European Medicines Agency

emea

Trade & Industry Inspection Agency of
Lower Saxony / Germany, Hannover office

EU GMP Requirements

- Quality Systems -

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Niedersachsen

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Biodata of the speaker

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- Education: Qualified pharmacist
  Certified expert for Pharmaceutical Technology
- Current position: GMP Inspector (since 2006)
- Further professional background: Pharma industry (1984 - 2005)
  various R&D-based companies
  mostly at interface Development vs. Production
- Special interests: Quality Risk Mgt, Quality by Design, Process Validation, Investigational Medicinal Products

Contents covered

1. Quality Management
2. Quality Risk Management
3. Change Control
4. Deviation Management & CAPA
5. Complaint & Recall Handling
6. Product Quality Review
7. On-going Stability Programme
8. ICH Q10 – Pharmaceutical Quality System

Preliminary note

- subject matters of the presentations are many and fairly broad …
- available time to present them is short …
- many aspects presumably not really new to you …

- Hence, what to do?
  - focus on specific EU legislative basis
  - 2nd focus on real-life (EU inspector's life …) interpretations
  - (3rd focus on recent trends / upcoming changes)
  - quite a large number of slides (as an aid for later use)
  - live presentation of the slides not as detailed
  - if questions related to details not answered in the discussion:
    → feel invited to contact me at any time! (contact data see slide no. 2)

1. Quality Management

Legal basis

- Commission Directive 2003/94/EC of 8 October 2003
  laying down the principles and guidelines of good manufacturing practice in respect of products for **human** use and **investigational** medicinal products for human use

- Commission Directive 91/412/EEC of 23 July 1991
  laying down the principles and guidelines of good manufacturing practice for **veterinary** medicinal products

- EudraLex Volume 4 – EU Guidelines to Good Manufacturing Practice for Human and Veterinary Use (**EC GMP Guide**)

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm

Definitions (1)

- **Quality**:
  - (not defined in EU GMP Guidances)
  - degree to which a set of inherent properties (of a product, system, or process) fulfills requirements [ISO 9000 / ICH Q9 and Q10]

- **Pharmaceutical Quality Assurance**:
  - the total sum of the organised arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use
    (Directives 2003/94/EC art. 2 no. 5, and 91/412/EEC art. 2)

- **Good Manufacturing Practice (GMP)**:
  - the part of quality assurance which ensures that products are consistently **produced** and **controlled** in accordance with the quality standards appropriate to their intended use
    (Directives 2003/94/EC art. 2 no. 6, and 91/412/EEC art. 2)

Definitions (2)

- **Quality Management (QM)**:
  - (not defined in EU GMP guidances)
  - Sum of quality control, quality assurance, and quality improvement(?)

- **Quality System = Quality Management System:**
  - (not defined in EU GMP guidances)
  - Instrument of the company management to ensure QM (?)

- **System of Quality Assurance (QA):**
  - Incorporates Quality Control, GMP, and Quality Risk Management [EC GMP Guide Part I chap. 1 / principle]

GMP and ISO standards

- GMPs developed in the late 1960s, ISO 9000 series in the 1990s …
- Comment in the Introduction to the EC GMP Guide:
  - CEN/ISO standards may be used at industry‘s discretion as a tool for implementing a quality system
  - CEN/ISO standards considered in the GMP Guide but terminology not implemented
  - It is recognised that there are other methods than those described in the Guide
  - It is not intended to place any restraints upon […] new concepts which […] provide a level of Quality Assurance a least equivalent
- Recent evolution: ICH Q10 [→ see separate section]

QA/QM Principles

- **Objectives** [EC GMP Guide Part I chap. 1 / principle]:
  - Product fit for intended use
  - Compliance with Market Authorisation
  - Patients not at risk due to inadequate safety, quality or efficacy
  - (‚first time right')
- Responsibility and active participation of **senior management**
- All quality related activities **defined** and **documented / recorded**
- **Responsibilities** defined (in writing)
- **Independent** quality unit [EC GMP Guide Part II = ICH Q7]
- **Release** of materials only after **controls** completed
- Evaluation of (unplanned) **deviations** and (intentional) **changes**

