The GMP Regulations Report 2020

Note: This is an abridged version. The detailed version is available to the GMP Compliance Adviser costumers. This long version is also available for download **here**.

For all of us, the year 2020 turned out quite differently than we had ever imagined. People everywhere are struggling with new challenges. The GMP world was not spared, either. To name just a few: inspections were carried out remotely to a large extent and many regulations remained in draft form for the time being. Only a small amount of documents was finalized parallel to the all-dominating COVID-19 pandemic. Other areas that kept GMP professionals on their toes were represented by nitrosamine impurities or the final Brexit, which came into force with the beginning of 2021. It will definitely ensure a flood of new regulations. To give you a better overview, we have divided this year's review into categories and marked the few final documents, accordingly.

EU and international

→ FINAL – EC: Updated version 18 of Q&A on safety features for medicinal products for human use, August 2020

On August 12, 2020, the European Commission published version 18 of the Q&A on safety characteristics for medicinal products. The document, which has now grown to 34 pages, was thus updated twice this year (March and August 2020).
New are the questions

- **4.6, 5.11, 5.12, 5.13 and 6.9**.

These questions were added

- **1.22, 1.8, 2.14, 4.4.**

Detailed information on the content of the questions can be found via the following news links:

- GMP News August 2020
- GMP News March 2020
- EC: Safety features for medicinal products for human use Questions and Answers – Version 18
- GMP Compliance Adviser Chapter C.8.2.1

→ FINAL – EMA: Guideline on the quality of water for pharmaceutical use, July 2020

On 20 July 2020, EMA published the final 10-page *Guideline on the quality of water for pharmaceutical use.*
The date of entry into force will be 1 February 2021.

On that date the guideline replaces

- the *Note for guidance on quality of water for pharmaceutical use* from 1 May 2002
- the *CPMP Position Statement on the quality of water used in the production of vaccines for parenteral use* from 20 October 2003.

It takes into account the following interim changes to the European Pharmacopoeia:

- the revised monograph on Water for Injection (0169), which offers the possibility of using processes other than distillation for WFI (Water for Injection), e. g. reverse osmosis
- new monograph on water for the production of extracts (2249) and
- the suppression of the monograph for HPW, highly purified water (1927)

It also reflects the expectations for the minimum acceptable water quality in the manufacture of active ingredients and medicinal products for human and veterinary use.

The guideline is to be understood as a guideline for the pharmaceutical use of different water qualities in the manufacture of active substances and medicinal products for use in human and veterinary medicine. The document also applies to ATMPs (Advanced Therapy Medicinal Products) and can in general also be applied to investigational medicinal products (IMPs).

Read the new guideline together with the corresponding Q&A paper *Questions and answers on production of water for injections by nondistillation methods – reverse osmosis and biofilms and control strategies.* This Q&A was already published in 2017 after the revision of the WFI monograph.

- GMP News
- EMA: Guideline on the quality of water for pharmaceutical use
- EMA: Q&A
- GMP Compliance Adviser: Chapter C.11

→ FINAL – WHO: Good storage and distribution practices for medical products, May 2020

The guideline *Good storage and distribution practices for medical products* was published in the WHO Technical Report Series, No. 1025, 2020 as Annex 7. It replaces the two previous documents

- *Guide to good storage practices for pharmaceutical products (GSP) und*
- *WHO good distribution practices for pharmaceutical products (GDP).*

The areas of transport and storage are thus being combined in one guideline. The scope of application has been expanded from mere pharmaceutical products to "medical products". By WHO definition these are „products including, but not limited to, finished pharmaceutical products, medical devices including in vitro diagnostic medical devices, and vaccines“.

The guideline is applicable to all entities involved in any aspect of the storage and distribution of medical products, from the premises of the manufacturer of the medical product to an agent, or the person dispensing or providing medical products directly to a patient. This includes manufacturers and wholesalers, as well as brokers, suppliers, distributors, logistics providers, traders, transport companies and forwarding agents.

- GMP News
- Good storage and distribution practices for medical products
- GMP Compliance Adviser: Chapter H.13

DRAFT – EU-GMP Annex 21 on import of medicinal products, March 2020

The European Commission published the 4-page draft version of the new Annex 21: Importation of medicinal products, on 20 March 2020. Apart from the main Chapters and Annexes of the EU GMP Guide, it has become necessary to establish specific guidelines for the activity of importing medicinal products.

The Annex summarises the principles and guidelines of good practice requirements that apply to holders of a manufacturing and import authorisation (MIA) who import medicinal products (human and veterinary) from outside the EU/EEA borders and thus from third countries. Medicinal products imported with the sole intention of being exported to the EU/EEA and which are neither processed nor released for marketing in the EU/EEA are not covered by this Annex.

The Annex 21 draft is of particular importance for importers (MIA holders) and companies involved in the supply chain. All stakeholders involved in activities related to importation of human and veterinary medicinal products, across EU/EEA borders, are invited to respond on this consultation which ended on 20 June 2020.

A date for the entry into force of Annex 21 has not yet been set.

