

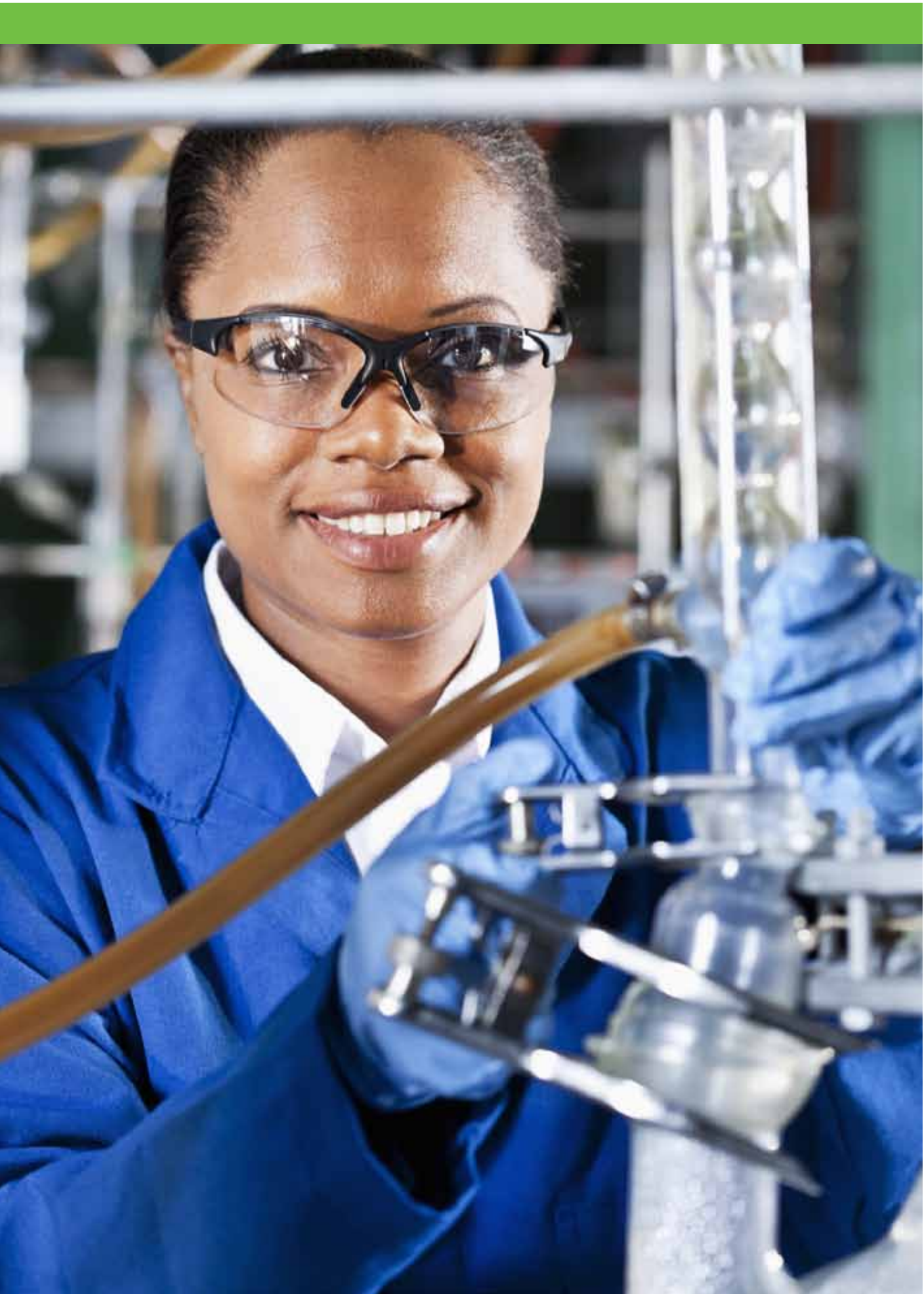
# Comparison of EU GMP Guidelines with WHO Guidelines

Identification of the cost-intensive requirements



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# List of abbreviations

<b>APIs</b>	Active pharmaceutical ingredients
<b>BCS</b>	Bio-pharmaceutics Classification System
<b>CoQ</b>	Cost of quality
<b>CPMP</b>	Committee for Proprietary Medicinal Products
<b>CTD</b>	Common technical document
<b>DQ</b>	Design qualification
<b>EMA</b>	European Medical Agency
<b>EU</b>	European Union
<b>FDA</b>	Food and Drug Administration
<b>FPPs</b>	Finished pharmaceutical products
<b>GAMP</b>	Good automated manufacturing practice
<b>GMP</b>	Good manufacturing practices
<b>HVAC</b>	Heating, ventilation and air-conditioning
<b>ICH</b>	International Conference on Harmonisation
<b>IPEC</b>	International Pharmaceutical Excipients Council
<b>IQ</b>	Installation qualification
<b>ISO</b>	International Organization for Standardization
<b>ISPE</b>	International Society for Pharmaceutical Engineering
<b>KPI</b>	Kampala Pharmaceutical Industries Ltd
<b>OQ</b>	Operational qualification
<b>PIC/S</b>	Pharmaceutical Inspection Co-operation Scheme
<b>PQ</b>	Performance qualification
<b>PQG</b>	Pharmaceutical Quality Group
<b>PQRs</b>	Product quality reviews
<b>QCIL</b>	Quality Chemical Industries Ltd
<b>QMS</b>	Quality management system
<b>QRM</b>	Quality risk management
<b>SMF</b>	Site Master File
<b>SOPs</b>	Standard operating procedures
<b>TPI-ARV</b>	Tanzania Pharmaceutical Industries – Anti Retro Viral
<b>TQM</b>	Total quality management
<b>TRS</b>	Technical report series
<b>UNAIDS</b>	The Joint United Nations Programme on HIV/AIDS
<b>UNFPA</b>	United Nations Population Fund
<b>UNICEF</b>	United Nations International Children's Emergency Fund
<b>WHO</b>	World Health Organization

# 1. Introduction

Every government allocates a substantial proportion of its total health budget to medicines. This proportion tends to be greatest in developing countries, where it may exceed 40%.

Without assurance that these medicines are relevant to priority health needs and that they meet acceptable standards of quality, safety and efficacy, any health service is evidently compromised. In developing countries considerable administrative and technical effort is directed to ensuring that patients receive effective medicines of good quality. It is crucial to the objective of health for all that a reliable system of medicines control be brought within the reach of every country.

Both for manufacturers and at national level, good manufacturing practices (GMP) are an important part of a comprehensive system of quality assurance.



The pharmaceutical industry of the European Union (EU) maintains high standards of Quality Management in the development, manufacture and control of medicinal products. A system of Marketing Authorisations ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality and efficacy.

## 1. Introduction

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Two directives laying down principles and guidelines of GMP for medicinal products were adopted by the European Commission. Directive 2003/94/EC applies to medicinal products for human use and Directive 91/412/EEC for veterinary use. Detailed guidelines in accordance with those principles are published in the Guide to Good Manufacturing Practice, which will be used in assessing applications for manufacturing authorisations and as a basis for inspection of manufacturers of medicinal products.

The Guide is presented in three parts and supplemented by a series of annexes. Part I covers GMP principles for the manufacture of medicinal products. Part II covers GMP for active substances used as starting materials. Part III contains GMP related documents, which clarify regulatory expectations.<sup>a</sup>

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. The setting of global standards is requested in Article 2 of the WHO Constitution, which cites as one of the Organization's functions that it should "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products."

The first GMP text published by WHO was developed during 1967-69 upon request by WHO's Member States and was revised in 1975.

Revised and expanded GMP guidelines were prepared during 1989-90, approved by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in late 1990 and subsequently published by WHO. At that time, Part One of these revised and expanded guidelines set out the philosophy and essential elements of GMP; Part Two dealt with good practices in production and quality control. These two parts together represented the "core" of the GMP guidelines published by WHO.<sup>b</sup>

The alert reader can easily detect that the EU and WHO guidelines are based on the same principles but differ in detail.

This study is supposed to compare the EU and WHO GMP guidelines and work out the differences, especially with regard to the question which GMP guideline contains the stricter and more expensive requirements and in which sections. The statement that the EU GMP guidelines are supposed to be more expensive with regard to the adaption and implementation of the requirements but lead to a higher quality shall be herewith reviewed.

Furthermore, it shall be stated exemplary where the critical and consuming requirements of the WHO with regard to the implementation of GMP can be seen, bearing in mind that especially developing countries adhere to WHO GMP guidelines. For this purpose, polls have to be executed with pharmaceutical producers in Africa and, for ease of reference, smaller manufacturers in Europe.

Finally, this study should inform, in how far the adaption of WHO GMP guidelines can be sensible or a harmonisation of requirements is unavoidable. Especially with regard to the compliance of requests developing countries are facing, a risk-orientated sensitivity is necessary, i.e. minimising requirements which are unnecessary and too expensive but implemented voluntarily in Europe / USA.

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<sup>a</sup> "EU Guidelines to Good Manufacturing Practise Medicinal Products for Human and Veterinary Use, introduction"

<sup>b</sup> WHO "Quality assurance of pharmaceuticals, Volume 2, 2nd edition, introduction, p. 1 - 6"

## 2. Comparison of the requirements of EU GMP guidelines versus WHO GMP guidelines



## 2.1. Main principles for pharmaceutical products

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### 2.1. Main principles for pharmaceutical products

#### 2.1.1. Quality management

Chapter 1 of the EU GMP guidelines presents an overview of the chapters to come. It is divided into the sections:

- Quality Assurance,
- Good Manufacturing Practice for Medicinal Products (GMP),
- Quality Control,
- Product Quality Review and
- Quality Risk Management.

Many of the requirements and recommendations listed in this chapter are mentioned again later in the subsequent chapters or treated there in more detail.

The corresponding requirements are also listed in chapter 1 of the WHO guidelines, titled “Good manufacturing practices: main principles for pharmaceutical products”.<sup>1</sup>

The contents and the requirements of chapter 1 of the “EU Guidelines” and the “WHO main principles” are in large parts the same.

The WHO additionally describes further general requirements in its introduction of Annex 3, Technical Report Series (TRS) 961, “Quality management in the medicines industry: philosophy and essential elements”.<sup>2</sup>

Some conceptional differences are existing, e.g.:

- the EU guidelines speak of “the holder of a Manufacturing Authorization”. WHO instead of “the manufacturer”.
- the EU guidelines use the term “medicinal products” instead of “pharmaceutical products”.

These differences are with regard to the aim of this study of no relevance.

#### Ad “Quality Assurance”

The requirements both guidelines state referring to item “Quality Assurance” are content-wise identical.

The WHO specifies some topics a little bit in more detail, e.g.:

- that managerial responsibilities have to be fixed in job descriptions,
- that controls are necessary for starting materials as well as bulk products,
- that calibration has to be carried out.

#### Ad “Good Manufacturing Practice for Medicinal Products (GMP)”

The WHO guidelines list their general requirements regarding “Good manufacturing practices for pharmaceutical products (GMP)” in chapter 2.<sup>1</sup>

The requirements are identical except for small deviations, e.g.:

- the WHO explains additionally two types of risks which exist in pharmaceutical production: cross-contamination and mix-ups;
- the EU guidelines explain that critical steps and significant changes have to be validated. The WHO points out that qualification has to be performed;
- only the WHO includes storage as a process which has to be monitored to minimise risks to product quality.