General Approaches to Inspection of Systems

- **Top-down**
  - Check of system structure and related internal procedures, e.g.:
    - **workflows** logical, feasible, and to the purpose?
    - **responsibilities** adequately assigned?
    - **staff resources** available? (number and qualification)
    - **life-cycle concept** for documents?
    - overall system design **compliant with regulations**?
  - Spot checks
    - for **compliance** to the system description
    - for **science-based** and **risk-oriented** treatment of the individual case

- **Bottom-up**
  - Start with a practical case out of a list of system applications …

Inspection of QA systems – Typical Elements (1)

- Commitment of **senior management** to Quality Assurance
  (support QA objectives, provide resources, build structure, participation)
- **QA organisation**
  - duties; adequate scope? defined?
  - structure: adequate? Incl. interfaces to other depts / to Qualified Person?
  - sufficiently staffed? (head-count and qualification)
  - assigned authorities sufficient?
- **Documentation** system
  - all quality-related areas covered?
  - document hierarchy logical?
  - document workflows acc. to life-cycle concept?
  - up-to-dateness regularly checked?
- **PDCA cycle** followed? (plan – do – check – act)

Inspection of QA systems – Typical Elements (2)

- Subsequent **areas** covered by the QA system and adequately dealt with?
  - Document management
  - Change control [→ separate section]
  - Deviation mgt / CAPA [→ separate section
  - Quality risk mgt [→ separate section]
  - Staff training
  - Appraisal of suppliers and third party service providers
  - Qualification / validation
  - Hygiene programmes and environmental monitoring
  - Release of materials / premises / equipment for use, execution of IPCs
  - Batch record review
  - Complaints handling
  - Self inspections
  - Product quality review [→ separate section]
  - On-going stability programme [→ separate section]

2. Quality Risk Management (QRM)

What is Quality Risk Management?

- **Quality Risk Management**:
  ‚a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product
  across the product lifecycle'
  [Annex 20 to EC GMP Guide = ICH Q9, section ‚Definitions']

  - **Risk:**
    ‚the combination of the probability of occurrence of harm and the severity of that harm' [dtto.]

  - **Risk Management:**
    ‚systematic application of quality mgt policies, procedures and practices to the tasks of assessing, controlling, communicating and review of risks' [dtto.]

  - **Product Lifecycle:**
    ‚all phases in the life of the product from initial development through marketing until the product's discontinuation' [dtto.]

Elements of a Risk Mgt Process

- **Risk assessment**:
  ‚a systematic process of organizing information to support a risk decision to be made with a risk management process [ICH Q9 / Definitions]

- **Risk control**:
  ‚actions implementing risk management decisions [dtto.]

- **Risk communication**:
  ‚the sharing of information about risk and risk mgt between the decision maker and other stakeholders' [dtto.]

- **Risk review**:
  ‚review or monitoring of outputs/results of the risk mgt process considering (if appropriate) new knowledge and experience about the risk [dtto.]

Further Useful Terms

- **Risk identification** – systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description [ICH Q9 / Definitions]
- **Risk analysis** – the estimation of the risk associated with the identified hazards [dtto.]
- **Risk reduction** – action taken to lessen the probability of occurrence and the severity of that harm [dtto.]
- **Risk acceptance** – the decision to accept risk [dtto.]
- **Stakeholder** – any individual, group or organisation that can affect, be affected by, or perceive itself to be affected by a risk […] Primary stakeholders are the patient, healthcare professional, regulatory authorities, and industry. [dtto.]

