THE GMP REGULATIONS REPORT

At a glance and always at hand– the most relevant regulatory developments of 2019.

EMA: Update of Q&A on EU/US MRA, December 2019

The European Medicines Agency (EMA) revised its four-page Q&A document on the EU-US Mutual Recognition Agreement (MRA) on marketing authorisation applications and variations.

Updated question 1: **How does the EU-USA Mutual Recognition Agreement (MRA) affect marketing authorisation applications or variations?**

The corresponding answer lists all available documents that have to be submitted as proof of GMP compliance for US manufacturing sites that have previously been inspected by the US FDA.

- GMP News
- EMA: Q&A on impact of EU/USA MRA on marketing authorisation applications and relevant variations

EMA: Revised Q&A on nitrosamine contamination, December 2019

End of December 2019, the EMA has updated the *Q&A document regarding information on nitrosamines for marketing authorisation holders* who are currently reviewing their medicines for the possible presence of nitrosamines and testing products at risk.

It should support companies in their ongoing review of their manufacturing processes. The 10-page updated document lists potential sources of nitrosamine contamination that have been identified so far and includes four new Q&As.

The Q&A contains track changes making it easier to find the updated information.

- GMP News
- EMA: Questions and answers on "Information on nitrosamines for marketing authorisation holders"

EDQM: Sartan monographs of the European Pharmacopoeia transiently revised, December 2019

Due to repeated cases of nitrosamine contamination in sartans new strict limits apply for the contamination of sartans with nitrosamines since 1 January 2020.

Important changes:

As N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) are classified as possible carcinogens for humans, manufacturers must ensure that these impurities do not occur in their manufacturing processes and must develop appropriate control strategies. To allow them to make the necessary changes to their processes, a two-year transitional period was agreed and strict provisional limits for the content of these impurities, which are included in the section "testing for purity". The corresponding Sartan monographs are:

- Candesartancilexetil (2573)
- Irbesartan (2465)
- Losartan potassium (2232)
- Olmesartanmedoxomil (2600)
- Valsartan (2423)

This step is in accordance with the European Commission's decision on limit values for valsartan, candesartan, irbesartan, losartan and olmesartan. These sartans have a tetrazole group in common which is responsible for the risk of contamination with nitrosamines.

- GMP News
- EDQM: Control of nitrosamine impurities in sartans: revision of five Ph. Eur. monographs
- EMA: Temporary interim limits for NMBA, DIPNA and EIPNAimpurities in sartan blood pressure medicines

EC: Eight technical guidelines for individual identifiers (UDIs), December 2019

On 4 December 2019, the European Commission published eight documents containing technical specifications for unique device identifiers (UDIs).

Four documents of

- GS1 (Global Standards One)
- HIBCC (Health Industry Business Communications Council)
- ICCBBA (International Council for Commonality in Blood Banking Automation) and
- IFA (Informationsstelle für Arzneispezialitäten)

deal with Basic UDI-DI. These are required for the upcoming Eudamed database and consist of an 18-character string reflecting the manufacturing facility, the type of product and the product description code. The four other documents address UDI human readable interpretation (HRI) formats.

- GMP News
- EC: Technical Guidance for UDIs

EC: Second corrigendum to MDR, November 2019

On 25 November 2019, the European Commission published the second corrigendum to the EU Medical Devices Regulation (MDR). The corrections mainly concern Class I medical devices.

The timetable for these products will be adjusted, thus giving manucfacturers of class I products additional four years to meet MDR requirements.

"[…] a device which is a class I device pursuant to Directive 93/42/EEC, for which the declaration of conformity was drawn up prior to 26 May 2020 and for which the conformity assessment procedure pursuant to this Regulation requires the involvement of a notified body, or which has a certificate that was issued in accordance with Directive 90/385/EEC or Directive 93/42/EEC and that is valid by virtue of paragraph 2 of this Article, may be placed on the market or put into service until 26 May 2024, provided that from 26 May 2020 it continues […]"

- GMP News
- EC: MDR Corrigendum 13081/19 (English version from p.43)

ICH: Final version of ICH Q12 on lifecycle management, November 2019

The new ICH guideline provides 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 product lifecycle.

Objectives and potential benefits of ICH Q12 i.e. include:

- Harmonisation of change management
- Facilitation of risk-based regulatory oversight
- Control strategy as a key component of the dossier
- Reduction of unnecessary costs and time for industry and regulators
- Support for continuous improvement
- Promotion of innovation in manufacturing

Two of the main tools that are presented for this purpose are:

- Established conditions (ECs), necessary elements that are critical for quality
- Post-approval change management protocol (PACMP), a tool for predictability of information required to support a CMC change to structure the ECs

ICH Q12 should be seen in line with ICH Q8 to Q11 and complements this series of ICH quality guidelines. It is an optional document and the introduced tools and concepts can be adopted, if appropriate. Under step 5 ICH Q12 is to be implemented in the ICH regions.