#### Ad “Quality Control”

The requirements of the WHO regarding Quality Control as the part of GMP concerned with sampling, specification and testing are listed in chapter 17.<sup>1</sup>

Again only minor differences could be observed between the two guidelines, e.g.:

- under point 17.3 the WHO accented the independence of the Quality Control department;
- the WHO included under point 17.4.c again “qualification” not only “validation”;
- the EU guidelines emphasise the need to release products through a Qualified Person (based on EU drug law).

#### Ad “Product Quality Review” and ad “Quality Risk Management”

No significant distinction could be assessed between the two guidelines regarding the two sub-items “Product Quality Review” and “Quality Risk Management”.

The EU guidelines additionally mentioned the need to compile Product Quality Reviews as well for Marketing Authorisations for third countries.

These elaborations, often called Annual Product Review, are periodic quality reviews dealing with starting materials, batches produced, results of critical in-process-controls and finished products, etc.

### **2.1.2. Personnel**

The existence of sufficient qualified personnel is a general requirement according to both guidelines with reference to the establishment and maintenance of an effective quality management system in the drug production.

This guarantees that the given tasks will be executed in time and in the requested quality.

In order to avoid overlaps and empty spaces the respective responsibilities have to be clearly defined and the employee in charge accordingly trained.

The executions of the EU guideline regarding “Personnel” (chapter 2, EU guidelines) can also be found in chapter 9 of the WHO Annex 3.<sup>1</sup>

## 2.1. Main principles for pharmaceutical products

The requirements of both guidelines are almost identical. Nevertheless the following minor differences can be detected:

- The WHO guidelines underline the necessity of establishing a Quality Management System (QMS) not only in the field of production but also in the field of control of pharmaceutical products and active ingredients.
- The EU guidelines explain the responsibilities of a so-called “Qualified Person” being the person in charge of the release of the produced batches and referred to in the EU Directive 2001/83/EC of the European Parliament and of the Council of 6<sup>th</sup> November 2001 on the Community code relating to medicinal products for human use.
- The WHO guidelines describe instead the “authorized person” in general. But, overall, the requirements in both guidelines are identical.
- The WHO guidelines additionally describe the qualification of key personnel responsible for production and quality control.
- Comparable executions can be found in the EU guidelines. These prerequisites can be found in the national drug law, e.g. the German drug law, § 15 “Experience”.
- Both guidelines define the responsibilities of the “Head of Production Department” and the “Head of Quality Control Department”.
- The WHO guideline is generally more detailed and mentions for example beside the “necessity of executions of validations” also the existence of “calibration of control equipment”.

Starting from point 2.13, the requirements of the so-called “Personnel Hygiene” are listed in the EU guideline.

Corresponding prerequisites can be found in the chapter 11 “Personal hygiene” of the WHO guideline as well as Annex 3, chapter 3, “Sanitation and hygiene”<sup>1</sup> and TRS 823, Annex 1, chapter 18, “WHO good manufacturing practices: starting materials”<sup>3</sup>.

The topic “Personnel Hygiene” is explained more explicitly in the WHO guideline than in the EU guideline. This higher grade of accuracy gives the people in charge additional implementation assistance. E.g. “All personnel should be trained in the practices of personal hygiene.” or “Used clothes, ..., should be stored in separate closed containers until properly laundered...”.

### 2.1.3. Premises and equipment

These requirements on “Premises and equipment” aim at ensuring an adequate construction of rooms and equipment to guarantee:

- suitability for the provisioned work tasks,
- minimizing the failure risk,
- easy to clean and maintain.

They therefore aim at avoiding cross-contamination and further possibilities of impairing the product quality.

Formally seen the EU guidelines state the requirements regarding premises and equipment within one chapter (chapter 3). The WHO guidelines divide this topic into chapter 12 “Premises” and Chapter 13 “Equipment”.<sup>1</sup>

The content relating to the prerequisites regarding:

- Production areas,
- Weighing areas,
- Storage areas,
- Quality control areas,
- Ancillary areas,
- Manufacturing equipment,
- Washing and cleaning equipment,
- Balances and measuring equipment,
- Pipework, etc.

is the same.

As before, the WHO guidelines are also on this topic partly more detailed and list not only the requirements e.g. “Production areas should be regularly monitored during both production and non-production periods ...” but as well the activities which have to be carried out to demonstrate that the requirements will be fulfilled.

Moreover, there are further WHO documents regarding the topic “Equipment”, e.g.:

- the WHO workout “WHO good manufacturing practices: starting materials”<sup>4</sup> or
- WHO guidelines on transfer of technology in pharmaceutical manufacturing<sup>5</sup> and
- others.<sup>6-9</sup>

#### 2.1.4. Documentation

According to the motto “not written, not done”, a good documentation praxis is closely linked to the implementation of a GMP system. Intelligible and detailed instructions and records are basic requirements for the production of medicinal products on a high quality level.

The respective recommendations can be found in chapter 4 of the EU guidelines and in chapter 15 “Documentation” of the WHO guidelines.<sup>1</sup>

Neither in the general part nor in the requirements concerning:

- specifications,
- manufacturing formulas / master formulae,
- packaging instructions,
- batch processing records,
- batch packaging records,
- procedures /standard operating procedures and records

decisive differences can be detected.

## 2.1. Main principles for pharmaceutical products

The WHO guidelines are again in its execution and explanations partly more elaborate, see e.g. points:

- 15.10 – 15.12      Labels,
- 15.13 – 15.17      Specifications and testing procedures,
- 15.25                Batch processing records,
- 15.28                Batch packaging records,
- 15.38 – 15.41      SOPs<sup>c</sup>,
- 15.43                Analysis records,
- 15.48                Cleaning and sanitation.

Again the WHO document gives the user additional information on how the guidelines have to be interpreted and what has to be taken care of.

Further information (regarding documentation) can be found in the WHO good manufacturing practices for starting materials (6.3 Batch production records).<sup>10</sup>

### 2.1.5. Production

The production of medicinal products on a continuously high quality level require the existence of a detailed process description based on the respective manufacturing and the relevant Marketing Authorisation.

The requirements and the recommendations in chapter 5 of the EU guideline correspond in general with the executions of chapters 16 and 14 of WHO TRS 961, Annex 3<sup>1</sup> and deal among others with the scopes:

- Prevention of cross-contamination in production,
- Validation,
- Starting materials,
- Processing operations: intermediate and bulk products,
- Packaging materials,
- Packaging operations,
- Finished products,
- Rejected, recorded and returned materials.

The topic “Validation” is treated very superficially in the basic EU documentation (points 5.21 – 5.24). The requirements of both guidelines do not distinguish significantly from each other.

Detailed information can be found in the additional guidelines (EU guideline, Annex 15: “Qualification and Validation”).

The WHO also treats this topic within a separate document (WHO TRS 937, Annex 4: “Validation”).<sup>11</sup>

Furthermore, additional recommendations referring to e.g. “Time limit for storage of equipment after cleaning” can be found in the WHO guidelines point 16.17/16.18 and 16.23 of TRS 961, Annex 3.<sup>1</sup>

<sup>c</sup> SOPs – Standard Operating Procedures

### 2.1.6. Quality control

The tasks of quality control are beside others:

- sampling,
- stating of specifications,
- execution of tests, as well as
- organisation and documentation of release methods.

In order to be able to execute these tasks in accordance with the requirements, the Quality Control has to be kept separate from the production.

Counterpart of chapter 6 of the EU guidelines is chapter 17 “Good practices in quality control” of the WHO guidelines.<sup>1</sup>

The preconditions to “Good Quality Control Laboratory Practice (EU guidelines point 6.5 – 6.10) can be found in Annex 2 and Annex 3 of WHO TRS 961.<sup>14, 15</sup>

The recommendations listed in the EU guidelines and regarding “Sampling” can also be found in the appendices of the WHO TRS.<sup>18</sup>

Almost the same applies to the points 6.18–6.22 of the EU guidelines. They are also mentioned in the appendices of the WHO TRS.<sup>20 - 23</sup>

The points 6.26–6.33 of the EU guidelines deal with the topic “On-going stability programme”. The counterpart can not be found identically in chapter 17 of the WHO guidelines.

But the necessity of execution of “On-going stability studies” can also be found in WHO TRS, Annex 2, 11.5 “Stability monitoring of APIs<sup>d</sup>” and in WHO TRS, Annex 3, 7.3.5 “Stability studies”.<sup>24, 25</sup>

Summing up the topic “On-going stability studies”, it can be said that the requirements of both guidelines are identical.

Partly, the WHO guidelines regarding the chapter “Quality Control” are more detailed than the EU guidelines and provide hints for a better understanding of the requirements and the performance activities.

Under e.g. “Test requirements” (point 17.13–17.21) the WHO guidelines list further recommendations to:

- Starting and packaging materials,
- In-process control,
- Finished products,
- Batch record review and
- Retention samples.

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<sup>d</sup> APIs – Active pharmaceutical ingredients

## 2.1. Main principles for pharmaceutical products

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### 2.1.7. Contract manufacture and analysis

Due to the complexity in the sequence of production processes and testings of drug products it is common praxis to delegate tasks to external providers.

In these cases a written contract has to be effected between the contracting parties, clearly defining the responsibilities of each party.

This topic is treated in chapter 7 “Contract manufacture and analysis” of the EU guidelines, which corresponds to the chapter 7 “Contract production and analysis” of the WHO guidelines.<sup>1</sup>

The requirements of both guidelines are identical, except for the references mentioned below, which can only be found in the EU guidelines:

- that a contract has to be effected in writing;
- that in case of contract analysis the Contract Acceptor should understand that he is subject to inspection by the competent Authorities.

### 2.1.8. Complaints and product recall

According to the EU GMP guidelines chapter 8, all complaints and all information on possible defective products have to be closely surveyed. Based on these activities and information, it should be possible to recall fast and effectively products proven or supposed to be defective. It is required to use a default list and state the respective procedures in writing.

The WHO guidelines describe the necessary procedures in the chapter 5 “Complaints” and 6 “Product recalls”.<sup>1</sup>

There are no decisive differences between the two guidelines on the issue of complaints and product recall.

The EU guidelines describe the requirements regarding the distribution records a little bit in more detail and underline additionally that the person designated as responsible for the co-ordination of recalls should normally be independent of the sales and marketing organisation.

### 2.1.9. Self inspection

The application and adherence to the rules of good manufacturing practice have to be controlled. One possibility to do so is the so-called self-inspection. Defaults detected during these inspections enable that respective corrective measurements can be discussed directly and if necessary agreed upon.

The corresponding references can be found in chapter 9 “Self inspection” of the EU guidelines and in chapter 8 “Self-inspection and quality audits” of the WHO guidelines.<sup>1</sup>

As the title implies, the WHO guidelines give some additional information on the execution of “Suppliers’ audit”. The EU guideline only mentions in chapter 5.26 “Production” that “Starting materials” should only be purchased from approved suppliers ...” and that “It is of benefit that all aspects of the production and control ... are discussed with the manufacturer and the supplier” but give no further assistance how to act.

