

Comparison of EU GMP guidelines with WHO guidelines

Identification of the cost-intensive requirements

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Aim of the study

I.) Comparison of the EU and WHO GMP guidelines

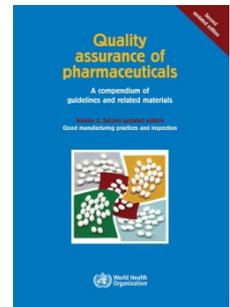
- to work out the differences,
- which GMP guideline is stricter and more expensive

The table compares EU and WHO GMP guidelines across various categories. The categories include: 1. The main objective of the GMP, 2. The scope of the GMP, 3. The responsibilities of the manufacturer, 4. The responsibilities of the regulatory authority, 5. The responsibilities of the inspector, 6. The responsibilities of the pharmacist, 7. The responsibilities of the pharmacist-in-charge, 8. The responsibilities of the pharmacist-in-charge-in-charge, 9. The responsibilities of the pharmacist-in-charge-in-charge-in-charge, 10. The responsibilities of the pharmacist-in-charge-in-charge-in-charge-in-charge.

EU GMP	WHO GMP
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II.) Definition of the critical and cost consuming requirements

- polls were executed with pharmaceutical producers in Africa and
- Small and medium-sized manufactures in Germany



III.) Recommendations

- to help African pharmaceutical manufacturers on their way to WHO prequalification



Comparison EU GMP versus WHO GMP guidelines

Main Principles for Pharmaceutical products

Quality Management

EU GMP guidelines

- **Chapter 1 (“Quality Management”)**
- **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 are mentioned again later in the subsequent chapters in more detail**

Main Principles for Pharmaceutical products

Quality Management

WHO GMP guidelines

- **TRS 961, Annex 3** (“WHO good manufacturing practices for pharmaceutical products: main Principles”)
 - **Chapter 1** (“Quality assurance”)
 - **Chapter 2** (“Good manufacturing practices for pharmaceutical products”)
 - **Chapter 17, Point 17.1, 17.3** (“Good Practices in quality control”)
 - **Page 103** (“Quality management in the medicines industry: philosophy and essential elements”)

Conclusion

- **The contents and the requirements are in large parts the same**
- **The WHO specifies some topics a little bit in more detail, e.g.:**
- **explains additionally two types of risks which exist in pharmaceutical production: cross-contamination and mix-ups**
- **includes storage as a process which has to be monitored to minimise risks to product quality.**

Main Principles for Pharmaceutical products

Personnel

EU GMP guidelines

- Chapter 2 (“Personnel”)
- specify the need of sufficient qualified personnel
 - given tasks will be executed in time and in the requested quality
 - the employee in charge accordingly trained
 - the respective responsibilities have to be clearly defined to avoid overlaps and empty spaces
- starting from point 2.13, the requirements of the so-called “Personnel Hygiene” are listed

Main Principles for Pharmaceutical products

Personnel

WHO GMP guidelines

- **TRS 961, Annex 3**
- **Chapter 9** (“Personnel”)
- **Chapter 10** (“Training”)
- **Chapter 11** (“Personal hygiene”)
- **Chapter 3** (“Sanitation and hygiene”)

Conclusion

- **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 QMS not only in the field of production but also in the field of control of pharmaceutical products and active ingredients.**

Main Principles for Pharmaceutical products

Personnel

WHO GMP guidelines

Conclusion

- Nevertheless the following minor differences can be detected:
 - **the WHO guidelines additionally describe the qualification of key personnel responsible for production and quality control**
 - **the topic “Personnel Hygiene” is explained more explicitly in the WHO guideline than in the EU guideline.**
 - **e.g. “used clothes, ..., should be stored in separate closed containers until properly laundered...”.**

Main Principles for Pharmaceutical products

Premises and Equipment

EU GMP guidelines

- **Chapter 3 (“Premises and equipment”)**
- **The 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.**

Main Principles for Pharmaceutical products

Premises and Equipment

WHO GMP guidelines

- **TRS 961, Annex 3**
 - **Chapter 12** (“Premises”)
 - **Chapter 13** (“Equipment”)
 - Chapter 9, Point 9.5 (“Personnel”)
 - Chapter 16, Point 16.9, 16.23, 16.24 (“Good practice in production”)