Please note: The document is fully in line with the US regulatory framework. In the EU legal adjustments will be necessary to achieve full compatibility with ICH Q12.

- ICH: ICH Q12 Guideline on technical and regulatory considerations for pharmaceutical product lifecycle management
- ICH: ICH Q12 Annexes

EC: Aide-Mémoire on GDP inspections of wholesalers, November 2019

Please note: A new version of the Aide-Mèmoire was released on 22 January 2020.

On 18 November 2019, the European Commission published the *Aide-Mémoire for GDP inspection of wholesalers compliance with commission delegated regulation (EU) 2016/161 for safety features*. As a checklist, the six-page document is intended to assist wholesalers in complying with the relevant GDP regulations on safety features.

The Aide-Mémoire lists questions to be asked during an inspection as well as the documents that should be ready at hand during the inspection. The questions range from general information such as

- How are the different requirements for the different products controlled/managed? Are the requirements built into to the product master data on the inventory/stock control system?
- Is the wholesaler a "designated wholesaler"? For what companies and products? If yes, show me the written contract, where the wholesaler is named as "designated wholesaler" by the MAH

but also includes specific questions about the

- quality system
- data management
- verification of security features
- handling of returns or
- handling of counterfeit products.

An additional column lists various references to corresponding text passages within suitable regulations.

- GMP News
- EC: Aide-Mémoire for GDP inspection of wholesalers

WHO: Draft guideline on data integrity, November 2019

WHO published a 28-page draft guideline on data integrity. It clarifies basic aspects to ensure reliable data and information in the manufacture and control of medicinal products. A 7-page annex provides additional examples for the practical implementation of the requirements.

The document has been harmonised with existing DI guidelines, e. g. of the US FDA, as far as possible.

In terms of content, the wheel might not be reinvented in this draft, but a clear structure and language speak for the document. The examples of quality risk management and data integrity assessments are well worth mentioning, as well as the ten examples of good documentation practices in data integrity. A final version can be expected for the end of the year.

- GMP News
- WHO Draft Guideline on data integrity

EMA: Revised Q&A regarding the implementation of the new MDR and IVDR, October 2019

On 22 October 2019, the European Medicines Agency released a revised MDR/IVDR Q&A including new sections on the basic requirements for combination products and the selection of a notified body.

Further topics consider

- the impact of MDR on a Mutual Recognition Procedure (MRP) and
- the applicability of unique device identifier (UDI) requirements to integral Drug-Device Combinations (DDCs)
- the impact of Article 117 on currently authorized integral DDCs
- the requirements for a provision of the notified body opinion, the EU certificate or a declaration of conformity together with an Marketing Authorization Application (MAA)
- the impact of MDR and article 117 on new MAAs.

The Q&A contains track changes making it easier to find the added information.

Please note: EMA has also published a 26-page draft guideline on the subject of quality requirements for combination products of medicinal products and medical devices.

- GMP News
- EMA: Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) (With Track Changes)
- EMA: Draft guideline on the quality requirements for drug-device combinations

ICH: Q3C(R6) reinstated with original ethylene glycol PDE, October 2019

According to the ICH, the **PDE value for ethylene glycol** was reinstated to its previous **PDE value of 6,2 mg/day and a concentration limit of 620 ppm.**

This value was changed in October 2018 with the ICH Q3C(R7) version to a PDE of 3.1 mg/day and a concentration limit of 310 ppm. The process was then preceded by an error correction procedure.

In 2019 the ICH received a request to suspend the error correction for ethylene glycol. Based on archive documents and in-depth literature research, the 2018-decision was reversed by the Expert Working

Group. As a consequence, the Q3C(R7) version has now been reverted back to the Q3C(R6) version.

- GMP News
- ICH: Newsroom
- ICH: Cover statement
- EMA: ICH Q3C, Impurities: Guideline for residual solvents

EC: Version 16 of Q&A on safety features for medicinal products for human use, October 2019

On 25 September 2019, the European Commission published Version 16 of the document on safety features for medicinal products for human use with two new questions:

- Q&A 2.23 explaining the requirements for the characters used in batch and serial numbers.
- Q&A 7.20 clarifiying what is meant by "investigation" of all potential incidents of falsification in Article 37(d) of Commission Delegated Regulation (EU) 2016/161.

- GMP News
- EC: Safety features for medicinal products for human use

EMA: Q&A for exemptions in re-testing batches of imported ATMPs, August 2019

This EMA Q&A published on 28 August 2019 clarifies when exemptions from batch re-testing of imported advanced therapy medicinal products (ATMPs) are permitted.