Furthermore they list in more detail the “Items for self-inspection”.

#### **2.1.10. Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms**

Heating, ventilation and air-conditioning (HVAC) is an important area of technical support for a pharmaceutical production unit. It has to ensure, on the one hand, that the manufacturing process is not negatively affected by any kind of climatic changes; on the other hand, it should provide comfortable working conditions for the operating staff. The prevention of contamination and cross-contamination (e.g. by use of pressure cascades) is an essential design consideration of the HVAC system.

WHO GMP guide is one of the few GMP guidelines worldwide that implemented an own chapter about HVAC systems. Annex 5 (Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms) of the WHO TRS 961<sup>26</sup> is limited to systems for non-sterile production but it delivers information that is valid for systems needed for sterile production too. A similar chapter is missing in the European guideline and only a few documents, beside the WHO text, are dealing with those systems and can deliver suitable information to pharmaceutical companies. Most of them are not free of charge so that companies have to pay for them. One of these text sources is the Handbook of the nonprofit technical organisation American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc. (ASHRAE)<sup>27</sup>. This Handbook is considered the practical repository of knowledge on the various topics that form the field of heating, ventilation, air-conditioning, and refrigeration. Other important publications are the EN<sup>e</sup> ISO<sup>f</sup> 14644 Standards<sup>28</sup> that define Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones. The series is currently composed of the following parts:

- ISO 14644-1: Classification of air cleanliness (currently under revision)
- ISO 14644-2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
- ISO 14644-3: Test methods
- ISO 14644-4: Design, construction, and start-up
- ISO 14644-5: Operations
- ISO 14644-6: Vocabulary
- ISO 14644-7: Separative devices  
(clean air hoods, gloveboxes, isolators and controlled environments)
- ISO 14644-8: Classification of airborne molecular contamination
- ISO 14644-9: Classification of surface particle cleanliness (draft)

<sup>e</sup> EN – European Standard

<sup>f</sup> ISO – International Organization for Standardization

## 2.1. Main principles for pharmaceutical products

The importance of this technical standard is due to the fact that many factors, beside airborne particulate cleanliness, have to be considered in the design, specifications, operations and control of clean rooms and other controlled environments. Part one (ISO 14644-1: Classification of air cleanliness) covers the classification of air cleanliness in clean rooms and associated controlled environments and has therefore a deep impact for the control of pharmaceutical manufacturing areas, particularly for those with sterile production (see: 2c Sterile pharmaceutical production). Clean area standards, such as ISO 14644-1, provide details on how to classify air cleanliness by means of particle concentrations, whereas the WHO GMP standard provide a grading for air cleanliness in terms of the condition (at-rest or operational), the permissible microbial concentrations, as well as other factors, such as gowning requirements. Particularly suitable for the handling of the WHO text is the supporting illustration of room design, air flow and -circulation.

### 2.1.11. Validation

Validation and qualification processes are essential parts of modern good manufacturing practice. Validation is defined as action of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results, whereas qualification is any action of proving that any premises, systems and items of equipment work correctly.

WHO published in their TRS 937 the detailed requirements for validation and qualification processes (Annex 4: Supplementary guidelines on good manufacturing practices: validation)<sup>11</sup>. The document is built up of a general main part and diverse appendices that cover the different areas of validation processes. These are in detail:

- 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 method validation
- Appendix 5. Validation of computerised systems
- Appendix 6. Qualification of systems and equipment
- Appendix 7. Non-sterile process validation

For the territorial validity within the European Union regulations regarding validation and qualification are defined in Annex 15 of the EU GMP guide<sup>30</sup>. Beside overall requirements and definitions (e.g. documentation), the text gives some information about qualification, process validation and cleaning validation. Nevertheless, the document does not cover all the areas of validation and qualification processes and additional documents like ICH (International Conference on Harmonisation) Q2 “Validation of analytical procedures”<sup>31</sup> have to be consulted. Thus, a comparative examination between the two guidelines is not easy and has to be done stepwise, following the different appendices of the WHO text.

#### Main text Annex 4 vs. Annex 15

The WHO guideline introduces the topic validation/calibration in a much more detailed way and provides information about scope of the document, differences between validation/qualification and additional information about calibration/verification. That information is missing in Annex 15 of the EU GMP guide<sup>30</sup>.

Likewise, the WHO document gives a more detailed information about revalidation and requalification cycles as well as requirements to staff that is involved in validation activities. This makes it easier for manufacturers in developing countries to follow the regulations. On the other hand, it has no consequences to the resulting costs of the different validation processes.

The qualification part of both guidelines, dealing with the four different stages of a qualification process – design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) – is similar and shows only little differences but WHO has additionally included an own Appendix 6 (Qualification of systems and equipment) that will be discussed later. For a few paragraphs of the EU Annex 15 (Process validation, cleaning validation, concurrent validation and retrospective validation) comparable sections cannot be found in the main text of the WHO guide, but those are discussed in the different appendices.

#### Appendix 1. Validation of heating, ventilation and air-conditioning systems

HVAC systems play an important role during manufacturing of medicinal products. They have a main function regarding protection of the product, personnel as well as the environment.

Appendix 1 of the WHO directive provides information about expected requirements regarding commissioning of new HVAC systems or parts of those, the whole qualification process, typical HVAC system parameters that should be qualified for a pharmaceutical facility and information about maximum time intervals between tests. Analogue data are missing in the EU GMP guide and only in the EN ISO 14644 series<sup>28</sup> some of that information can be found. For industries using WHO GMP standards this information is very helpful because it is not necessary to study other documents and guidelines in order to find sufficient information for the validation process. Therefore, these additional and detailed data sources are strongly timesaving.

#### Appendix 2. Validation of water systems for pharmaceutical use

Water is the major commodity used by the pharmaceutical industry, and the water system presents one of the most important technical equipment in a pharmaceutical plant. Appendix 2 gives information about the validation of water systems, following a three phase program that is based on the US Food and Drug Administration (FDA) Guide to Inspections of High Purity Water Systems. It is stated that all used water systems for the different water qualities in a pharmaceutical plant – Water for pharmaceutical use (WPU), purified water (PW), highly purified water (HPW) and water for injections (WFI) – can have an impact to the final quality of the product. Therefore, the water systems have to be validated. The qualification should follow the validation convention of design review or DQ, IQ, OQ and PQ. Only information about this general qualification part can be found in the European GMP guideline (Annex 15)<sup>30</sup>. For manufacturers that are planning for WHO prequalification this information is helpful and eases the development of validation plans for water systems.

#### Appendix 3. Cleaning validation

Cleaning validation is the main tool that is used to assure that a cleaning process removes all residues of an active pharmaceutical ingredients of a product manufactured in any equipment with direct contact to the surface. All residues of an active substance have to be removed to predetermined levels to ensure the quality of the next product manufactured is not compromised by traces of APIs from the previous product (cross contamination).

## 2.1. Main principles for pharmaceutical products

Annex 15 of the EU GMP guide<sup>30</sup> gives few general information regarding cleaning validation in paragraph 6 (no. 36-42) and nearly all of this content can be found in the much more detailed Appendix 3 of WHO's Annex 4<sup>11</sup>. Only the allowance that toxic or hazardous substances can be substituted under special conditions for the validation process and the hint that "Test until clean" is not considered an appropriate alternative to cleaning validation are two points that are not covered by the WHO guide. On the other hand, WHO is much more explicit regarding protocols and reports, personnel, equipment, detergents to be used, microbiology, sampling and the establishing of acceptable limits. Again, the more detailed information in the WHO document makes it much easier for companies to fulfill the requirements; this is more a time than a cost saving effect.

### Appendix 4. Analytical method validation

Analytical method validation is the process of demonstrating that analytical procedures employed for specific tests are suitable for their intended use. This is one of the most important and challenging GMP aspects for analytical laboratories both in quality control and research and development. There is no chapter of analytical method validation included in the current EU GMP guideline<sup>30</sup>, but in 1995 the European Medical Agency (EMA) published a Note for guidance on validation of analytical procedures (CPMP/ICH/381/95)<sup>32</sup> which is based on the ICH Q2 document<sup>31</sup> published in 1994. Compared with Appendix 4 of the WHO guide, both documents show a different text structure but have a very similar content. Slight differences can be found in the area of Pharmacopoeial methods (not included in EU guide) and the definition of typical validation characteristics that should be considered during validation of analytical methods. Part II of CPMP (Committee for Proprietary Medicinal Products) document<sup>32</sup> deals with methodology; this part of the document gives more detailed information regarding definition and calculation than the WHO text.

### Appendix 5. Validation of computerised systems

For a few years validation of computer systems has been an upcoming challenge for pharmaceutical manufacturers; the purpose is to prove that a computer system will meet its specification. This definition does not refer to a computer application or a computer system but to a process. The main implication is that the validation should cover the whole process including the application, related hardware, interfaces, users, training, documentation as well as the management of the whole system.

EU GMP guide as well as the WHO GMP guide included a separate chapter about computerised systems (Annex 11)<sup>33</sup> and validation of computerised systems (Appendix 5)<sup>11</sup>, respectively. The general part in both directives is very similar and covers the main aspects of requirements. Annex 11 is more detailed and parts like risk management, personnel, incident management, data exchange, electronic signature or batch release are missing in the WHO text. On the other hand, the main validation part in Appendix 5 of WHO TRS 937 is much more detailed than the European guideline with regards to explicit validation requirements for hardware and software.

However, it should be mentioned, that in Europe the GAMP (Good Automated Manufacturing Practice) guide<sup>34</sup> is in general considered as state of the art in respect to scientific and technical knowledge regarding computerised systems. This guideline is currently probably the best known industry guidance available. Its fifth edition, known as GAMP5<sup>34</sup>, was published by ISPE (International Society for Pharmaceutical Engineering) in 2008.

#### Appendix 6. Qualification of systems and equipment

The qualification process is a necessary step to prove that the used systems and equipment for pharmaceutical production and analytical testing are appropriately designed, located, installed, operated and maintained to suit their intended purpose. Appendix 6 of the WHO guideline<sup>11</sup> picks up the explanation from the main text about qualification and the different qualification steps and elaborates more details. Information regarding DQ, IQ, OQ and PQ are comparable to Annex 15 of the EU GMP guide<sup>30</sup>, whereas the general introduction is much more detailed. Especially the attachment of examples of qualification protocols and reports for the different qualification steps makes the WHO text more informative.

#### Appendix 7. Non-sterile process validation

Pharmaceutical process validation should cover all the critical elements in a manufacturing process for pharmaceutical products and is normally done at the production scale with typically a number of 3 production batches. The aim is to provide documented evidence that a process is capable of reliably and repeatedly rendering a product of the required quality.

Requirements regarding process validation given in EU Annex 15<sup>30</sup> are comparable to the requirements in WHO's Appendix 7<sup>11</sup>, even if those are more detailed in a few paragraphs, e.g. regarding a prospective validation. Additional information for European manufacturers can be found in the EMA/CPMP Note for guidance for process validation<sup>35</sup> published 2001.

In general, the WHO validation guideline is much more detailed than the EU GMP document. It is an advantage for the user of the text that information is concentrated in one document and that some examples of reports and protocols are attached.