- GMP News
- EC: Annex 21 draft
- EC: Consultation information for stakeholders
- GMP Compliance Adviser: Chapter C.4.21

SECOND DRAFT – EU-GMP Annex 1 on sterile manufacture, February 2020

The EMA received more than 6000 comments on the completely revised draft of Annex 1, published at the end of 2017. The long-awaited second draft followed in February 2020:

The new title *Annex 1: Manufacture of Sterile Products* (formerly *Manufacture of Sterile Medicinal Products*) clarifies the extended scope of application also for active substances, sterile excipients, primary packaging materials and finished dosage forms, packed sizes from single to multiple units, processes (from highly automated systems to manual processes) and technologies such as biotechnology, classical manufacturing of small molecules and closed systems.

The application of the principles of quality risk management (QRM) is further emphasized. QRM applies to this document in its entirety and is not dealt with in a single section only. In the case of specific information such as limit values, these should be regarded as minimum requirements. Microbial, particulate and pyrogen contamination in the finished product should be prevented this way. For this purpose, the use of appropriate technologies such as Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid microbial testing and monitoring systems are mentioned.

In the area of quality assurance, all critical control points must be defined and the effectiveness of all controls (design, procedures, technical and organisational measures) and monitoring measures must be evaluated. The CCS (Contamination Control Strategy) should be continuously updated with the aim of continuously improving the manufacturing and control methods over the entire life cycle of the product. Non-conformities should be comprehensively analysed.

Update December 2020: More than 2000 comments have been submitted for the second draft that need to be reviewed and evaluated. The main topics considered are rooms and equipment. With an additional delay due to the Corona pandemic, the final version is not expected to be available until late 2021.

- GMP News
- EC: Medicinal Products
- EC: Second Draft: Annex 1 Manufacture of Sterile Products

↳ GMP Compliance Adviser: Chapter C.4.1.1

DRAFT – EMA: Reflection paper on GMP-related responsibilities of MAHs, January 2020

On 14 January 2020, the EMA published a draft reflection paper on the GMP-related obligations of marketing authorisation holders (MAHs). In general, these responsibilities relate to outsourcing and technical agreements. However, they are spread over the different chapters and annexes of the EU GMP Guideline and are also quite numerous. The aim of the reflection paper now is to clarify in a single document what the different responsibilities are and what they mean for MAHs at a practical level. It also addresses the legal provisions in European Directives and other Directives that relate to GMP and also affect marketing authorisation holders.

To summarize all these aspects in their totality and what they mean for MAHs at a practical level is presented under a number of different themes:

- Outsourcing and technical agreements
- Audits and qualification activities
- Communication with manufacturing sites (e.g. MA dossier information, variations, regulatory commitments, etc.)
- Product Quality Reviews
- Quality defects, complaints and product recalls
- Maintenance of supply of medicinal products
- Continual improvement activities.

It is intended that this 31-page reflection paper will provide increased clarity for MAHs in this area, and that it will serve as a useful resource for MAHs when designing (or reviewing) their internal systems as well as their interactions with manufacturing sites.

↳ GMP News
↳ EMA draft: Reflection Paper on GMP and Marketing Authorisation Holders

Nitrosamines

→ FINAL – FDA: Guidance on control of nitrosamine impurities in human drugs, September 2020

How can manufacturers of pharmaceuticals and APIs detect and prevent nitrosamine impurities in pharmaceutical products and what are possible causes of the contaminations? Answers are provided by the 24-page guidance on *Control of Nitrosamine Impurities in Human Drugs*, which was published by the US FDA on 1 September 2020.

Based on the FDA's current understanding, the guideline discusses potential causes for the formation of nitrosamines and presents a comprehensive risk assessment strategy to detect and prevent their presence.

↳ GMP News
↳ FDA: Control of Nitrosamine Impurities in Human Drugs
↳ GMP Compliance Adviser: Chapter D.27

→ FINAL – EMA: Q&A on nitrosamine impurities for marketing authorisation holders, August 2020

Shortly after the publication of the EMA's final assessment report on nitrosamine impurities in medicinal products, a 15-page Q&A for marketing authorisation holders and applicants was published on 6 August 2020.

It replaces the document '*Information on nitrosamines for marketing authorisation holders*' *EMA/428592/2019* published in September 2019, which was withdrawn.

Which expectations are placed on MAHs and applicants in the future?

- Design their manufacturing processes and controls to prevent if possible or mitigate as much as possible the presence of N-nitrosamines in their API and FP(s);
- Assess the risk of presence nitrosamine impurities in their API(s) and FP(s) and introduce any resultant changes to the dossier as needed (e.g. changes to their manufacturing processes);
- Ensure that active substances and excipients used in their FPs are manufactured in compliance with good manufacturing practices in line with Article 46(f) of Directive 2001/83/EC.

Important deadlines for marketing authorisation holders to submit the results from step 1:

- For products containing chemically synthesised APIs: **until 31 March 2021**
- For products containing biological APIs: **until 1 July 2021**

- GMP News
- EMA: Nitrosamine Website
- EMA: Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products
- GMP Compliance Adviser: Chapter C.19