ICH Q9 on Quality Risk Management …

- ... was the trigger to incorporate QRM in EU GMP requirements
- … is itself part of a broader initiative (ICH Q8/Q9/Q10)
  - originally aiming at facilitation of innovation and global harmonisation of regulatory requirements for innovative drugs and technologies
- … is not just a means to improve quality standards
- … is not a classical GMP guidance document
  - neither relates only to GMP
  - nor is merely an *industry* guidance
- … has only in parts legally binding character in EU
- … requires specific methodological knowledge
  (for both, implementation and surveillance)

→ requires a somehow different approach by the GMP inspector!

Addressees of ICH Q9

- **Pharma industry**
  - Development, manufacture / control, and distribution of drugs
- **Regulatory authorities**
  - Granting of market authorisations (MAs)
  - Approval of variations to MAs
- **Supervisory authorities**
  - Granting of manufacturing / import authorisations
  - GMP inspections
  - Non-compliance / complaint / recall handling

Objectives of ICH Q9

- **Better** and better informed **risk decisions**
  - through systematic and science-based treatment of risks

→ Enhanced **predictability** / **uniformity** of risk decisions

- Better **documentation** and **transparency** of risk decisions

  → well-informed stakeholders

  → Increase knowledge about risks
- Facilitate **innovation** and continuous **improvement**
- Effective use of **resources**, commensurate with level of risk for patient safety
- Improve **confidence**
  - between companies and authorities
  - authorities amongst each other

Contents of ICH Q9

- **Principles** of Quality Risk Management
- Model of a risk **management process**
  (identification → assessment → control → communication → review)
- Proposals for applicable risk mgt **methods**
- Proposals for **fields of application** for QRM
- **Definitions**
- **Literature** references

http://www.ich.org/LOB/media/MEDIA1957.pdf

Implementation of QRM in the EU – a Brief History

- 2005: adoption of current ICH Q9 version by EU, US and JP
- since 2006: adaptation of EU **regulatory** guidances
  - e.g. ICH Q8 → ‚Note for Guidance on Pharm. Development‘
- 2008: in EU implementation of ICH Q9 as a **GMP standard**
  - principles in EC GMP Guide Part I chapters 1.5 and 1.6
  - options in Annex 20 to EC GMP Guide
- since 2008: integration into EC/EMEA ‚Compilation of Community Procedures on **Inspections** and Exchange of Information‘ (on-going)
- further implementations intended (e.g. GMP for APIs)

Introduction to EC GMP Guide with respect to QRM

- *GMP Part 1, **Chapter 1** on Quality Management has been revised to include aspects of **quality risk management** within the quality system framework. In **future revisions** of the guide the opportunity will be taken to introduce QRM elements when appropriate.*

- *The new GMP **Annex 20** […] provides guidance on a systematic approach to QRM leading to compliance with GMP and other quality requirements. It includes **principles** to be used and **options for processes, methods and tools** which may be used when applying a formal QRM approach …*

- *With its principles, methods and tools Annex 20 provides a systematic approach which may be used to demonstrate such*) equivalence.*

  **): equivalence of methods, technologies etc. not described in the Guide with the principles of the Guide*

EC GMP Guide Part I Chap. I (1)

- *Principle*
  … To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of ***Quality Assurance*** *incorporating Good Manufacturing Practice, Quality Control, and* ***Quality Risk Management****.*
  It should be fully documented and its effectiveness monitored. All parts of the Quality System should be adequately resourced …

  … The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control and ***Quality Risk Management*** *are inter-related.*

  …

EC GMP Guide Part I Chap. I (2)

- *Quality Risk Management*
  *1.5 Quality risk management is a **systematic process** for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.*

  1.6 The quality risk management should ensure that
  *- the evaluation of risk to quality is based on **scientific knowledge**, **experience** with the process and ultimately links to the **protection of the patient***
  *- the **level of effort**, formality and documentation of the quality risk management process is **commensurate with the level of risk**.*

  *Examples of the processes and applications of quality risk management can be found inter alia in **Annex 20**.*

Fields of Application of QRM in the GMP Area – Examples:

- (Product and process development)
- Change management
- Deviation management & CAPA
- Supplier and service provider qualification / auditing
- Equipment qualification, computer validation, maintenance programmes
- Environmental monitoring / hygiene programmes
- Prevention of cross-contamination
- Process validation / technology transfer
- Cleaning validation
- Validation / transfer of analytical methods (e.g. robustness testing)
- On-going stability monitoring programme
- Complaints handling

QRM Methods and Tools – Examples

- **Informal** methods
  - Flowcharts, checklists, fishbone diagrams, brainstorms, etc.
- **Formal** methods
  - FME(C)A – Failure Modes (Criticality) & Effects Analysis
  - FTA – Fault Tree Analysis
  - HACCP – Hazard Analysis & Critical Control Points
  - HAZOP – Hazard Operability Analysis
  - …
  - (customised) Combination of different methods
- **Supportive** tools
  - Statistical analyses, control charts, process capability, etc.

Inspection of QRM Systems - Typical Elements

- **Integration** of QRM into the quality management system:
  - **areas of application** of QRM sufficiently defined?
  - **responsibilities** defined?
  - sufficient **qualification / training** of personnel considered?
  - adequate involvement of **senior management** envisaged?
  - risk mgt **procedures** defined?
  - application of general QA standards with respect to **documentation**?
- Risk mgt **procedures** adequate?
  - **workflow** systematic? logical order? complete?
  - **patient safety** oriented? commensurate with level of risk?
  - Way of selecting **methods and tools**? Suitable degree of formality?
- Procedure for definition of **risk acceptance** criteria adequate?
- **Resources** sufficient to execute QRM?

Inspection of Individual Risk Cases - Typical Elements

- Clear-cut definition of the **risk question / problem**?
- People involved **qualified**? Did all relevant **stakeholders** participate?
- **Systematic** approach applied? Selected **methods / tools** suitable?
- Risks adequately **identified** and **analysed**?
  - e.g. all relevant data considered / generated?
- **Risk acceptance** criteria adequate for the case?
- **Risk decision** well-informed, science-based and comprehensible?
  - e.g. reliability of data base considered?
  - in compliance with pre-set acceptance criteria?
- **Risk reduction measures** realised? success reviewed?
- **Documentation** complete and traceable?
- **Internal QRM and QM procedures** adhered to?
- **Level of effort** and **reaction time** proportionate?

3. Change Control (CC)

Legal basis of CC

- EC GMP Guide **Part I** (drug products)
  - significant changes to the [manufacturing] process have to be validated [chapter 1.2 (ii)
  - changes carried out to the processes or analytical methods have to be reviewed regularly [chapter 1.4 (v), on PQR]
  - no explicit requirement of a CC *system* (→ but inherent from the definition of quality assurance)
- **Annex 15** to EC GMP Guide
  - written procedures [no. 43]
  - all changes treated formally, impact to be evaluated, need of revalidation to be determined [no. 44]
- EC GMP Guide **Part II** (active ingredients)
  - a formal CC system should be implemented [section 13.]

Principles of Change Control

- Changes in general should be regarded as something **positive**
- No execution of changes subject to **official consent** prior to
  - notification of regulatory and/or supervisory authority
  - approval by competent authority (where approval is required)
- No execution of any proposed change without **prior assessment** of potential impact on product quality and / or patient safety!
  - including changes having only indirect impact (e.g. computer software)
- **Prior validation** or any other testing, as required by the individual nature and extent of the change
- **Formal procedure** for proposal, assessment, definition of accompanying measures, approval and follow-up of each change
- **Full documentation** of each change control procedure
- After execution of a change, **evaluation** of its success

Reporting of Changes to Authorities

- related to **manufacturing / import authorisation**
  - all changes outside scope of the authorisation
  - all other siginificant changes – depending on national legislation (e.g. key staff, name / site of contract manufacturers or QC labs)
  - Site Master File contents (where up-to-dateness is required)
- related to **market authorisation**
  - according to Variation Regulation (1234/2008/EC as of Jan. 2010)
  - or national equivalent
- related to aspect of the **labelling** or the **package leaflet**, if change not covered by SPC (Specification of Product Characteristics)
- related to **wholesale distribution authorisation**