### **2.2. Starting materials**

The quality of the starting materials for the production of medicines has an important influence upon the quality of the finished product and is, therefore, a main target of GMP. Similarly to the manufacturing process of pharmaceutical products, the EU GMP guideline as well as the WHO GMP guideline define rules and recommendations for the production process of raw materials and appropriate control by quality units.

Part II of the current EU GMP guideline<sup>36</sup> is named "Basic Requirements for Active Substances used as Starting Materials" and establishes GMP rules for the production of active pharmaceutical ingredients, so called APIs. This part of the EU GMP regulation is directly comparable with Annex 2 "WHO good manufacturing practices for active pharmaceutical ingredients" of the WHO TRS 957 document<sup>37</sup> (44. report of WHO expert committee on specifications for pharmaceutical preparations).

Both documents are very well comparable and from section 3 to the end there are no differences in the text. Slight differences can be found in chapter 1 and chapter 2. WHO included an additional section 1.2 "Regulatory applicability" and defines in section 1.3 "Scope" that the guideline applies to the manufacture of APIs for use in finished pharmaceutical products (FPPs). The EU guideline applies for the manufacture of active substances for medicinal products for both human and veterinary use.

## 2.3. Sterile pharmaceutical products

An additional chapter about quality risk management has been included to section 2 (2.2. Quality Risk Management) of the European text with a link to Part III of the main EU GMP guideline - Quality Risk Management<sup>38</sup> (former planned as Annex 20).

In addition, an older WHO document, published in 2006 under the name “Quality assurance of pharmaceuticals - A compendium of guidelines and related materials”<sup>39</sup>, gives detailed information about the requirements for the production of pharmaceutical excipients. Chapter 2, Part 2 has no direct comparable part in the EU GMP guidelines.

APIs represent normally only a small percentage of a pharmaceutical drug and ordinary 80 % of the formulation consists of excipients. Only a few of these are produced for the pharmaceutical industry. Most of them are needed for production in the food and cosmetic industry and, therefore, the manufacturing practice can be different. In contrast to finished dosage forms and APIs, there are no specific European GMP regulations for pharmaceutical excipients. However, some few information and requirements can be found in the Annex of ISO 9001:2008 (Quality management systems - Requirements)<sup>40</sup>, and in 2001 the International Pharmaceutical Excipients Council (IPEC) and the Pharmaceutical Quality Group (PQG) published a new guideline that proposes GMP appropriate for the manufacture of excipients (“The joint IPEC-PQR Good Manufacturing Practices Guide”)<sup>41</sup>. But in difference to the WHO paper, this guideline has no official character and can be used on an optional basis by manufacturers.

In addition to existing documents, ICH is currently in the implementation process of a new quality guideline Q11 “Development and Manufacture of Drug Substances”<sup>42</sup>. The final draft has been transmitted to EMA/CHMP (The European Medicines Agency, Committee for Medicinal Products for Human Use) in May 2011 and the deadline for comments is set to September 2011. The new text focuses on the developing process, life cycle management, selection of starting and source materials. It will provide information about the transmission of information in the Common Technical Document (CTD) format.

### 2.3. Sterile pharmaceutical products

Manufacturing of sterile pharmaceutical products is one of the most challenging and risky processes in the pharmaceutical industry and, therefore, strict GMP guidelines are defined in the EU regulations as well as in the WHO documents. Annex 1 of the EU GMP guideline<sup>43</sup> (Manufacture of Sterile Medicinal Products) is very similar to Annex 6 (WHO good manufacturing practices for sterile pharmaceutical products) of the WHO TRS 961<sup>44</sup>. Both directives give comparable rules to minimise the risk of a microbial contamination and insufficient sterilisation processes.

With the new guideline published in 2011, WHO adapted its regulations regarding sterile production to the European text and both guidelines are now focusing on standards given in the EN ISO 14644-1 (Classification of air cleanliness)<sup>28</sup>. All former major differences between EU GMP and WHO GMP guidelines (e.g. airborne particulate classification, bioburden tests, media fill, 100% integrity testing) have been adapted and both directives are now nearly identical.

Minor differences between both guidelines can be found with the EU GMP guideline having a higher level of requirements. In most of these cases the postulation of validation processes for different areas

is missing in the WHO document. E.g. a validation of loading patterns is required for all sterilisation processes or the maintenance of laminarity in the grade A areas should be demonstrated and validated (Smoke studies). The missing information in the WHO document does not automatically mean that these validation activities have not to be carried out by the validation team. It depends to a large degree on the different inspectors that are doing the GMP inspections if they expect it to be done.

#### 2.4. Site master file

A Site Master File (SMF) is a document prepared by the manufacturer containing specific and factual GMP information about the quality management policies, about pharmaceutical production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. The purpose of the SMF is to provide an inspector with a detailed introduction to the company and its activities including plans, schemes, organisational chart, etc.

The EU GMP guideline lists the SMF in Chapter 4 “Documentation”<sup>45</sup> as a required GMP document. Since 2010 information about content and structure has been included in the new Part III (GMP related documents) of the EU guideline<sup>46</sup>.

WHO decided at the beginning of 2011 to align the current WHO format with the new PIC/S (Pharmaceutical Inspection Co-operation Scheme) format (Explanatory notes for pharmaceutical manufacturers on the preparation of a site master file; 01.01.2011)<sup>47</sup> and published the new text as Annex 14 of the WHO TRS 961<sup>48</sup>.

A comparison of both texts shows a nearly 100% correlation, only one slight difference can be found in section 4.1 and 8. Listed examples for different markets are changed from “e.g. local, EU, USA” to “e.g. local country or regional economic areas”. This change makes sense and takes into account the different potential target marketplaces for manufacturers in developed and in developing countries. Those minor differences are negligible and have no effect on the workload or the costs.

#### 2.5. Quality risk management

Since few years Quality Risk Management (QRM) has become an important obligatory regulatory requirement towards pharmaceutical manufacturers and other organisations that are working in the health sector. Quality risk management is a systematic process for the assessment, control, communication and review of risks that can influence the quality of the medicinal product. It should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient. It can be applied both proactively and retrospectively.

The European Union adopted the ICH Q9 guideline<sup>49</sup> concerning QRM in 2008 and added it as Annex 20 to Part I of the current EU GMP guide<sup>38</sup>. WHO has not implemented any risk management requirements yet, but initiated a drafting of own WHO guidelines on quality risk management. The initial draft structure was reviewed at the informal consultation on quality assurance systems, medicines and risk

## 2.6. Pharmaceutical quality systems

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analysis held in May 2010 and it was announced in TRS 961<sup>50</sup> that the new guideline will include more detail than other international guidance, e.g. the ICH Q9.

### 2.6. Pharmaceutical quality systems

In June 2008 ICH approved a new guideline about „Pharmaceutical Quality Systems” (Q10)<sup>51</sup> that has been consequently implemented by European Countries, the United States of America and Japan. The EU published the note for guidance of pharmaceutical quality systems under Part III (GMP related documents) of the current EU GMP guide<sup>52</sup>.

The document describes a model for an effective quality management system for the pharmaceutical industry. It is based on the quality concept of the ISO. It includes GMP and completes the two ICH guidelines Q8 (Pharmaceutical Development)<sup>53</sup> and Q9 (Quality Risk Management)<sup>49</sup>. ICH Q10 is not intended to raise new standards that are overlapping existing and valid regulatory requirements. Therefore, the content of ICH Q10 that is additional to the scope of GMP is optional. Its use should facilitate innovation, continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

Up to now, WHO has not published any notification about an implementation of ICH Q10 in the WHO GMP guideline.

## 3. Identification of most cost-intensive requirements

In the year 2001 the World Health Organisation (WHO) started its Prequalification Program to support access to medicines that meet uniform quality, safety and efficacy standards. With support by UNAIDS (The Joint United Nations Programme on HIV/AIDS), UNICEF (United Nations International Children's Emergency Fund), UNFPA (United Nations Population Fund) and the World Bank, as well as in close cooperation with national regulatory agencies, this program was launched with the objective of making medicines, produced under GMP aspects, available all over the world. WHO evaluation and inspection activities, as well as a concerted development of national capacity for sustainable drug manufacturing and monitoring, have been building the basis for the achievement of this objective. The program is focusing on medicinal products used to treat HIV/AIDS, malaria, tuberculosis, influenza and for reproductive health.



The intention was to verify the “Cost of Quality” (CoQ) by means of literature research and interview of respective pharmaceutical associations. In the literature, indeed, it is mentioned by Thomas<sup>54</sup> that CoQ is defined in four categories, two “conformance” and two “non-conformance”.

### 3.1. Survey with African pharmaceutical companies

Conformance costs include: 1- Preventive Activities which are costs incurred from activities designed to prevent poor quality. 2- Appraisal Costs which are costs of measuring, evaluating, auditing, and so on. “Non-conformance” costs include: 1- Internal Failure Costs which result from products not conforming prior to shipment. 2- External Failure Costs which result from products not conforming post-shipment. However, CoQ is usually understood as the sum of conformance and non-conformance costs. According to Dale and Plunkett<sup>55</sup>, it is now widely accepted that quality costs are the costs incurred in the design, implementation, operation and maintenance of a quality management system.

Another cost factor indication can be found in the “International Benchmarking Study: Operational Excellence in the Pharmaceutical Industry, Industry Report”<sup>56</sup>. The CoQ varies from 16 – 2 % of total costs depending on whether the pharmaceutical company is a so-called “Low or High performer”. A “Low performer” is a company which guarantees the quality of its products as a result of its high inspection activity/costs. A “High performer” has a total quality management (TQM) established, the quality “is built into the system”.

To identify the most difficult and most expensive GMP requirements for companies, interviews were conducted with African companies and questionnaires analysed.

### 3.1. Survey with African pharmaceutical companies

Up to now only 9 companies in 4 African countries attained WHO prequalification for one or more of their products. In total, 21 different medicines produced by African manufacturers have been registered and qualified by the WHO. Beside South Africa (5 companies with 14 products) and Morocco (1 company with 3 formulations) only two companies in Sub-Saharan Africa took this hurdle (see Table 1). Quality Chemical Industries Ltd. in Kampala/Uganda reached WHO prequalification in 2010 for a triple HIV combination and a malaria medication. Varichem Pharmaceuticals Ltd. located in Harare, Zimbabwe, prequalified a triple and a double HIV formulation in 2010. Kenya’s Universal Corporation Ltd. managed the WHO inspection in June 2011 successfully and received the prequalification certificate for one HIV combinational product in October 2011. Currently, there is no pharmaceutical company prequalified by WHO in whole West Africa.

Table 1: WHO prequalification achieved by African companies.

Country	Companies	Products		
		HIV	Malaria	Tuberculosis
Morocco	1	--	3	--
South Africa	14	11	--	3
Uganda	1	1	1	--
Zimbabwe	1	2	--	--
Kenya	1*	1	--	--

\* Universal Corporation has successfully managed the WHO inspection

To obtain direct input from local pharmaceutical companies about the challenges and obstacles of the prequalification process as well as cost drivers and time-consuming parts, visits and interviews of some of the involved manufacturers in Sub-Saharan Africa were carried out as a part of this study.

