What's New in Update No. 6/2018?

Dear Reader of the GMP Compliance Adviser,

just before taking your well-deserved summer break here comes this year's 6th update. The topic in focus is quite suitable: water – in this context of course in pharmaceutical quality. Pharmaceutical water occupies a unique position in the pharmaceutical industry and is regarded as being extremely critical.

Are you familiar with the many specifications in the pharmacopoeia monographs? Do you know the different techniques for water production? Immerse yourself in the completely revised Chapters on **Water Qualities** and the **Pharmaceutical Water Generation** to stay at the cutting edge of technology.

Are you struggling with the implementation of the new ICH Q3D guideline? The new chapter on **Elemental impurities** provides you with a roadmap to set up the project in your company together with a step-by-step explanation on how to perform the risk assessment. Take the chance to improve your expertise in this challenging field!

Last but not least, you definitely should take a closer look at the revised **Annex 17: Real Time Release Testing and Parametric Release** of the EU GMP Guide. It will come into operation on 26 December 2018 with the new requirement of an RTRT approach. As always, it is best to change before you have to!

With this in mind simply login and check out!

GMP in Practice		
Chapter 5	5.A 5.B	Water qualities Pharmaceutical Water Generation
Chapter 14	14.O	Elemental impurities

GMP Regulations		
Chapter C	C.6.2 C.6.17	Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use Annex 17: Real Time Release Testing and Parametric Release

GMP in Practice

Chapter 5 Pharmaceutical Water

5.A Water Qualities

The European Pharmacopoeia contains requirements for Purified Water, Highly Purified Water and Water for Injection. As a result of the European Pharmacopoeia now permitting the use of membrane systems when producing WFI, "Highly Purified Water" is theoretically redundant because it was only ever seen as a temporary solution. Since the new WFI monograph was introduced in April 2017, the two water qualities can be seen as equivalents. Due to the fact that "HPW" is still to be found in the various registration documents for medicinal products, the monograph is likely to remain in place for the foreseeable future. The US Pharmacopeia contains requirements for Purified Water and Water for Injection. In addition, the two pharmacopoeias also describe other water qualities for special applications. There is no monograph for pharmaceutical steam in the European Pharmacopoeia, whereas the USP does include a monograph for Pure Steam.

The quality of each water type must be proven using a number of tests that are described in the monographs. The physical and chemical tests include the determination of conductivity, tests for specific ions and the determination of TOC. All of the water qualities have to undergo microbiological monitoring. (Herbert Bendlin, PhD, Fritz Röder)

5.B Pharmaceutical Water Generation

When producing pharmaceutical water, drinking water is pre-treated to remove substances that are not desired during further processing. The pre-treatment processes include filtration, chemical stabilisation, UV irradiation and softening of the water using ion exchange. The processes that are used depend on the initial quality of the feed water. This is determined by water analysis.

To produce Purified Water, different processes are combined in so-called treatment plants. Reverse osmosis is widely used to produce Purified Water and is often combined with electro-deionisation.

Purified Water is the starting product for the generation of Highly Purified Water (HPW) and Water for Injections (WFI). HPW may be produced using membrane technology. However, until recently, distillation was the only process permitted in Europe when generating WFI. The new "Water for Injections" monograph in the European Pharmacopoeia came into effect in April 2017. As a result, membrane technology can now also be used to produce WFI in Europe. The advantages and potential risks of the cold production of WFI using membrane technology are discussed in detail.

The functionality and potential application of different technologies such as ion exchange, reverse osmosis, electro-deionisation, ultrafiltration and the various other technologies used during distillation are described in detail and eval-

uated based on their advantages and disadvantages. (Herbert Bendlin, PhD, Fritz Röder)

Chapter 14 Laboratory Controls

14.O Elemental Impurities

The implementation of the ICH Q3D Guideline on Elemental Impurities in the European legal framework as well as in the European Pharmacopoeia entails substantial consequences. The guideline not only applies for the marketing authorisation of new products with new drug substances, but also with existing drug substances and for all marketed products. In any case a risk assessment on the potential presence of elemental impurities must be performed, taking all potential sources of contamination into account. Based on the outcome of the risk assessment and the analytical data obtained, it may be necessary to adapt the control strategy. One of the biggest challenges when implementing the guideline is obtaining the information and data required from all suppliers. (Markus Veit, PhD)

Risk assessment is of key importance for implementing the guideline in a company. The risk assessment is a complex task, and therefore good planning is highly relevant to optimize resources in all their forms: human, time and cost. The decision which approach to follow (component or product) should be made on a case by case basis. To achieve this, expertise regarding the requirements and consequences is the starting point to make sure that the project is successful without a negative impact on resources. The risk assessment is explained in detail and examples are given. (Paulino Alonso, PhD)

GMP Regulations

Chapter C EU Directives and Guidelines

C.6.2 EU GMP Guide Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use

Annex 2 is no longer applicable to Advanced Therapy Medicinal Products as the European Commission has published a standalone guideline on the Good Manufacturing Practice for ATMPs. The guideline is listed under Part IV of Eudralex Volume 4. In alignment with this, Annex 2 had to be revised and came into force on 22 May 2018.

C.6.17 EU GMP Guide Annex 17: Real Time Release Testing and Parametric Release

Almost two years after publishing a draft document of Annex 17: *Real Time Release Testing* the European Commission has now published the final version newly entitled Annex 17: *Real Time Release Testing and Parametric Release*. The eight-page document will come into operation on 26 December 2018 and will then replace the preceding version which came into force in the year 2002.

The document outlines the requirements for application of an RTRT approach as an alternative to routine end-product testing. It applies to finished products, active substances, and intermediates. Advances in the application of process analytical technology (PAT), quality by design (QbD) and quality risk management (QRM) principles are now taken into account.

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