Quality control and auditing

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Conflicts of interest?

No conflicts of interest!

Position

- Director clinical pharmaceutical and toxicological laboratory
- Clinical pharmacologist in a large teaching hospital
- Member of the expert group on ´pharmaceutical waters´ of the European Pharmacopoeia
- Member of the expert group on ´dialysis´ of the European Pharmacopoeia

Overview presentation

- Role of the quality control laboratory in hospital compounding in The Netherlands
- Monitoring
- Auditing

Quality control laboratory

Analytical quality control
Microbiological quality control

Analytical quality control

Analytical quality control

- Substances for pharmaceutical use (including pharmaceutical waters if applicable!)
- Packaging materials
- Drugs that are produced:
  - Small scale compounding for individual patients
  - Large scale compounding for own hospital or for other hospitals
  - Drugs for clinical research

Dutch system of vendor auditing

- Joined initiative of professional organisations (KNMP, NVZA) and vendors
- Periodic audit of vendors by an audit team of professionals
- Written report of their findings available to all pharmacists
- Certification for 3 year
- Aiming at:
  - Improving quality of vendors (to comply with GMP)
  - Reducing the effort for individual compounding pharmacists to audit vendors
- Covered fields: substances for pharmaceutical use, primary packaging materials, medicinal gases

Analytical quality control

Substances for pharmaceutical use

- That comply with the European Pharmacopoeia and
- That are bought from audited vendors who comply to GMP
- Check of Identity (e.g. IR spectroscopy) suffices

Substances for pharmaceutical use

- That do not comply with the European Pharmacopoeia or
- That are not bought from audited vendors
- Should be analysed according to the total monograph

Analytical quality control

New active pharmaceutical ingredient (API) for clinical research:

- Not described in Ph Eur
- The Ph Eur general monograph ´Substances for pharmaceutical use´ applies
- Set your own additional requirements based on literature, state-of-the-art knowledge, etc.
- With help of ICH quality guidelines:


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2010 Training workshop on Quality Guidelines Q8, Q9 and Q10
Contact the Quality IWG with your comments and questions on Q8, Q9, Q10
ICH Press Release Tallinn, June 5-10, 2010
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GCG related
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ICH Guidelines
The ICH Topics are divided into four major categories and ICH Topic Codes are assigned according to these categories.
Q
"Quality" Topics, i.e., those relating to chemical and pharmaceutical Quality Assurance (Stability Testing, Impurity Testing, etc.)
S
"Safety" Topics, i.e., those relating to in vitro and in vivo pre-clinical studies (Carcinogenicity Testing, Genotoxicity Testing, etc.)
E
"Efficacy" Topics, i.e., those relating to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.)
M
"Multidisciplinary" Topics, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories (MedDRA, ESTRI, M3, CTD, M5)
Download here the Quality Guidelines in Word-format
Download here the Safety Guidelines in Word-format
Download here the Efficacy Guidelines in Word-format.
Download here the Multidisciplinary Guidelines in Word-format.
Notes on implementation in the three ICH Regions
EU
The ICH guidelines are submitted to the Committee for Human Medicinal Products (CHMP) for endorsement once they have reached Step 2 or Step 4 of the ICH Process. The CHMP, in consultation with the European Commission decides on the duration for consultation with interested parties (up to 6 months).
The European Agency for the Evaluation of Medicinal Products publishes and distrubutes the Step 2 guidelines for comments. At Step 4 the guidelines are endorsed by the CHMP and a timeframe for implementation is established (usually 6 months).
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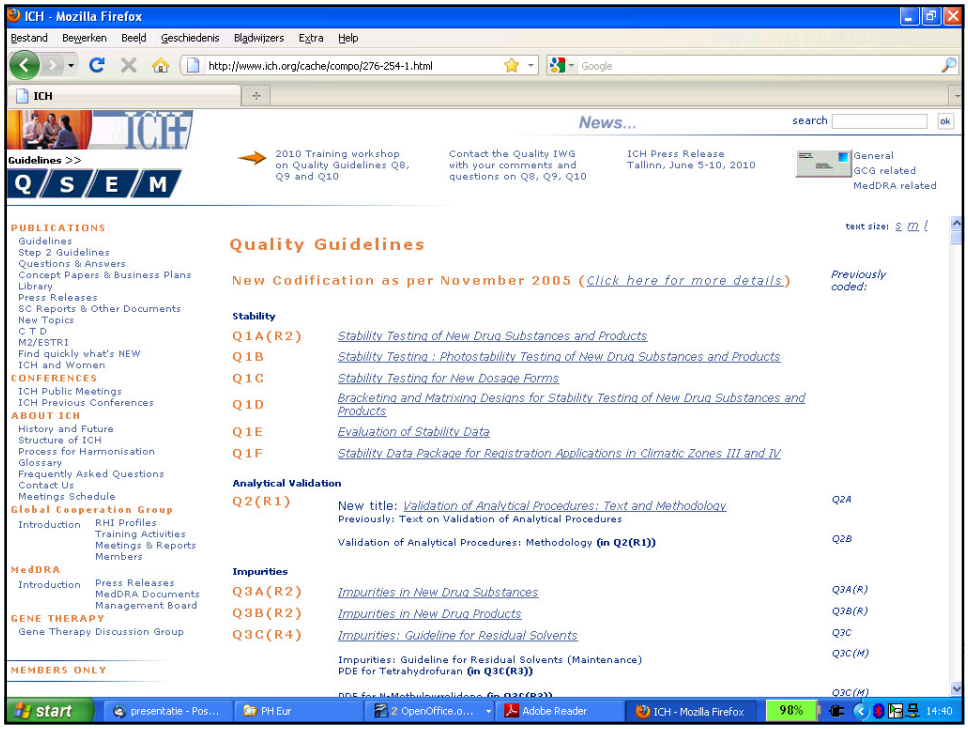
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Quality Guidelines
New Codification as per November 2005 (Click here for more details)
Previously coded:
Stability
Q1A(R2) Stability Testing of New Drug Substances and Products
Q1B Stability Testing : Photostability Testing of New Drug Substances and Products
Q1C Stability Testing for New Dosage Forms
Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
Q1E Evaluation of Stability Data
Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV
Analytical Validation
Q2(R1) New title: Validation of Analytical Procedures: Text and Methodology
Previously: Text on Validation of Analytical Procedures
Q2A
Validation of Analytical Procedures: Methodology (in Q2(R1))
Q2B
Impurities
Q3A(R2) Impurities in New Drug Substances
Q3A(R)
Q3B(R2) Impurities in New Drug Products
Q3B(R)
Q3C(R4) Impurities: Guideline for Residual Solvents
Q3C
Impurities: Guideline for Residual Solvents (Maintenance)
PDE for Tetrahydrofuran (in Q3C(R3))
Q3C(M)
Q3C(M)
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Example of testing of a substance