### 3.1.1. Methodology

Dr. Feldmann undertook three journeys between September and October 2011 and visited 9 production sites in 7 East and West African countries. The intention was to meet responsible representatives from upper management, quality departments or those who are directly involved into the WHO prequalification process of each company. The interviews were done with the help of a questionnaire (Appendix 2) developed to obtain comparable and evaluable results.

Table 2: Companies participating in the survey

Company	Country	Town	Date of visit	Status
Tanzania Pharmaceutical Industries – Anti Retro Viral (TPI-ARV)	Tanzania	Arusha	02.09.2011	WHO PQ in preparation
Kampala Pharmaceutical Industries Ltd. (KPI)	Uganda	Kampala	05.09.2011	Not started
Quality Chemical Industries Ltd (QCI)	Uganda	Kampala	05.09.2011	PQ achieved in 2010
Biodeal Labs Ltd.	Kenya	Nairobi	06.09.2011	Not started
Universal Corporation Ltd.	Kenya	Nairobi	07.09.2011	PQ achieved in 2011
Varichem Pharmaceuticals Ltd.	Zimbabwe	Harare	09.09.2011	PQ achieved in 2010
La Gray Chemical Company	Ghana	Nsawam	03.10.2011	Planned for Q1 2012
Cinpharma	Cameroon	Douala	05.10.2011	Planned for Q4 2012

The focus was on companies that already had achieved WHO prequalification or those that are currently in the process. The main goal was to obtain sufficient information about cost drivers, challenges and problems of the whole qualification activity. Furthermore, interviews were done with a few other companies that have not started WHO prequalification yet, to find out the major reasons for obstacles, barriers and impact factors that block, stop or slow down the prequalification start.

### 3.1.2. Findings

#### Products

Medicine to treat HIV, malaria, and tuberculosis infections is still not available in sufficient quantities in all parts of the African continent. Large quantities of these drugs are purchased and delivered to Africa by international donor organisations, e.g. The Global Fund. These donor organisations invite

### 3.1. Survey with African pharmaceutical companies

manufacturers of needed medicines worldwide to submit an expression of interest. To participate in those open tenders, a WHO prequalification of the corresponding formulation is normally the indispensable precondition for all manufacturers. Therefore, these three categories of products are in the focus of African pharmaceutical companies regarding the achievement of WHO prequalification. The following medicinal products of East African manufacturers have been prequalified by WHO in 2010 and 2011 (see table 3).

Table 3: WHO prequalified products of East African companies.

	Product 1	Product 2
<b>Quality Chemical Industries Ltd. (QCI)</b>	Lamivudine/Nevirapine/Zidovudine 150/200/300	Artemether/ Lumefrantrine 20/120
<b>Varichem Pharmaceuticals Ltd.</b>	Lamivudine/Nevirapine/Stavudine 150/200/30	Lamivudin/Zidovudine 150/300
<b>Universal Corporation Ltd.</b>	Lamivudin/Zidovudin 150/300	--

All of these companies are currently in the preparation to qualify more products within the next year; among those are special pediatric formulations that are strongly needed to treat children in a sufficient way. Other companies like TPI-ARV, La Gray Chemicals or Cinpharm have built up new pharmaceutical manufacturing plants and are still in the preparation to start the prequalification process. It can be expected, that within the next two years up to 5 additional West and East African companies will achieve the WHO certificate and that 5 to 10 additional prequalified African products will come into the market.

#### Prequalification process

##### *Time frame*

The time frame for such prequalification projects highly depends on the condition of the manufacturing facility and equipment as well as on the status of the quality systems. Most of the companies, that decided to go through the whole prequalification process, built up new production plants and bought new equipment. From the first planning phase to the successful inspection, all companies needed approximately a period of 5 to 7 years. On the other hand, a company that already has everything in place and has achieved WHO prequalification for one product, can reach prequalification of further formulations within one year. Time limiting factors are here development of the formulation, stability investigations and bioequivalence studies.

##### *Financial aspects*

The financial situation and the upcoming costs that are associated with an upgrade of a manufacturing plant are difficult to manage by local pharmaceutical manufacturers. Strategic co-operations are often essential to reach an international standard. Nearly all African companies, that were prequalified by WHO or those that are in the middle of the process, have formed a co-operation either with a big global acting pharmaceutical company (e.g. Cipla, Cadila) or with an international financial investor (eg. Finnfund). Co-operation with a pharmaceutical global player has the advantage of both financial support and technical knowledge transfer. Document structures and standards already applied can be used and adjusted, respectively, experts can be sent as consultants and raw materials can be delivered by a central purchasing system with associated economies of scale. The national governments also support

the development of an own pharmaceutical industry on an international quality level. Public support for the buildup of a new production plant is indirectly given by some governments. Tax exemption, facilitation of import or preference in national tenders are examples for those subsidies.

Total costs for the buildup of a new manufacturing facility, including sufficient manufacturing and testing equipment, are high and should be calculated with more than 5 Mio. USD. The needed investment depends on the size and product range of the company. Production of solid dosage forms (tablets, capsules), liquids (sirups, suspensions) or sterile formulations (i.v. therapies, eye drops) has completely different requirements in regard to manufacturing equipments, layout of the facility and specific standards regarding the HVAC system. Manufacturing of beta-lactam antibiotics e.g. requires a dedicated manufacturing facility and own dedicated production equipment.

Asked for the expected investment for a single WHO prequalification process of one new product, the companies calculate between 250.000 and 2.000.000 USD. Beside the costs for the formulation development itself, required stability and bioequivalence studies are seen as the main cost drivers.

#### *Human resources*

Sufficient, well educated and motivated personal is one of the key factors of a successful prequalification process and, furthermore, for the sustainable production of high-quality medicines. Nearly all interviewed companies employed new staff for the preparation of the WHO inspection. Especially the production and quality departments depend on highly skilled pharmaceutical personal (pharmaceutical assistants and technicians as well as pharmacists). The ratio between the total number of employees and the number of employees working in the quality department of a pharmaceutical company is a good indicator for capacity building and personnel ramp-up initiated by the prequalification process. Companies, that have achieved prequalification or are currently in the preparation phase, have usually a significant higher ratio than companies that have not started any activities yet (see table 4).

Table 4: Ratio of employed staff members working in quality departments

	QCI	Varichem	Universal	TPI-ARV	La Gray	Cinpharm	Cadila	KPI	Biodeal
WHO Pre-qualification	2010	2010	2011	in preparation	planned Q1 2012	planned Q4 2012	not planned	not planned	not planned
Total number of employees	170	150	300	20	100	200	215	250	230
Employees in quality departments	24	35	47	5	13	30	31	14	13
Ratio	14 %	23 %	16 %	25 %	13 %	15 %	14 %	6 %	6 %

Unfortunately this demand for human resources marks one of the biggest problems the companies are faced with. Two major facts are responsible for the lack of qualified personnel. On the one hand, the number of students graduating each year from the pharmaceutical education institutions is too small. On the other hand, jobs in the local pharmaceutical industry are not attractive enough. Salaries are seen as too low with regard to the time consuming and intensive workload. Compared with jobs in governmental institutions or in the public health sector (private pharmacies, hospitals etc.) they are

### 3.1. Survey with African pharmaceutical companies

unattractive for young professionals. For one company the current situation regarding human resources is very serious and the lack of pharmaceutical professionals can slow down or even block the whole prequalification process.

Beside the employment of new permanent staff, all companies contracted external consultants or got professional support by their co-operation partner (Cipla, Cadila). Especially for the layout and design of new facilities and/or media systems (HVAC, water) as well as for different validation and qualification processes (cleaning validation, process validation etc.) external help was obtained.

#### Premises

The main reason for African pharmaceutical companies not to start any prequalification activities is the lack of a sufficient manufacturing facility that complies to the requirements of the WHO GMP guideline. Refurbishment of old, existing structures is often not possible or unprofitable. From the visited companies, only Universal Corporation Ltd. in Kenya refurbished parts of their production site and upgraded one manufacturing line successfully. All other companies planned from the beginning to build up new plants. Critical points in existing manufacturing sites are inadequate room concepts (quality by design), insufficient HVAC systems, overaged water systems, and a lack of quality control capacities.

#### Quality systems

The field of documentation was often named as a time and cost intensive area of improvement. Regarding expected quality systems in place, WHO requirements are nowadays very similar to GMP guidelines in Europe and the US. Therefore, all companies had to implement missing systems and to upgrade their quality documents like batch records, manufacturing and testing instructions. Preparation of documents is a time consuming act but can be managed without greater difficulties. The challenge is to implement new systems in all areas of the manufacturing process and to train the whole workforce from management level down to the manufacturing lines. Acceptance of these new processes is essential. The problems companies noted during the implementation process were often linked to the shortage of sufficiently qualified pharmaceutical team members.

#### **3.1.3. Challenges, problems and obstacles of the prequalification process**

Two factors were named by all interviewed companies as most important challenges for the prequalification process:

- the financial investment for refurbishment or new constructions, and
- the lack of well trained and educated staff.

Other problems arising during the preparation phase were identified and referred to as follows:

Companies and especially the employees are suddenly faced with numerous new regulations, procedures, systems and documents based on an upgraded quality environment. Rising workload and problems during implementation of those new quality systems (e.g. deviations) deserve a fundamental mind change and are challenges for each manufacturer. This increase of work and documentation

within the quality and production departments is unavoidable in order to successfully fulfill the GMP requirements.

Interviewed pharmaceutical manufacturers moan a lack of information and the missing of a good and functional linkage to a proper information pool. This includes data and links to e.g. qualified raw material suppliers, consultants or companies that could support the process, or advanced training focusing to the prequalification (WHO training).

Validation and qualification activities are time and cost intensive but also need a sufficient level of knowledge and training. Companies that start validation processes are often feeling overstrained. Intensive external and internal training and/or the support of external consultants would be required and ease the implementation processes.

#### **3.1.4. Benefit of the prequalification certificate for the companies**

It is self-explanatory and comprehensible that pharmaceutical manufacturers that invest high amounts of money and that undergo a financial risk (that should not be underestimated) are looking for countable benefits as a result of the WHO certification. The chance to open new markets and to have the possibility to participate in open tenders of donors (e.g. The Global Fund), are undoubtedly the main drivers for African pharmaceutical companies to undergo the prequalification process. Beside this, other factors like a better advertisement of the own brand, a higher national and international reputation and upcoming new co-operations are definitely seen as required profits. But also more internal benefits have a deep positive impact to certified manufacturers. Confidence in the own products and the knowledge that a robust quality system is in place are positive factors that motivate staff members. Furthermore, companies report that the achieved higher quality standard reduces the number of rejected lots and the value of scrap.

Unfortunately, not only positive effects are caused by those deep changes in the manufacturers production and quality process. It is indeed a positive fact that by the change in all quality systems and higher testing schemes for incoming goods, the overall quality of the product portfolio, not only for those drugs that are prequalified, can be increased. But on the other hand, the costs of all products increases too and companies are suddenly struggling to compete on the local market with competitors that have not started an upgrade of their quality program yet.