Conclusion

- **The content relating to the prerequisites 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.**

Main Principles for Pharmaceutical products

Premises and Equipment

WHO GMP guidelines

Conclusion

- **Moreover, there are further WHO documents regarding the topic “Equipment”, e.g.:**
 - **“WHO good manufacturing practices: starting materials” or**
 - **“WHO guidelines on transfer of technology in pharmaceutical manufacturing” and**
 - **others**

Main Principles for Pharmaceutical products

Dokumentation

EU GMP guidelines

- Chapter 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.**

Main Principles for Pharmaceutical products

Dokumentation

WHO GMP guidelines

- TRS 961, Annex
 - Chapter 15 (“Documentation”)
 - Glossary, Point “Specification”

Conclusion

- Neither in the general part nor in the requirements for special documents like:
 - specifications,
 - manufacturing formulas / master formulae etc.decisive differences can be detected.

Main Principles for Pharmaceutical products

Dokumentation

WHO GMP guidelines

Conclusion

- **The WHO guidelines are again in its execution and explanations partly more elaborate, and gives the user additional information on how the guidelines have to be interpreted and what has to be taken care of**
- **see e.g. points:**
 - **15.10 – 15.12 Labels,**
 - **15.13 – 15.17 Specifications and testing procedures,**
 - **15.43 Analysis records,**
 - **15.48 Cleaning and sanitation.**

Main Principles for Pharmaceutical products

Production

EU GMP guidelines

- **Chapter 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 Authorization.
- **The requirements and the recommendations in this chapter deal among others with the scopes:**
 - Prevention of cross-contamination in production,
 - Validation,
 - Finished products,
 - Rejected, recovered and returned materials
 - etc.

Main Principles for Pharmaceutical products

Production

WHO GMP guidelines

- **TRS 961, Annex 3**
 - **Chapter 14** (“Materials”)
 - **Chapter 16** (“Good practices in production”)
 - **Chapter 3** (“Sanitation and hygiene”)
 - Chapter 15, Point 15.10 (“Documentation”)
 - Chapter 4, Point 4.4, 4.8 (“Qualification and validation”)

Conclusion

- **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 Technical Report Series 961**

Main Principles for Pharmaceutical products

Production

Conclusion

- 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 Technical Report Series No. 937, Annex 4: “Validation”).¹¹

Main Principles for Pharmaceutical products

Quality Control

EU GMP guidelines,

- **Chapter 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.**

Main Principles for Pharmaceutical products

Quality Control

WHO GMP guidelines

- **TRS 961, Annex 3**
 - **Chapter 17** (“Good practices in quality control”)
 - Chapter 14, Point 14.34, 14.35, 14.39, 14.42 (“Materials”)
 - Chapter 9, Point 9.12 (“Personnel”)
- TRS 961, Annex 4 (“WHO guidelines on good manufacturing practices for blood establishments”)
 - Chapter 2, Point 2.2 (“Glossary and abbreviations”)
- TRS 961, Annex 6 (“WHO good manufacturing practices for sterile pharmaceutical products”)
 - Chapter 10, Point 10.3 (“Personnel”)
- **TRS 957, Annex 2** (“WHO good manufacturing practices for active pharmaceutical ingredients”)
 - Chapter 7, Point 7.33 (“Materials management”)

Main Principles for Pharmaceutical products

Quality Control

WHO GMP guidelines

Conclusion

- the requirements and the recommendations of the EU guideline **regarding “sampling” or “On-going stability studies”** are not included in Chapter 17 “Good practices in quality control” but can be found in other appendices of WHO Technical Report Series
- summing up, it can be said that the requirements of both guidelines are identical.
- again, the WHO guidelines are more detailed than the EU guidelines and provide hints for a better understanding of the requirements and the performance activities.

Main Principles for Pharmaceutical products

Quality Control

Conclusion

- 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

Main Principles for Pharmaceutical products

Contract Manufacture and Analysis

EU GMP guidelines,

- **Chapter 7** (“Contract manufacture and analysis”)
- **Due to the complexity in the sequence of production processes and testing 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**

Main Principles for Pharmaceutical products

Contract Manufacture and Analysis

WHO GMP guidelines

- TRS 961, Annex 3
 - Chapter 7 (“Contract production and analysis”)

Conclusion

- The requirements of both guidelines are identical, except for some references, which can only be found in the EU guidelines:
 - e.g. that in case of contract analysis the Contract Acceptor should understand that he is subject to inspection by the competent Authorities.

