms of complex manufacturing chains or worldwide manufacture with prolonged holding times and transportation conditions are addressed.
- ICH Q8 is taken into account.
- The guideline replaces the *Note for guidance on the manufacture of the finished dosage form* (CPMP/QWP/486/95) and will be effective as of January 2018.

- Official Guideline

EC: Commission Directive (EU) 2017/1572, September 2017

This document is supplementing Directive 2001/83/EC (Art. 40) regarding the principles and guidelines of GMP for medicinal product for human use.

Since Directive 2017/1572 has to be converted into national law, Article 16 of this Directive asks member states to adopt and publish, until March 31, 2018, at the latest, the laws, regulations and administrative provisions necessary to comply with this Directive.

- Commission Directive (EU) 2017/1572

Note:
According to Article 15, Directive 2003/94/EG will be suspended as of 1 April 2018. References to the repealed Directive shall be construed as references to Directive 2017/1572 and to Delegated Regulation 2017/1569 and read in accordance with the correlation table in the Annex of Directive 2017/1572.

ICH: Q11 Q&A in Step 4, September 2017

- The final Q&A document on the development and manufacture of drug substances provides additional clarification for the selection of starting materials (Section 5 in ICH Q11) and on the information that should be provided in marketing authorisation applications and/or Master Files.
- The focus is on chemical entity drug substances.
- The scope of the document follows that of ICH Q 11.
- The 16 Q&As are complemented by a decision tree in Annex 1.

↳ GMP News summary

↳ Official Q11 Q&A document

Note: The ICH provides a training presentation on the ICH Q11 Q&A document.

↳ GMP News summary
↳ Official Presentation

Switzerland: Revision of Medical Devices Legislation, November 2017-ongoing

Switzerland is revising its medical devices legislation, closely modelled on the various new EU requirements aiming at an improvement on the safety and quality of medical devices.

The early revision of the Medical Devices Ordinance (MedDO) was adopted by the Swiss Federal Council on 25 October 2017 and covers all points arising from the new EU regulations that apply as of 26 November 2017:

- Switzerland can continue to participate as an equal partner in the European internal market for medical devices.
- Swissmedic can continue its effective and efficient market supervision of medical devices.
- For Swiss manufacturers, the access to the European internal market remains ensured.

The complete revision of the MedDO and the new Ordinance for in vitro diagnostics is scheduled to enter into force in the first half of 2020.

↳ GMP News summary

↳ Medical Devices Legislation, Oktober 2017

↳ Status spring 2018

EC/EMA: Guidelines on GMP specific to ATMPs, November 2017

- The 90-page document shall facilitate the development and authorisation of ATMPS as they offer ground-breaking new opportunities for the treatment of diseases and injuries.
- Summarises requirements to the specific characteristics of ATMPs and addresses the novel and complex manufacturing scenarios utilised for these products. A risk-based approach to

manufacture and testing of such products is fostered.
- Specific to ATMPs only, other documents developing GMP requirements for medicinal products in Eudralex Vol 4 are not applicable to ATMPs, unless specific reference is made.

ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.

- GMP News summary
- Official Guideline

EMA: Practical Guidance for Procedures related to Brexit for Medicinal Products for Human and Veterinary Use, November 2017 – January 2018

On 24 November 2017, EMA has published a guidance document on post-Brexit changes. It comes in the form of nine questions and answers and outlines the practical and simplified requirements that companies should follow when they apply for changes to their marketing authorisation. The document is constantly updated.

The anticipated UK withdrawal from the EU is scheduled on 30 March 2019.

- GMP News summary
- Official Guidance, Revision 1, January 2018

ICH: Draft of ICH Q12 to Pharmaceutical Product Lifecycle, November 2017

- Now in **Step 2,** including an Annex with illustrative examples.
- The intention behind ICH Q12 is to provide guidance on a framework to facilitate the management of post-approval chemistry, manufacturing and controls (CMC) changes in a more predictable and efficient manner across the lifecycle of a product.
- The guidance addresses the commercial phase and should be seen as the logical continuation of the ICH Q8 – Q11 Guidelines.

- GMP News summary
- ICH Q12 Draft

EC: Detailed Guidelines on GMP for Investigational Medicinal Products for Human Use, November 2017

The 17-pages guidelines are currently listed as a separate document together with Annex 13 of the EU GMP Guide. This step followed a public consultation, where stakeholders were asked to comment on whether the guidelines on GMP for IMPs should be separated from Annex 13 or stay part of it. The separation was accepted.

These guidelines lay down appropriate tools to address specific issues concerning IMPs when it comes to GMP and complements Commission Delegated Regulation (EU) 2017/1569. They apply to manufacture or import of IMPs for human use.

- Official Guideline

EC: Draft to Annex 1 on Sterile Manufacturing, December 2017

- The long awaited draft of Annex 1 “Manufacture of Sterile Medicinal Products” was published on December 20, 2017.
- The public consultation period was open until 20 March 2018.
- The multitude of regulatory changes required the most extensive and thorough revision since the first publication took place in 1971.
- This revision is intended to add clarity, introduce the principles of Quality Risk Management to allow for the inclusion of new technologies and innovative processes and to change the structure to a more logical flow.

The key changes in short:

- Introduction of new sections: scope, utilities, Environmental and process monitoring sections and glossary
- Introduction of QRM Principles
- Introduction of new technologies such as closed single-use and disposable systems
- Restructured to give more logical flow
- Added detail to a number of the previous sections to provide further clarity.

The proposed revised version was prepared in cooperation with WHO and PIC/S.

- GMP News summary
- Annex 1 Draft
- Detailed analysis by our experts

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