Case Examples Requring Formal CC Procedures

- Changes to:
  - **Starting materials** (incl. specifications, suppliers)
  - **Product components** (incl. labelling and packaging materials)
  - **Process equipment** (incl. computer hard- and software)
  - **Process environment** (facilities, media, support systems, …)
  - **Method of production**
  - **Method of testing**
  - **any other** change that **may affect product quality** or reproducibility
    - e.g. cleaning procedures, transport conditions, …

Sorts of Changes

- **planned** vs. **unplanned** (= deviations) [→ see sep. section]
- **major / minor** (optional; → enables variable level of effort / formality)
- may affect**:**
  - **official** authorisations (marketing, manufacture, wholesale, …)
  - **internal** quality system only
- as to **areas** concerned
  (site specific, corporate, involving 3rd parties)
- as to **subjects / objects**
  (personnel, facilities & equipment,materials / products)
- as to **processes**
  (e.g. purchasing, flow of materials, manufacture, cleaning, quality control, release, storage, distribution, complaints handling, …)
- as to **systems / programmes**
  (QA, documentation, computers, monitoring, on-going stability, …)

Typical Triggers of CC procedures

- Proposals for preventive actions following occurred deviations, OOS/OOL/OOT/OOE results or ‚near accidents'
- Audit / inspection findings
- Sourcing problems
- Poor robustness of manufacturing processes or test methods
- Lacking regulatory or GMP compliance
- Tightened product quality / safety requirements
- Tightened HSE requirements
- New drug regulations
- Economical considerations (e.g. material cost, productivity)
- Lacking efficiency of internal business processes
- Upgrades of technical environment (e.g. buildings, IT)
- Changes of product portfolio and volumes
- New company strategies (e.g. missions, organisational, technology, quality mgt)

Inspection of CC Systems – Typical Elements (1)

- CC system **integrated** into overall QA system?
  (same Q's as for QRM system → see previous slide no. 29)
- **All** potentially product quality affecting change **proposals covered**?
  - incl. purchasing, distribution, transport, …?
  - incl. QA system itself?
  - incl. contracted out activities?
  - incl. introduction of new products? [→ risk of cross contamination?]
- **Responsibilities** defined / CC team composition suitable?
  - incl. project manager / coordinator, task owners?
  - incl. for categorisation of significance (if done)?
  - incl. suitable involvement of Qualified Person?
  - technical expertise from all relevant disciplines involved?
  - QA and Regulatory Affairs departments involved?

Inspection of CC Systems – Typical Elements (2)

- CC **procedure**:
  - incl. documentary **capture of each CC case** in a list?
    → status control? (proposed / approved / implemented / reviewed)
    → list complete for periodic review?
  - incl. consideration of possible **impact on other products**?
  - incl. check for need of notification / approval by **authorities**?
  - incl. check for need of notification / approval by **third parties**?
  - incl. check for need of **re-qualification / re-validation**?
- adequate use of **quality risk management**? [→ see previous section]
- **documentation** of CC cases traceable / comprehensible?
- CC system part of **self-inspections / audits at 3rd parties**?