Main Principles for Pharmaceutical products

Complaints and Product Recalls

EU GMP guidelines

- **Chapter 8 (“Complaints and product recalls”)**
- **According to the EU GMP guidelines, 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.**

Main Principles for Pharmaceutical products

Contract Manufacture and Analysis

WHO GMP guidelines

- **TRS 961, Annex**
 - **Chapter 5** (“Complaints”)
 - **Chapter 6** (“Product recalls”)
 - **Chapter 14, Point 14.32** (“Materials”)

Conclusion

- **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 coordination of recalls should normally be independent of the sales and marketing organisation.**

Main Principles for Pharmaceutical products

Self inspection

EU GMP guidelines

- **Chapter 9 (“Self inspection”)**
- **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**

Main Principles for Pharmaceutical products

Contract Manufacture and Analysis

WHO GMP guidelines

- **TRS 961, Annex 3**
 - **Chapter 8** (“Self-inspection, quality audits and supplier`s audits and approval”)

Conclusion

- **As the title implies, the WHO guidelines give some additional information on the execution of “Suppliers’ audit”.**
- **Furthermore they list in more detail the “Items for self-inspection”.**

Main Principles for Pharmaceutical products

Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

EU GMP guidelines,

Chapter ---

- 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.

Main Principles for Pharmaceutical products

Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

WHO GMP guidelines

- **TRS 961, Annex 5** (“Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms”)

Conclusion

- **WHO GMP guide is one of the few GMP guidelines worldwide that implemented an own chapter about HVAC systems**
- **A similar chapter is missing in the European guideline**

Main Principles for Pharmaceutical products

Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

WHO GMP guidelines

Conclusion

- Other text sources are
 - the ASHRAE Handbook of the non-profit technical organisation **American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc. (ASHREA)**.
 - the **EN ISO 14644** Standards that define Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones.”.

Main Principles for Pharmaceutical products

Validation

EU GMP guidelines

- **Annex 15** (“Qualification and 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.

Main Principles for Pharmaceutical products

Validation

WHO GMP guidelines

- **TRS 961, Annex 3**
 - **Chapter 4** (“Qualification and validation”)
- **TRS 937, Annex 4** (“Supplementary guidelines on good manufacturing practices: validation”)

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

Main Principles for Pharmaceutical products

Validation

WHO GMP guidelines

Conclusion

- In general, the WHO validation guideline is much more detailed than the EU GMP document
- Some information is missing in the EU GMP guide e.g.
 - commissioning of new **HVAC systems** or parts of those
- or are listed in other guidelines of the EMA e. g. analytical method validation → “Note for guidance on validation of analytical procedures”

Main Principles for Pharmaceutical products

Validation

WHO GMP guidelines

Conclusion

- regarding Cleaning validation, the EU GMP guide include two additional points
 - the allowance that **toxic or hazardous substances** can be substituted under special conditions for the validation process and
 - that **"Test until clean"** is not considered an appropriate alternative to cleaning validation,
- over all it is an advantage for the user that the information in the **WHO guide is concentrated in one document** and that some examples of reports and protocols are attached.

Main Principles for Pharmaceutical products

Starting Materials

EU GMP guidelines

- **Part II** (“Basic Requirements for Active Substances used as 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, rules and recommendations for the production process of raw materials and appropriate control by quality units were defined.**

Main Principles for Pharmaceutical products

Validation

WHO GMP guidelines

- **TRS 957, Annex 2** (“WHO good manufacturing practices for active pharmaceutical ingredients”)

Conclusion

- **Both documents are very well comparable. Only slight differences can be found, e. g.**
 - **the EU guideline applies for the manufacture of active substances for medicinal products for both human and veterinary use.**
 - **an additional chapter about quality risk management has been included to section 2 of the EU guide**

Main Principles for Pharmaceutical products

Sterile pharmaceutical products

EU GMP guidelines

- **Part I, Annex 1** (“Manufacture of Sterile Medicinal 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.**

Main Principles for Pharmaceutical products

Sterile pharmaceutical products

WHO GMP guidelines

- **TRS 961, Annex 6** (“WHO good manufacturing practices for sterile pharmaceutical products”)

Conclusion

- **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). 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.**

Main Principles for Pharmaceutical products

Sterile pharmaceutical products

WHO GMP guidelines

Conclusion

- **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”)**

Main Principles for Pharmaceutical products

Site Master File

EU GMP guidelines,

- **Part III (“GMP related Documents”)**
- 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.