Literature: Ph Eur 6	requirement	observation
Characters	White cristalline powder	
Identity • IR	Complies with reference spectrum	
Certificate of analysis	Complies with Ph Eur requirements	
If substance is not bought from an audited vendor, the complete monograph must be reworked		

Analytical quality control

Packaging materials

- Primary packaging material
- Secondary packaging material
- Labels

Define your specifications

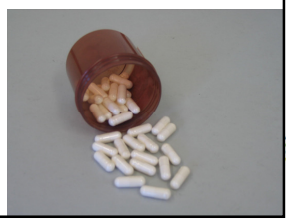
Make a set of specimens

Check certificate of analysis of each batch against specifications and a sample of the batch against specimen

Analytical quality control

Drugs that are produced:

- Preparation for stock (GMP): Tested according to a testing protocol (selected or random sample from every batch is tested for identity, content, sterility, pH, bacterial endotoxins, dissolution, decomposition, … whatever is applicable)
- Small scale preparations (GMP-H): Risk analysis, identify critical products or steps, selected samples are drawn and analysed for critical steps.



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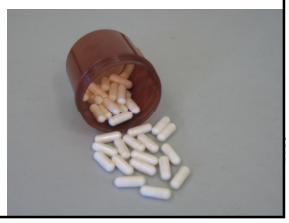


Analytical quality control

Drugs for clinical research (Clinical Trials Directive):

Manufacturing according to GMP (IMPD):

- Specifications of starting materials
- Method of compounding
- Validation of compunding
- Motivation of specifications
- Methods of testing described and validated
- Batch results
- Stability results

Microbiological quality control

Microbiological quality control

Microbiological quality control of substances for pharmaceutical use

Microbiological control of the finished drugs

Simulation with media

Environmental monitoring

Microbiological quality control

Microbiological quality control of substances for pharmaceutical use

- The pharmacopoeia requires different microbiological qualities for substances for pharmaceutical use according to the use of that substance
- If bought from an audited vendor you may rely on the certificate of analysis
- If not bought from an audited vendor or if the material is not of Ph Eur quality, you should verify the microbiological quality
- Requirements and methods are described in the Pharmacopoeia (5.1.4, 2.6.12, 2.6.13 and monographs)

Microbiological quality control

Relevant monographs:

5.1.4 Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use

2.6.12 Microbiological examination of non-sterile products: microbial enumeration test

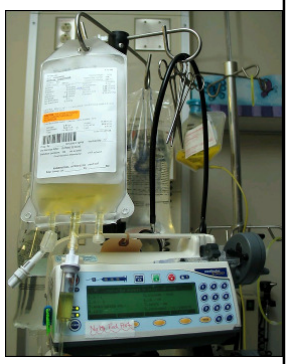
2.6.13 Microbiological examination of non-sterile products: test for specified micro-organisms

Monographs of substances for pharmaceutical use with microbial reqiurements

Microbiological quality control

Microbiological control of aseptic preparations in small scale compounding

- Parenteral drugs are sterile
- Control of all aseptic preparations is not possible
- Sterility testing has its limitations
- Testing must be done based on a risk analysis
- A selected sample from a batch of a high-risk drug can be taken and tested (e.g. the last prepared parenteral nutrition bag, the last eluate from a Technetium(99m) generator)
- During process simulation samples can be taken for microbiological quality control



Microbiological quality control

Simulation with media: process validation and personal qualification

Process validation:

The production process is simulated with growth media (e.g. the content of one or more vials with TSB is added to a bag with TSB and the bag is incubated. The bag should show no growth).