#### **3.1.5. Summary of the survey of African pharmaceutical companies**

WHO guidelines have rapidly changed in the last few years. Within a short timeframe nearly all WHO requirements have been adopted to international standards that identically are implemented in North America, Japan and Europe. While the WHO GMP handbook, published in 2006, provided GMP regulations on a slightly reduced level, the changes that were made with the WHO TRS 957 (2010) and 961 (2011) increased the WHO requirements substantially. Pharmaceutical manufacturers that prepare for a WHO prequalification have now to fulfill similar changes and adoptions as companies in Europe that prepare for local EU GMP inspections.

### 3.2. Survey of German medium-sized pharmaceutical companies

Main problems of WHO prequalification for African pharmaceutical companies are hidden in the paragraphs 9 (Personnel) and 12 (Premises) of the WHO good manufacturing practices for pharmaceutical products: main principles (TRS 961). An adequate pharmaceutical production site has to fulfill several requirements and it is difficult to upgrade existing pharmaceutical plants to this level. Therefore most of the companies that decided to go for the prequalification invested high amounts of money to build new facilities that were directly planned under quality aspects (quality by design). The financial situation does not allow most of the local manufacturers to invest millions of dollars, therefore they have only two options: finding a financially strong co-operation partner or to renounce the WHO prequalification. Furthermore, the actual prequalification of a formulation needs additional investment that is caused by high costs for the pharmaceutical development, stability tests and bioequivalence studies.

The other big obstacle is human resources. A quality upgrade of a company requires sufficient and well qualified pharmaceutical personnel. This includes pharmacists, pharmaceutical assistants, pharmaceutical technicians and technical staff from cognate disciplines, that is well GMP trained. Finding staff is a time consuming and expensive process. A not well-balanced ratio of workload and payment makes jobs in the pharmaceutical industry not attractive. In addition, the output of universities and pharmaceutical schools do not fill all existing gaps in the African health sector. Competition for available candidates is high. Beside a basic pharmaceutical education, advanced ongoing training for the whole pharmaceutical staff in a production unit is required and states an additional requirement of GMP guidelines. Offers for such trainings are rare and travelling for participating is normally necessary which is associated with higher costs and the absence of respective team members from the production area.

The lack of good and effective communication channels and information platforms is another factor that has an impact to companies that are preparing for WHO prequalification. Valid information is essential in any case, especially if support or help is needed. Also, the contact to WHO officials or access to WHO support were seen as fields of improvement by the local manufacturers.

### 3.2. Survey of German medium-sized pharmaceutical companies

In addition to the interrogation of African companies, medium-sized enterprises in Germany were requested to fill out questionnaires.

#### 3.2.1. Methodology and findings

A questionnaire (see Appendix 3) was developed and addressed to the medium-sized pharmaceutical companies and analysed the responses respectively.

A total of 10 questionnaires were analysed (for summary: see Appendix 4). The size of the interviewed companies varied with regard to the turnover from a about 260 million EUR to almost 1 million EUR and regarding the number of employees between 2000 and 12. The total production range of pharmaceutical products was represented starting from solid forms, oral liquids and semi-solid forms to sterile products.

To give an insight into the quality related costs, the number of employees working in quality control or quality assurance were related to, on the one hand, the total number of employees and, on the other hand, to the employees from production department. Regrettably, not every questionnaire conveyed the relevant information. Regrettably also the request posed to the BAH e.V.<sup>§</sup> as well as the BPI e.V.<sup>h</sup> were not enlightening.

In relation to the total number of employees, approx. 8 % of the personnel works in quality control or quality assurance. In special cases, for example with regard to the production of small lots of injectables or in case of contract manufacturing, the percentage can rise to 20 % and more.

Comparing the number of employees in quality control / quality assurance to the number of employees in production, it can be said that one employee in quality control department faces three in production. This value is in special cases also subject to fluctuations.

Beside the relationship of the respective employees to each other, we tried to detect the relationship of the quality related costs to the turnover. Unfortunately only few informative data were given by the asked companies. The indications vary between 1 % of turnover strictly referring to the Quality Assurance to 20 % in case of the company producing smallest lots of injectables.

The most difficult and most expensive implementation of requirement was to meet the requirements in production of sterile products (for those companies offering this feature), thus posing special requirements to the air-conditioning technology and the necessary change rates of air ventilation and the respective qualification and validation tasks.

Furthermore, it was difficult to realize the implementation of computing validation as well as the zone concept and the adherent building restructuring.

Additionally, the implementation of product quality reviews (PQRs) as well as auditing of suppliers and contract manufacturers were mentioned.

In realisation of these requirements, external support – especially technical support – was made use of. Consultants were engaged or maintenance and calibration tasks as well as qualification measures were outsourced.

With regard to smaller companies, even the necessary key personnel (Head of Quality Control, QP) was externally solved.

An additional aim was to make use of this questionnaire to find prospective companies interested in co-operation with the GIZ. A joint venture is of interest for:

- Argon Pharma GmbH,
- Engelhard Arzneimittel GmbH & Co. KG,
- Haupt Pharma AG,
- Kneipp-Werke GmbH Co. KG.

<sup>§</sup> Bundesverband der Arzneimittel-Hersteller (German Federal Association of Pharmaceutical Product Manufacturers)

<sup>h</sup> Bundesverband der Pharmazeutischen Industrie (German Federal Association of the Pharmaceutical Industry)

### 3.2. Survey of German medium-sized pharmaceutical companies

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#### 3.2.2. Summary of the survey of German pharmaceutical companies

The quality related costs in Germany, necessary to uphold the GMP status, vary dependent on the company size and respective structure as well as the product range from 2 – 16 % of the turnover. This indication matches the literature indications.

A pharmaceutical company in a developing country striving for GMP status should also calculate with costs in the same relation. Due to the purchase of e.g. measuring and test or control equipment in foreign countries the quality related costs will certainly rise distinctively.

Even higher investments have to be calculated for companies working on the implementation of a quality management system.

For cost and time reasons external support is paid for in Germany to meet with the several GMP requirements (e.g. validation and maintenance tasks). It goes without saying that the developing countries will also face these costs.



## 4. Harmonisation of GMP guidelines

Finally, an object of this study was to analyse if WWW harmonisation between EU GMP and WHO GMP guidelines as well as PIC/S GMP guidelines could be achieved.

Working with the different guidelines during this study showed their harmonisation to 90%. Great differences with regard to the requirements addressed to the pharmaceutical companies could not be detected.

Amendment/enhancement applications with regard to the EU GMP guideline or the PIC/S GMP guideline have to be addressed to national authorities (BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte, Federal Institute for Drugs and Medical Devices, and BMG, Bundesministerium für Gesundheit, German Federal Ministry of Health).

The “WHO Expert Committee on Specifications for Pharmaceutical Preparations” is the responsible committee for developing or discussing quality documents. Questions regarding the requirements for pharmaceutical products can be posed to the department “Quality Assurance and Safety: Medicines”.

To achieve a change of the EU GMP will be difficult due to the fact that this guideline is harmonised all over Europe. Every nation has its special interests and every amendment has to be discussed in every national administration.

Formally it seems to be easier to address a change request to the WHO office. But the same goes for this case – the request has to be very good and logically justified. Moreover and provided that everything works out well, it will take a really long time and a lot of manpower to achieve a change.

Over all, looking from the point of view of the authors and considering a medium-term time frame, it makes much more sense to assist in supporting measures rather than to try to change the guidelines.

## 5. Summary and recommendations

When comparing WHO and European GMP requirements, it can be stated that both guidelines have been quite clearly aligned in the last few years. All reviewed chapters are basing on international standards like PIC/S or ICH guidelines. In order to require a WHO certificate a manufacturer in Africa has to implement nowadays very similar quality standards as companies in Europe, America or Asia for achieving GMP compliance. Some recommendations for improvements focusing on described obstacles during the prequalification process are given below. These recommendations result from visits and meetings with African pharmaceutical manufacturers and should be discussed and addressed in order to support companies on their way to WHO prequalification.



### Local WHO offices

All companies that achieved WHO prequalification in the previous years had close contact to the WHO before and benefit by offered training and conducted pre-audits. Regional WHO center or offices (e.g. responsible for and located in East Africa) would strengthen and simplify close cooperation between pharmaceutical companies and the WHO as certifying authority. The first contact would be much easier and WHO officials could be integrated into the planning and development process from the first moment. Furthermore, costs for training, workshops and mock audits could be reduced and fast support in case of arising problems could be assured.

### Biowaivers

In the WHO Prequalification of Medicines Programme, biowaivers based on the Bio-pharmaceutics Classification System (BCS) are intended to be one alternative method to investigate bioequivalence<sup>57</sup>. They do not apply to other bioavailability or pharmacokinetic studies. The concept underlying the BCS finally leads to introducing the possibility of waiving *in vivo* bioequivalence studies in favor of specific comparative *in vitro* testing in order to conclude bioequivalence of oral immediate release products with systemic actions. This approach is meant to reduce unnecessary *in vivo* bioequivalence studies. However, it is restricted to non-critical drug substances in terms of solubility, permeability, and therapeutic range, and to non-critical pharmaceutical forms.<sup>58</sup>

## 5. Summary and recommendations

Overall, BCS-based biowaivers are intended only to address the question of bioequivalence between a test and a reference product. WHO identified two groups of APIs to be eligible for BCS-based biowaiver applications: Antiretroviral Medicines (lamivudine, stavudine and zidovudine) as well as anti-tuberculosis medicines (ethambutol, isoniazid, levofloxacin, ofloxacin and pyrazinamide)<sup>57</sup>.

Pharmaceutical manufacturers in East Africa that have already worked on biowavers, postulate a revision of the WHO guideline and an adaption to the European regulations. A more pragmatic approach based on the BCS classification and dissolution speed (rapidly/very rapidly dissolving where applicable) should be encouraged without the limitation to certain drugs within the groups. Companies would like to gain more responsibility to justify eligibility of drugs containing APIs of BCS group I or III for biowaiver to increase the local drug portfolio with simultaneous reduction of development costs.

### Exchange forum

Getting sufficient information, input or templates for upcoming requirements (e.g. cleaning validation) is a big challenge for local manufacturers. Extensive search in the internet or in pharmaceutical literature is a time and cost intensive matter. Also getting contact to professional consultants that are able to initiate and accompany different areas of prequalification preparations and projects is very difficult. Therefore, the implementation and expansion of a pan-African internet platform (currently under preparation by GIZ<sup>i</sup>) should be intensified. Especially a database that can be used as “knowledge pool” and additionally an exchange forum to share experience from inspections or to get quick answer in case of problems, are missing. Links to international consultants for the different pharmaceutical areas of expertise should be easily available as well as contact data of different centers of excellence (e.g. universities, training centers, etc.).

### Activity check list

Companies aiming at a WHO and prequalification could be assisted by receiving a check list stating and interpreting the requirements to reach GMP standards. Thus the companies could, on the one hand, easier evaluate the necessary effort to be effected to pass successfully a GMP inspection and, on the other hand, to co-ordinate external training measurements.

### Provision of SOP's/forms

The work with Ethiopian companies conveyed the impression that the requirements of the GMP guidelines are already well-known but the implementation poses great difficulties. Even if the respective forms are available, e.g. by the WHO via internet, complex measurements are difficult to be realised.