Main Principles for Pharmaceutical products

Site Master File

WHO GMP guidelines

- **TRS 961, Annex 14** (“WHO guidelines for drafting a site master file (based on the explanatory notes for pharmaceutical manufacturers on the preparation of the Pharmaceutical Inspection Convention”)

Conclusion

- **A comparison of both texts shows a nearly 100% correlation**

Main Principles for Pharmaceutical products

Quality Risk Management

EU GMP guidelines,

- **Part I, Annex 20 (“Quality Risk Management”)**
- **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 can be applied both proactively and retrospectively**
- **based on the ICH Q9 guideline (“Quality Risk Management”)**

Main Principles for Pharmaceutical products

Quality Risk Management

WHO GMP guidelines

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Conclusion

- WHO has not implemented any risk management requirements yet
- an initial draft of own WHO guidelines on quality risk management was discussed

Main Principles for Pharmaceutical products

Pharmaceutical Quality Systems

EU GMP guidelines,

- **Part III** (“GMP related Documents”)
- In June 2008 ICH approved **a new guideline** about „Pharmaceutical Quality Systems" (Q10) that has been implemented by European Countries, the United States of America and Japan.
- The document describes a model for an effective quality management system for the pharmaceutical industry.
- It completes the two ICH guidelines Q8 (Pharmaceutical Development) und Q9 (Quality Risk Management).

Main Principles for Pharmaceutical products

Pharmaceutical Quality Systems

WHO GMP guidelines

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Conclusion

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

Comparison EU GMP versus WHO GMP guidelines

Summary

- **Since the WHO GMP handbook, published in 2006, provided GMP regulations on a slightly reduced level, the changes that were made with the WHO Technical Report Series 957 (2010) and 961 (2011) increased the WHO requirements substantially.**
- **When comparing WHO and European GMP requirements, it can be stated that both guidelines have been quite clearly aligned in the last few years.**
- **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.**

B.) Definition of the most critical and cost consuming requirements

Cost of Quality

CoQ is usually understood as the sum of **conformance** and **non-conformance costs**.

“Conformance costs”

Preventive Activities

- costs which are incurred from activities designed to prevent poor quality.

Appraisal Costs

- Costs which are costs of measuring, evaluating, auditing, and so on

“Non-conformance costs”

Internal Failure Costs

- Costs which result from products not conforming prior to shipment.

External Failure Costs

- Costs which result from products not conforming post shipment

B.) Definition of the most critical and cost consuming requirements

Cost of Quality

- The “Cost of Quality” varies from 16 – 2 % of total costs depending on whether the pharmaceutical company is a so-called “Low or High performer”.

“Low performer”

- is a company which guarantees the quality of its products as a result of its high inspection activity/costs.

“High performer”

- has a total quality management (“TQM”) established, the quality “is built into the system”.

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

- 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, Dr. Feldmann visited 9 production sites in 7 East- and West African countries
- The focus was on companies that already had achieved WHO prequalification or those that are currently in the process.
- 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 bloc, stop or slow down the prequalification start.

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

- **The intention was to meet responsible representatives from upper management, from 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 developed to obtain comparable and evaluable results.**

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

Findings

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**
- **Time limiting factors** are here development of the formulation, stability investigations and bioequivalence studies.

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

Financial aspects

- **Total costs** for the build-up of a new manufacturing facility, including sufficient manufacturing and testing equipment, are high and should be calculated with more than 5 Mio. US\$. The needed investment depends on the size and product range of the company.
- 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 US\$.
- Furthermore the **costs for the development** of the formulation, required stability and bioequivalence studies are seen as the main cost drivers.