However, GMP requires 3000-5000 preparations with no growth before sterility can be demonstrated.

Microbiological quality control

Simulation with media: process validation and personal qualification

Personal qualification

The production process is simulated with growth media (e.g. the content of one or more vials with TSB is added to a bag with TSB and the bag is incubated. The bag should show no growth).

This can be part of a training program for technicians or nurses and can be performed at the end of the training program and repeated daily by the technician who made the preparations that day.

Microbiological quality control

Microbiological control in GMP-H is a combination of:

- Process validation
- Personal qualification Every technician injects 30 media samples in an infusion bag. The resulting product is incubated. With 30 samples and no growth, there is a 10% chance that the product is not sterile. This is acceptable. This is repeated yearly.
- Process simulation Blank simulation of the aseptic preparation at the end of each working shift with gowth media. When growth occurs, that person has to be qualified again.
- Environmental monitoring

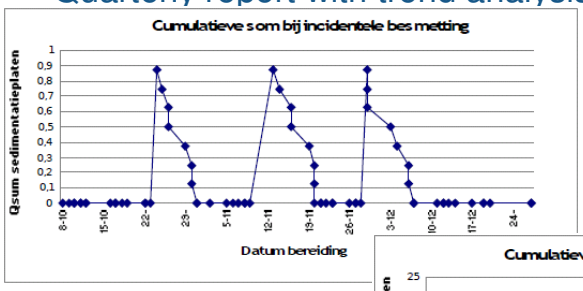
Microbiological quality control

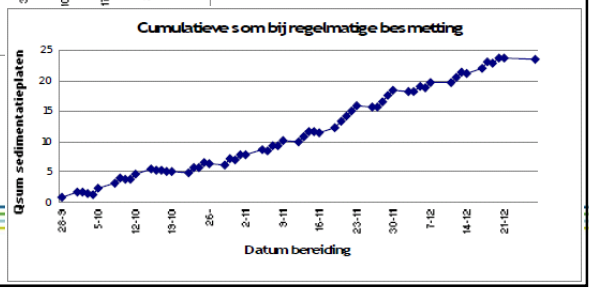
Environmental monitoring

- Continuous process
- Monitoring of the surroundings in the production area by sedimentation disks (to establish the in-house flora)
- Monitoring of the critical work place by sedimentation disks (to establish the risk for contamination; GMP max 1 cfu/4 hours work)
- Monitoring of the gloves by contact disks (to establish the risk for contamination)
- Monitoring of the number of cfu per volume of air by air sampler

Microbiological quality control

Quarterly report with trend analysis of results:





Auditing

Auditing

Principles:

- Every health-care organisation has a written quality system
- And is subject to internal and external auditing
- Standards are internationally set
- Before an external audit can take place, enough internal audits must have taken place

Pharmacy laboratory quality system

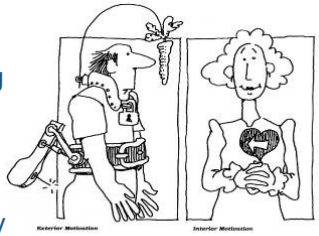
Must comply to GcLP

Criteria for GcLP are not well defined in the European GMP or Pharmacopoeia

Usefull criteria to build a quality system can be found for example in the EN-ISO-15189

Pharmacy laboratory quality system

- Quality system with SOP´s
- New personnel is trained according to a training scheme
- Analytical procedures are validated (Ph Eur procedures can be considered validated)
- Analytical procedures must have internal quality control samples for internal validation of the analysis and acts on deviations
- The laboratory takes part in external quality control schemes (e.g. the scheme organised by the EDQM) for external validation of analytical procedures and acts on deviations



Quality must come from inside

Aspects of auditing

- Working system of internal audits
- By personnel trained as internal auditors
- Every aspect of the quality system is audited yearly
- All analyses are audited at least once every three years
- Working system of ´plan-do-check-act´
- Quality deviations are investigated according to the 4-O system: reason / is this the only / solution / operationality
- The laboratory applies for accreditation by an external accreditation organisation

Quality must come from inside

ISO 9001 BUREAU VERITAS Certification
STS 382
TÜV AUSTRIA ROMANIA
BELAC
CCKL

Hospital quality control laboratory

After years of hard work:

Many documents,
all assays validated and
many internal audits:

Thank you for your attention

Group tasks

- Describe quality control facilities needed for your facility depending on your activities
- Describe the monitoring system you need for your facility depending on your activities
- Describe whether you perform them yourself or outsource, what do you require from your external labratory
- Describe the auditing system you need for your facility and/or external laboratory