Presenting SOPs with detailed information on the execution of the necessary activities using and creating the presented/necessary forms could be of help.

### Process validation

The implementation of process validation for already existing products poses often great problems due to the necessary planning and co-ordination tasks. Therefore, retrospective process validation could be a means of interest. The respective batch manufacturing records (BMRs) have to be assorted and revised if applicable to ensure that all critical process parameters are measured and documented.

<sup>i</sup> GIZ – Gesellschaft für Internationale Zusammenarbeit GmbH (German Organisation for International Cooperation)

# References

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- <sup>2</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles, Page 103**
- <sup>3</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Thirty-second report, (WHO Technical Report Series 823), Annex 1: Good manufacturing practices for pharmaceutical Products, 18. Good pharmaceutical practice for active pharmaceutical ingredients (bulk drug substances), Page 73 and 75**
- <sup>4</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Thirty-second report, (WHO Technical Report Series 823), Annex 1: Good manufacturing practices for pharmaceutical Products, 18. Good pharmaceutical practice for active pharmaceutical ingredients (bulk drug substances), Page 74**
- <sup>5</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 7: WHO guidelines on transfer of technology in pharmaceutical manufacturing, Page 300**
- <sup>6</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Thirty-second report, (WHO Technical Report Series 823), Annex 1: Good manufacturing practices for pharmaceutical Products, 18. Good pharmaceutical practice for active pharmaceutical ingredients (bulk drug substances), Page 74**
- <sup>7</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fourth report, (WHO Technical Report Series 957), Annex 1: WHO good practices for pharmaceutical quality control laboratories, Page 106**
- <sup>8</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fourth report, (WHO Technical Report Series 957), Annex 2: WHO good manufacturing practices for active pharmaceutical ingredients, Page 144**
- <sup>9</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles, Page 140**
- <sup>10</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Thirty-fifth report, (WHO Technical Report Series 885), Annex 5: Pharmaceutical excipients, Page 61-62**
- <sup>11</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Fortieth report, (WHO Technical Report Series 937), Annex 4: Validation, Page 107-178**
- <sup>12</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Fortieth report, (WHO Technical Report Series 937), Annex 4: Validation, Page 117**
- <sup>13</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Fortieth report, (WHO Technical Report Series 937), Annex 4: Validation, Page 113**

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- <sup>14</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 2: WHO good practices for pharmaceutical microbiology laboratories, Page 69-93**
- <sup>15</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles, Page 123**
- <sup>16</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles, Page 129-138**
- <sup>17</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fourth report, (WHO Technical Report Series 957), Annex 2: WHO good manufacturing practices for active pharmaceutical ingredients, Page 149-150**
- <sup>18</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 4: WHO guidelines on good manufacturing practices for blood establishments**
- <sup>19</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fourth report, (WHO Technical Report Series 957), Annex 2: WHO good manufacturing practices for active pharmaceutical ingredients, Page 152**
- <sup>20</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles, Page 135-138**
- <sup>21</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles, Page 128**
- <sup>22</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles, Page 128-129**
- <sup>23</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 6: WHO good manufacturing practices for sterile pharmaceutical products, Page 279**
- <sup>24</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fourth report, (WHO Technical Report Series 957), Annex 2: WHO good manufacturing practices for active pharmaceutical ingredients, Page 161-162**
- <sup>25</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Thirty-fifth report, (WHO Technical Report Series 885), Annex 5: Pharmaceutical excipients, Page 69-70**
- <sup>26</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Annex 5: Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms, Page 215-216**
- <sup>27</sup> **American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc. (ASHRAE), The 2011 ASHRAE Handbook – HVAC Applications, ASHRAE, 1791 Tullie Circle, Atlanta, GA 30329**
- <sup>28</sup> **International Organization for Standardization (ISO), ISO 14644 Series - Cleanrooms and associated controlled environments, Part 1-9**

- <sup>29</sup> **European Union – Eudralex Volume 4 - Good manufacturing practice (GMP) Guidelines**
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- <sup>31</sup> **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)**, Harmonised Tripartite Guideline Q2(R1): Validation of analytical procedures: Text and methodology
- <sup>32</sup> **European Medicines Agency (EMA)**, Note for guidance on validation of analytical procedures: Text and methodology (CPMP/381/95)
- <sup>33</sup> **European Union – Eudralex Volume 4 - Good manufacturing practice (GMP) Guidelines**, Annex 11: Computerized Systems
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- <sup>37</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fourth report, (WHO Technical Report Series 957)**, Annex 2: WHO good manufacturing practices for active pharmaceutical ingredients
- <sup>38</sup> **European Union – Eudralex Volume 4 - Good manufacturing practice (GMP) Guidelines**, Part III – GMP related documents – Q9 Quality Risk Management
- <sup>39</sup> **WHO - Quality assurance of pharmaceuticals - A compendium of guidelines and related materials**, Volume 2, 2nd updated edition, Good manufacturing practices and inspection
- <sup>40</sup> **International Organization for Standardization (ISO)**, ISO 9001:2008 - Quality management systems - Requirements
- <sup>41</sup> **International Pharmaceutical Excipients Council Europe (IPEC Europe) / Pharmaceutical Quality Group (PQG)**, The joint IPEC-PQR Good Manufacturing Practices Guide, 2006
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- <sup>50</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Forty-fifth report, (WHO Technical Report Series 961), Paragraph 8 – Quality Assurance-new approaches, Page 35**
- <sup>51</sup> **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Harmonised Tripartite Guideline Q10: Pharmaceutical Quality Systems**
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- <sup>53</sup> **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Harmonised Tripartite Guideline Q8: Pharmaceutical Development**
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- <sup>55</sup> **Dale, B.G. and Plunkett, J.J. (1995), Quality Costing, 2nd Edition, Chapman and Hall, London.** Retrieved on 1<sup>st</sup> February 2012 from <http://books.google.com/books>
- <sup>56</sup> **University of St. Gallen, Institute of Technology Management; The International Association for Pharmaceutical Technology (APV); International Benchmarking Study: Operational Excellence in the Pharmaceutical Industry; Industry Report (2004).** Retrieved on 1<sup>st</sup> February 2012 from [http://www.nipte.org/docs/Operational%20Excellence Industry%20Report.pdf](http://www.nipte.org/docs/Operational%20Excellence%20Industry%20Report.pdf)
- <sup>57</sup> **WHO Expert Committee on specifications for pharmaceutical preparations, Fortieth report, (WHO Technical Report Series 937), Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish inter-changeability, Page 347-390**
- <sup>58</sup> **WHO Prequalification of Medicines Programme, General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications, Guidance Document, 2009**

# Appendix

## Appendix 1. Comparison of the respective chapters EU guideline - WHO guideline, overview

	Topic	EU GMP Guide	WHO GMP Guide	Additional Documentation
2.1.1.	Quality Management	Part I, Chapter 1	<b>TRS 961, Annex 3, Chapter 1</b> <b>TRS 961, Annex 3, Chapter 2</b> <b>TRS 961, Annex 3, Chapter 17, Point 17.1, 17.3</b> TRS 961, Annex 3, Page 103	
2.1.2.	Personnel	Part I, Chapter 2	<b>TRS 961, Annex 3, Chapter 9</b> <b>TRS 961, Annex 3, Chapter 10</b> <b>TRS 961, Annex 3, Chapter 11</b> <b>TRS 961, Annex 3, Chapter 3</b>	TRS 823, Annex 1, Chapter 18, Point 18.10, 18.22 German drug law, § 15 "Experience"
2.1.3.	Premise and Equipment	Part I, Chapter 3	<b>TRS 961, Annex 3, Chapter 12</b> <b>TRS 961, Annex 3, Chapter 13</b> TRS 961, Annex 3, Chapter 9, Point 9.5 TRS 961, Annex 3, Chapter 16, Point 16.9, 16.23, 16.24	TRS 823, Annex 1, Chapter 18, Point 18.14, 18.15, 18.17 TRS 961, Annex 7, Chapter 5, Point 5.20 TRS 957, Annex 1, Chapter 12, Point 12.5 TRS 957, Annex 2, Chapter 5, Point 5.30
2.1.4.	Documentation	Part I, Chapter 4	<b>TRS 961, Annex 3, Chapter 15</b> TRS 961, Annex 3, Glossary, Point "Specification"	TRS 885, Annex 5, Chapter 6, Point 6.3
2.1.5.	Production	Part I, Chapter 5	<b>TRS 961, Annex 3, Chapter 14</b> <b>TRS 961, Annex 3, Chapter 16</b> <b>TRS 961, Annex 3, Chapter 3</b> TRS 961, Annex 3, Chapter 15, Point 15.10 TRS 961, Annex 3, Chapter 4, Point 4.4, 4.8	TRS 937, Annex 4, Chapter 11, Point 11.17 TRS 937, Annex 4, Chapter 3, Point 3.1
2.1.6.	Quality Control	Part I, Chapter 6	<b>TRS 961, Annex 3, Chapter 17</b> TRS 961, Annex 4, Chapter 2, Point 2.2 TRS 957, Annex 2, Chapter 7, Point 7.33 TRS 961, Annex 3, Chapter 14, Point 14.34, 14.35, 14.39, 14.42 TRS 961, Annex 6, Chapter 10, Point 10.3 TRS 961, Annex 3, Chapter 9, Point 9.12	TRS 961, Annex 2 TRS 961, Annex 3, Chapter 12, Point 12.33 – 12.36 TRS 961, Annex 3, Chapter 15, Point 15.37, 15.43, 15.31 – 15.48 TRS 957, Annex 2, Chapter 6, Point 6.6 TRS 957, Annex 2, Chapter 11, Point 11.5 TRS 885, Annex 5, Chapter 7, Point 7.3.5

	Topic	EU GMP Guide	WHO GMP Guide	Additional Documentation
2.1.7.	<b>Contract Manufacture and Analysis</b>	Part I, Chapter 7	TRS 961, Annex 3, Chapter 7	
2.1.8.	<b>Complaints and Product Recall</b>	Part I, Chapter 8	TRS 961, Annex 3, Chapter 5 TRS 961, Annex 3, Chapter 6 TRS 961, Annex 3, Chapter 14, Point 14.32	
2.1.9.	<b>Self Inspection</b>	Part I, Chapter 9	TRS 961, Annex 3, Chapter 8	
2.1.10.	<b>Heating ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms</b>	--	TRS 961, Annex 5	ASHRAE Handbook, EN ISO 14644 Standards
2.1.11.	<b>Validation</b>	Part I, Annex 15	TRS 961, Annex 3, Chapter 4 TRS 937, Annex 4	
	Validation of heating, ventilation and air-conditioning systems	--	TRS 937, Annex 4	EN ISO 14644 series
	Validation of water systems for pharmaceutical use	Part I, Annex 15	TRS 937, Annex 4	US FDA Guide to Inspections of High Purity Water Systems
	Cleaning validation	Part I, Annex 15	TRS 937, Annex 4	
	Analytical method validation	Note for guidance CPMP/ICH/381/95	TRS 937, Annex 4	
	Validation of computerized systems	Part I, Annex 11	TRS 937, Annex 4	GAMP5
	Qualification of systems and equipment	Part I, Annex 15	TRS 937, Annex 4	
	Non-sterile process validation	Part I, Annex 15	TRS 937, Annex 4	
2.2.	<b>Starting Materials</b>	Part II	TRS 957, Annex 2	IPEC-PQR GMP Guide
2.3.	<b>Sterile pharmaceutical products</b>	Part I, Annex 1	TRS 961, Annex 6	
2.4.	<b>Site Master File</b>	Part III	TRS 961, Annex 14	
2.5.	<b>Quality Risk Management</b>	Part I, Annex 20	--	
2.6.	<b>Note for Guidance on Pharmaceutical Quality Systems</b>	Part III	--	