Four questions and their answers clarify

- The obligations of the Qualified Person regarding the testing of imported ATMP batches or
  a batch release without renewed testing
- Which cases grant a exemption from EU batch re-testing
- Which data are to be submitted in the marketing authorisation application
- The responsibilities of the Qualified Person in case of an exemption from re-testing.

- GMP News
- EMA: Q&A on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country

EMA: Q&A on EU/US MRA, July 2019

As of 15 July 2019 the US FDA grants all 28 EU member states the ability to conduct GMP inspections at a level equivalent to that of the US. The competent authorities in the US and the EU no longer have to carry out their own inspections of manufacturing sites, but can rely on reliable inspection results from the other side.

EMA has published a Q&A paper on the key points of the MRA, which is updated continuously.

It deals, e.g., with inspections outside the EU and the USA, with American combination products that are medical devices in the EU or with post-import controls.

- GMP News
- EMA: EU and US reach a milestone in mutual recognition of inspections of medicines manufacturers
- EMA: Q&A on the impact of Mutual Recognition Agreement between the European Union and the United States
- FDA: Mutual Recognition Agreement (MRA)

WHO Draft: Production of water for injection by means other than distillation, July 2019

In response to changes in the European Pharmacopoeia, WHO has published a 10-page draft guideline on WFI production without the means of distillation. It is intended to be the guideline WHO Good Manufacturing Practices: Water for Pharmaceutical Use. A publication date of a final version is currently not known.

- WHO Draft: Production of water for injection by means other than distillation

WHO: Technical Report Series 1019, 2019 published, June 2019

With the publication of the 53nd TRS No. 1019 two revised guidelines in the area of "Quality Assurance – GMP" were adopted:

- **Interpretation of guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products, PART 2**
  This document reflects the interpretation of the recommendations in *Part 1 Supplementary guidelines for good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms*

- **Good manufacturing practices for validation**
  The overarching text presented constitutes the general principles of the completely revised guidance on validation. Included are various appendices that address specific aspects of validation and complement the general text:

Appendix 1: *Validation of heating, ventilation and air-conditioning systems*
Appendix 2: *Validation of water systems for pharmaceutical use*
Appendix 3: *Cleaning validation*
Appendix 4: *Analytical procedure validation*
Appendix 5: *Validation of computerized systems*
Appendix 6: *Guidelines on qualification*
Appendix 7: *Non-sterile process validation*

- GMP News
- WHO: TRS 1019
- WHO: Interpretation of guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products
- WHO: Good manufacturing practices: guidelines on validation

EMA Q&A regarding OOS-batches of ATMPs, April 2019

The Q&A points out how companies should handle OOS batches of authorized cell or tissue-based advanced therapy medicinal products (ATMPs). For manufacturers, importers and Marketing Authorisation Holders of ATMPs this 2-page document will be of good value.

Six pairs of questions and answers explain a possible pathway for the administration of such out-of-specification (OOS) batches that have already been granted a marketing authorisation. Answers are given, e.g., on the following questions:

- Who should be notified and when?
- Are National Competent Authorities involved?
- How should the manufacturer/importer/MAH notify the EMA of the OOS batch(es)?
- What are the obligations or expectations the manufacturer/importer/MAH should follow?
- What information should be provided to the patient?

- GMP News
- EMA: Q&A on the use of out-of-specification batches

EMA Publishes Sterile Manufacturing Guidance, March 2019

The 25-page final version of the guideline "*Sterilisation of the Medicinal Products, Active Substance, Excipient and Primary Container"* has entered into force on 1 October 2019.

The selection of appropriate sterilsation methods for sterile products is explained. The document comprises the

- sterilisation by steam, dry heat and ionising irradiation
- sterilisation by filtration and aseptic processing and the

- sterilisation by gas.

The optimal selection of a suitable sterilisation process is supported by decision trees.

- GMP News
- EMA Guideline

ICH: New Inhalation-PDE for Cadmium in Q3D-Guideline, March 2019

On 22 March 2019, ICH published a revision of the Guideline for Elemental Impurities Q3D (R1) with an adjustment of the PDE value for cadmium by inhalation.

Cadmium is now listed with a new inhalation PDE value of 3.4 µg/day. The original value published in 2014 was 1.7 µg/day. It did not agree with the oral and parenteral PDE calculations, which are also given. Obviously, a modifying factor was not taken into account.

- GMP News
- ICH Q3D(R1)

PIC/S: Guidance on classification of GMP deficiencies (PI 040-1), January 2019

The guidance is intended to provide a tool to support the risk based classification of GMP deficiencies from inspections and to establish consistency amongst Inspectorates. It lays down the principles used to classify GMP deficiencies and also provides examples of the classification of different types of deficiencies.

The guidance entered into force on 1 January 2019.

- PIC/S: Guidance on classification of GMP deficiencies (PI 040-1)