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

Financial aspects

- **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 or with an international financial investor

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

Human resources

- Sufficient, well educated and motivated personal is one of the key factors of a successful prequalification process
- 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
- 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

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

Human resources

- **Companies, that have achieved prequalification or are currently in the preparation phase,**
 - **have usually a significant higher ratio (13 – 25 %)**
 - **than companies that have not started any activities yet (6 – 14 %)**

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

Human resources

- **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.**

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

Human resources

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

B.) Definition of the most critical and cost consuming requirements

Survey with African pharmaceutical companies

Quality systems

The field of **documentation** was often named as a time and cost intensive area of improvement.

- sufficiently qualified pharmaceutical **manpower**
- **implementation** of new systems in all areas of the manufacturing process and
- **acceptance** of these new processes is essential
- **training** of the whole workforce from management level down to the manufacturing lines

B.) Definition of the most critical and cost consuming requirements

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 because it was not possible to get the corresponding information from “German Associations of Pharmaceutical Manufacturers”

- Questionnaires of 10 companies were analysed
- The size of the interviewed companies varied
 - with regard to the **turnover** from a about 260 million EUR to almost 1 million EUR or
 - regarding the **number of employees** between 12 and 2000

B.) Definition of the most critical and cost consuming requirements

Survey of German medium-sized pharmaceutical companies

- 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, **(~ 8 % → 20%)**
 - on the other hand, to the **employees from production department** **(~ 1 : 3)**

B.) Definition of the most critical and cost consuming requirements

Survey of German medium-sized pharmaceutical companies

- and additionally the relationship of the **quality related costs to the turnover** was worked out.
(1 % → 20 %)

B.) Definition of the most critical and cost consuming requirements

Survey of German medium-sized pharmaceutical companies

The **most difficult and most expensive** implementation of requirement were

- to meet the requirements in production of **sterile products**
 - the air-conditioning technology
 - necessary change rates of air ventilation
 - zone concept and the adherent building restructuring

B.) Definition of the most critical and cost consuming requirements

Survey of German medium-sized pharmaceutical companies

The most difficult and most expensive implementation of requirement were

- **qualification and validation tasks** (implementation of computing validation)
- implementation of **“Product Quality Reviews”** (PQRs)
- **auditing of suppliers** and contract manufacturers

B.) Definition of the most critical and cost consuming requirements

Survey of German medium-sized pharmaceutical companies

External support

- **Technical support**
 - **Consultants for maintenance and calibration**
 - **qualification measures were outsourced.**
- **Key personnel**
 - **QP, Head of Quality Control**

C.) Summary and recommendations

The following recommendations result from visits and meetings with African pharmaceutical manufacturers

Regional WHO centre or offices

- **the first contact would be much easier**
- **WHO officials could be integrated into the planning and development process from the first moment**
- **costs for training, workshops and MOCK audits could be reduced and**
- **fast support in case of arising problems could be assured**

C.) Summary and recommendations

Biowaivers

- **one alternative method to investigate bioequivalence**
- **there is a wish for a more pragmatic approach based on the BCS classification and dissolution speed**
- **reduction of development costs**

C.) Summary and recommendations

Exchange Forum

- The implementation and expansion of a pan-African internet platform (currently under preparation by GIZ) should be intensified.
- Especially a **database** that can be used as “knowledge pool” and additionally an exchange forum
 - to get
 - sufficient information,
 - input or
 - templates
 - for upcoming requirements (e.g. cleaning validation) as well as

C.) Summary and recommendations

Exchange forum

- **contact to**
 - **external consultants for the different pharmaceutical areas of expertise**
 - **different centres of excellence e.g.**
 - **universities,**
 - **training centres**
 - **etc.**

C.) Summary and recommendations

Activity check list

- a check list stating and interpreting the requirements to reach GMP standards
- to evaluate easier the necessary effort to be effected to pass successfully a GMP inspection and
- to co-ordinate external training measurements

Provision of SOP's/forms

- GMP guidelines are already well-known but the implementation poses great difficulties
- **presenting SOP's** with detailed information on the execution of the necessary activities using and creating the presented/necessary forms

C.) Summary and recommendations

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 (BMR's) have to be assorted and revised if applicable to ensure that all critical process parameters are measured and documented.



Thank you for your attention!