## Appendix 2. Questionnaire: African companies

### Questionnaire:

Company: \_\_\_\_\_  
 Number of employees (total): \_\_\_\_\_  
 Number of employees working in Quality: \_\_\_\_\_

Status:

- |  |                          |                      |
|--|--------------------------|----------------------|
| a) WHO Prequalification for one or more products | <input type="checkbox"/> | When: _____          |
| b) Inspection for qualification was done         | <input type="checkbox"/> | When: _____          |
| c) Inspection for qualification is planned       | <input type="checkbox"/> | Scheduled for: _____ |
| d) Prequalification is in preparation            | <input type="checkbox"/> | Scheduled for: _____ |
| e) Not started yet                               | <input type="checkbox"/> | Scheduled for: _____ |

### **If a-c**

How long took the whole prequalification process: \_\_\_\_\_

Which products are qualified or should be qualified (New products?): \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Is it planned to qualify more products:

Which product: \_\_\_\_\_

Timeframe: \_\_\_\_\_

Did you increase your marked volume by this prequalification? \_\_\_\_\_

Did you get external support for this process by an international parent company or cooperation partner? \_\_\_\_\_

If yes, which one: \_\_\_\_\_

Did you get support by your national government? \_\_\_\_\_

Did you hire external professionals or consultants to support this process? \_\_\_\_\_

Was it necessary to build up new facilities or to refurbish old structures? \_\_\_\_\_

What was done? \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Did you refurbish the HVAC system? \_\_\_\_\_

Did you refurbish the water system? \_\_\_\_\_

Was it necessary to buy and install new computer systems e.G. LIMS? \_\_\_\_\_

## Questionnaire: African companies

**Production:**

Did you buy new manufacturing equipment? \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Did you hire new staff in the manufacturing department? \_\_\_\_\_  
 How much and what education: \_\_\_\_\_

Did you do changes in your manufacturing workflow? \_\_\_\_\_

**Quality departments:**

Did you install new quality systems? \_\_\_\_\_  
 Which ones: \_\_\_\_\_  
 \_\_\_\_\_

Did you build more testing capacity (Laboratories)? \_\_\_\_\_

Did you hire new staff in the Quality department? \_\_\_\_\_  
 How much and what education: \_\_\_\_\_

Did you do major changes in your documentation or did you implement those new documents?

- |   |                          |
|---|--------------------------|
| a) SOPs   | <input type="checkbox"/> |
| b) Master batch records                         | <input type="checkbox"/> |
| c) Manufacturing instructions and protocols     | <input type="checkbox"/> |
| d) Testing instructions and protocols           | <input type="checkbox"/> |
| e) Site Master File                             | <input type="checkbox"/> |
| f) Quality handbook                             | <input type="checkbox"/> |
| g) Validation Master Plan                       | <input type="checkbox"/> |
| h) Validation/qualification protocols and plans | <input type="checkbox"/> |

Did you change your release process? \_\_\_\_\_

Did you start to do supplier approval? Was it necessary to do external supplier audits? \_\_\_\_\_  
 \_\_\_\_\_

Did you change your API handling? \_\_\_\_\_

How do you manage shelf-life and retesting? \_\_\_\_\_  
 \_\_\_\_\_

**Validation/Calibration:**

Did you hire new staff for validation and calibration processes? \_\_\_\_\_

How much and what education: \_\_\_\_\_

Which part of the process was the biggest challenge or claimed the biggest investment?

In terms of money: \_\_\_\_\_

In terms of human resources: \_\_\_\_\_

Which part of the GMP certification process generated the biggest obstacles or problems? \_\_\_\_\_

Which part of the WHO GMP requirements could or should be reduced to obtain GMP certification? \_\_\_\_

Can you estimate the total costs of the GMP certification process? \_\_\_\_\_

How do you value the benefit of the GMP certification for your company and does the WHO GMP certification strengthen your position compared to the competitors? \_\_\_\_\_



Appendix 3. Questionnaire: German companies

Interview of medium-sized  
companies with regard to their GMP status



A) Company indications

1)

Contact

a)

Company name

Address

b)

Interview partner

Position / task in the company

2)

Company size

a)

Turnover

b)

Employees

total

in Production dept.

in Quality Control

in Quality Assurance

3)

Portfolio

Product range

solid forms

oral liquids

semi-solid forms

sterile pharmaceuticals

others

Which?

4)

Joint ventures

a)

Do you have co-operations with companies in developing countries?

Yes

No

b)

If so, for what products / product groups

Interview of medium-sized  
companies with regard to their GMP status



## B) Questions regarding GMP requirements

- 5 a) Which GMP requirements were the most difficult ones for your company to realise? .....
- b) Which GMP implementation was the most expensive one for your company? .....
- c) For the implementation of GMP requirements do you have/or have you asked for external support? Yes ☐ No ☐
- d) If so, which? .....
- 6) What are the quality related costs per year? .....

## C) Interest in joint ventures

- 7 a) Is your company interested in co-operation with GIZ/ companies in developing countries? Yes ☐ No ☐
- b) If so, for what products / product groups? .....

## Appendix 4. Summary table of German questionnaires

Angaben zum Unternehmen				Anzahl Mitarbeiter					Produktspektrum Arzneimittel				
Name	Anschrift	Interview-partner	Position	Umsatz Mio. EUR/Jahr	ges.	Prod.	QK	QS	Feste Formen	Orale Liquida	Halbfeste Formen	Sterile Arzneimittel	andere
AGON Pharma GmbH	Stuttgarter Str. 2, 73240 Wendlingen	Günter Stephan	CEO	1	12	n.a.	8	2	x	x	x		
bene-Arzneimittel GmbH	Herterichstr. 1-3, 81479 München	Christian Metz	Leitung Pharmazie	14 (2011)	ca. 90*	40	15	3,5	x	x	x		
Engelhard Arzneimittel GmbH & Co. KG	Herzbergstr.3, 61138 Niederdorfelden	Dr. Oliver Schmidt	Pharmazeutische Leitung	ca. 70	ca. 250	ca. 90 <sup>a</sup>	11	3	x	x	x		
Haupt Pharma AG	Pfaffenrieder Str. 5-7, 82515 Wolfratshausen	Dr. Karl Heinz Brücher	COO	262 FC (2011)	2000	n.a.	n.a.	n.a.	x	x	x	x	Gefrier-trocknung
Unternehmen möchte namentlich nicht genannt werden			Bereichs-leiter Qualität	150	720	200	40	15	x				
Kneipp-Werke GmbH & Co. KG	Steinbachtal 43, 97082 Würzburg	Dr. Rainer Wohlfahrt	Leiter Entw. & Zulassung	ca. 100	400	n.a.			x		x		Körper-pflegem. m. Fokus Baden
Merck Selbstmedika-tion GmbH	Rösslerstr. 96, 64293 Darmstadt	Dr. Olaf Sichler	Head of Quality Assurance	ca. 98 **	ca. 180	n.a. <sup>b</sup>	14 <sup>c</sup>	2	x	x	x	x	
PASCOE pharm. Präparate GmbH	Schiffenberger Weg 55, 35394 Giessen	Dr. R. Unger	Leiter der Produktion	ca. 20 (2007) ***	150	38	10	2	x	x	x	x	
SymbioPharm GmbH	Auf den Luppen 8, 35745 Herborn	Peter Eilbert	Geschäfts-führer	17	69	12	3	3		x		x	
SymbioVaccin GmbH	Auf den Luppen 8, 35745 Herborn	Dr. E. Laskowska	Leiterin der Herstellung	ca. 0,7	26	17	5	1		x		x	Nasen-u. Mund-spray, stoffsp. Impf-stoffe

## Quellen:

\* Internet, bene Unternehmensprofil, Stand 09/2007

<sup>a</sup> inkl. Instandh.

\*\* Internet, Firmenhomepage, Stand 11/2011

<sup>b</sup> Herst. auss. Lohnauftrag

\*\*\* Internet, Wer zu wem, Stand 2007

<sup>c</sup> QK ebenf. z.T. in Lohnauftr. durchgef.

## Summary table of German questionnaires

JV	GMP-Anforderungen					Indices		Interesse an JV	
	am schwierigsten	kosten-intensivsten	externer Support	welchen?	Q-bezogene Kosten/Jahr	Gesamtzahl MA/MA in QK + QS (%)	Anzahl MA Produktion/MA in QK + QS	Zusammenarb. GIZ/Entwicklungsländern	Wenn ja, Produkte/-gruppen?
nein	n.a.	n.a.	nein	n.a.	n.a.	83	./.	ja	alle
nein	./.	Implementierung PQR	ja	Ext. Verant. z.B. Forum, PCS, etc.	nicht bekannt	21	2,2	nein	
nein	Umgest. baul. Strukturen im Bestand (z.B. konsequente Trennung Primär-Sekundärverp., konsequenter Materialfluss ohne überkreuzende Wege)	Teilumsetzungen der o.g. Umstrukt.	nein			6	6,4	ja	n.a.
nein	n.a.	n.a.	ja	1. Schulungen 2. Umbaumassnahmen	n.a.	./.	./.	ja	n.a.
nein	FDA-Anforderungen	Zonenkonzept, Kennzeichnung (DataMatrix-Code) QK-Kosten	ja	Consultants	ca. 1,5 Mio. EUR (QS)	8	3,6	nein	
nein	n.a.	n.a.	nein		n.a.	./.	./.	ja	pharmakonforme ätherische Öle
nein	Computer System Validierung, zeitliche Umsetzung neuer Anford.	Auditieren von Auftragnehmern (Reisek., Zeitaufw.)	ja	Zeitarbeiter zur Unterst. Tagesgesch. (kein spez. Support für best. GMP Inhalte)		8	./.	nein	
nein	Umsetzung der Anford. an Luftwechsel im Sterilbereich	Ums. d. Anf. an Luftw. im Sterilb., Requalifizierung d. Anl. im Sterilb.	ja	Wartungen, Qualifiz., Kalibr. etc. teilw. durch Herstellerfirmen bzw. Dienstleister	n.a.	8	3,2	nein	
nein	Steriltechnik	Steriltechnik, Klimatechnik	ja	Techn. Beratung, Sachkundige Person	5,50%	9	2,0	nein	
nein	Lieferantenaudits, EDV-Validierung (sehr personalintensiv), Pharmakovigilanz, on-going stability	EDV-Validierung (personal-intensiv), Validierung der Ausrüstung	ja	ext. QP, Leiter QK, Leiter Herst. Laborunters., Stabi-Test, Validierung von Ausrüstung, Pharmakovigilanz	ca. 20 % d. Ums. bzw. 140.000	23	2,8	nein	

n.a. = nicht ausgewiesen

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