The Impact of the changing EU Guidance and the MRA

EU GMPs are under constant revision with quite some consequences.

The new Mutual Recognition Agreement (MRA)

The new Mutual Recognition Agreement (MRA) with the USA came into force on 01 November, 2017. Since then, the competent authorities of the EU have not conducted any inspections in the USA. In return, the FDA approved twelve European authorities so far: Croatia, France, Italy, Malta, Spain, Austria, Sweden, the United Kingdom, the Czech Republic, Greece, Hungary and Romania. Other EU member states will be added as soon as their evaluation by the USA is complete; by 15 July, 2019, all authorities resp. countries are supposed to be evaluated and approved.

Challenges: the MRA is not as simple as it sounds. For example, the FDA does not perform routine inspections of IMP manufacturers. After the implementation of Delegated Regulation 2017/1569 however, IMP manufacturing in third countries is to always be inspected by national EU authorities. If and how EU authorities will inspect IMP manufacturers in the US in spite of the MRA is still not clear (the regulation has not come into force, yet, after all).

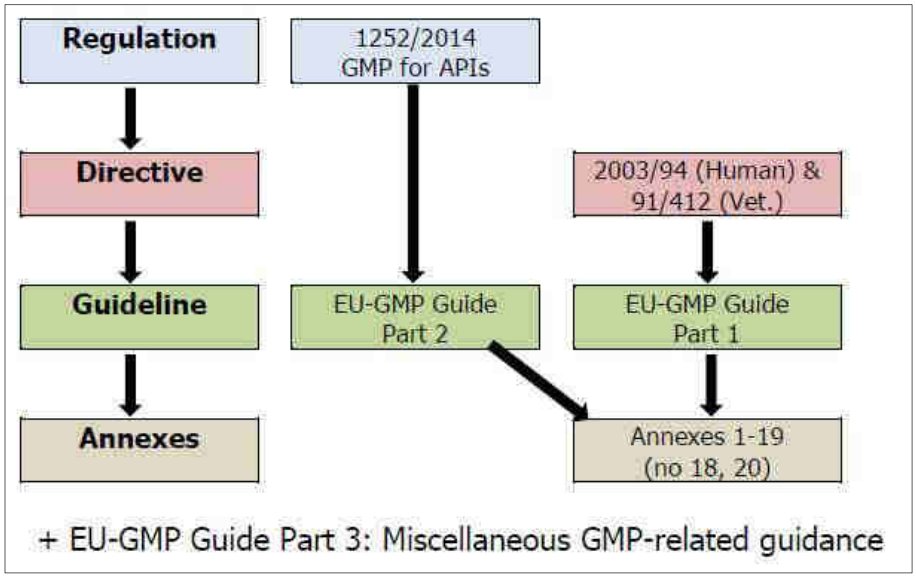
New Structure of EU Guidance

The reorganization of the guidelines on clinical trials in the EU was decided upon in May 2014, already. The reason for this was the so far different implementation of Directive 2001/20/EG in the individual EU member states. The objective of Regulation (EU) No 536/2014 *"... on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*" of 16 April, 2014 is therefore to establish standardized regulations for the execution of clinical trials in the EU.

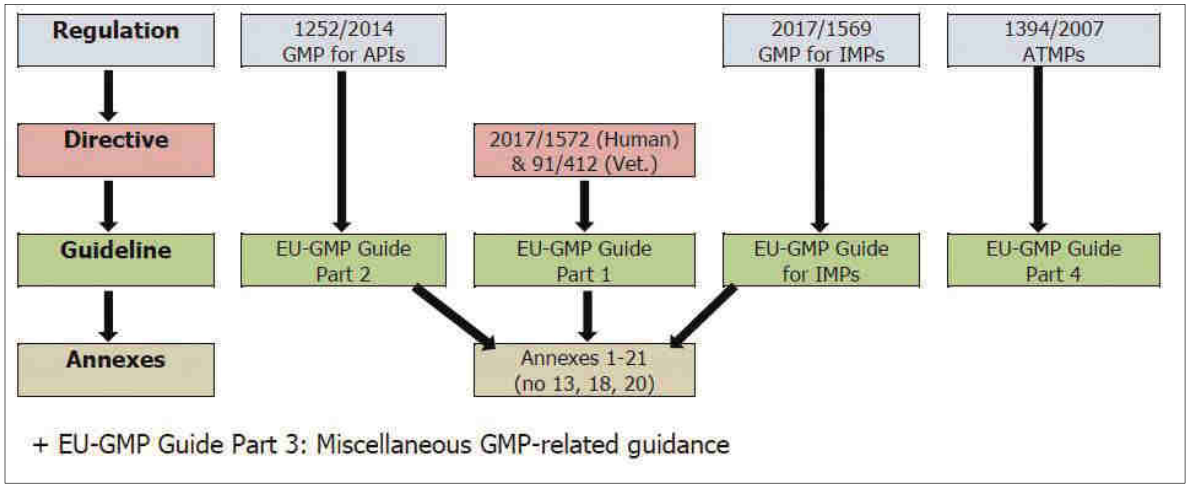
To prevent future deviations, the restructuring won't be in the form of a directive, but a regulation (the **Clinical Trial Regulation** = CTR), which is directly applicable without needing to be transformed into national law. Therefore, the **GMP requirements for IMPs** must be revised as well.

All this will come into force as soon as the EU's new submission portal for clinical trials has been implemented (with a transitional period of three years).

The aforementioned changes ultimately lead to a new structure of EU specifications. While it is difficult to describe in writing, the following diagrams show it quite clearly.
Structure of EU specifications so far:



Future structure of EU GMP specifications (without GDP - they remain the same):



Revision of Annex 1 of the EU GMP Guidelines (sterile medicinal products)

The long awaited draft of Annex 1 (Manufacture of Sterile Medicinal Products; Targeted stakeholders consultation) was published on 20 December 2017. What's special about it is that the revised Annex 1 won't be an independent EU document. Instead, it will also apply for the PIC/S guidelines. Even though it is still just a draft (comments can be submitted until 20 March 2018), the pharmaceutical industry will have to prepare for several changes.

Detailed analyses of these and other EU GMP developments are presented in the conference "**After the MRA: Understand European GMPs and the Role of the Qualified Person (QP)"**, and they are also published regularly in ECA's GMP Newsletter.