Need for Re-validation Following a Change

- May be required by **regulatory authority** in the course of approval of a variation application
  [cf. NfG on Process Validation, Sept. 2001]

- GMP principles
  - validation requirements are basically **same for new and changed** processes [Annex 15] but
  - **prior knowledge** could reduce scope of validation effort
  - Rationale for non-necessity or reduced scope should be based upon a **risk analysis**

Types of Changes Likely *) to Require Re-validation

- Physical properties of a raw material
- Starting material manufacturer
- Substitution of a packaging material
- Manufacturing process parameters
- Equipment (e.g. addition of automatic detection systems)
- Production area (incl. rearrangement)
- Support systems (e.g. water treatment method)
- Transfer of process to another site

*): according to PIC/S recommendation PI-006-3, section 6.6 *(http://www.picscheme.org/publication.php?id=8)*

Post-implementation review of a CC case

- **check on necessity of review measures should be routine element of each change management process**

- **if applicable, kind of review measures, responsibilities and timelines should be specified**
  - obligatory for APIs [EC GMP Guide Part II, sections 13.15f.]:
    - evaluation of the first batches produced under the change
    - evaluation of potential of the change to affect established retest or expiry dates; if necessary, placing of samples on stability testing

- **periodical review (e.g. within frame of regular Product Quality Review)**

4. Deviation Management & CAPA

Legal Basis for Deviation Mgt

- **EC GMP Guide Part I (products):**
  - ‚Any significant deviations [from defined procedures and instructions] are fully **recorded** and **investigated**‘ [Chapters 1.2 (vi) and 1.3 (vi)]
  - ‚Any deviation […] should be **avoided** as far as possible. If a deviation occurs, it should be **approved** in writing by a competent person, with the involvement of the QC departement when appropriate‘ [Chapter 5.15]

- **EC GMP Guide Part II (APIs):**
  - ‚Any deviation from established procedures should be **documented** and **explained**. Critical deviations should be **investigated**, and the investigation and its conclusions should be documented.‘ [Section 2.16]

Typical Sources of Information triggering Deviation Mgt Processes

- Staff observations
- Service requests
- Internal complaints
- Self-inspections, third party audits, official inspections
- Product quality reviews
- Process monitoring
- Environmental monitoring
- Otherwise generated trend data (e.g. on-going stability programme)
- Supplier / service provider communications

Inspection of Deviation Mgt – Typical Elements

- **Standard procedure available for handling of deviations?**
- **All kinds of deviations covered by the SOP?**
  - incl. e.g. deviations at suppliers / contract partners?
- **All relevant staff trained on the SOP?**
- **All deviations recorded? (in batch records, QC log books, etc.)**
- **Clearly assigned responsibilities?**
- **All reported deviations captured in a list? (e.g. for review in the PQR)**
- **Routine check for other potentially associated batches?**
- **Ensured that all deviations evaluated prior to batch release?**
- **Failure investigation and conclusion adequate?** [next slides]

Failure Investigation

- **Each** discrepancy / non-conformity should be investigated and evaluated
- Each failure investigation must be **fully documented**
- Clear **definition** of the problem
- Level of **effort** commensurate with level of related **risk**
  - If **categorization** of failures is applied: comprehensible criteria
- **Initiation** of investigation promptly after occurrence
- Systematic **data collection**
- **Methodology of analysis** suitable for nature / complexity of failure
  - incl. identification of similar potential problems
- **Reporting** of investigation findings
  - incl. identified root-causes (or combinations thereof)
- **Conclusion** adequate (→ next slide on CAPA)

Corrective and Preventive Action (CAPA)

- **Corrective action**:
  to prevent recurrence of the existing discrepancy
- **Preventive action**:
  to prevent potential (similar) discrepancies from occurence
- **Measures** complementary to results of **investigation** [→ previous slide]
  - incl. employee training, as appropriate
  - Incl. stability testing, as appropriate
  - incl. follow-up of success, as appropriate
  - immediate action until permanent solution, if necessary
- **Communication** of intended actions to all potentially affected parties
- Timely and effective **completion** of approved actions
- Regular **review of effectiveness** of measures
- **Formal close out** of each CAPA process once follow-up completed

5. Complaint & Recall Handling

Background on Complaint & Recall Handling

- **Legal basis**
  - EC GMP Guide Part I Chapter 8 (products)
  - EC GMP Guide Part II Section 15 (APIs)

- **Principles**
  - All complaints concerning potential quality defects should be **recorded** and **investigated** according to written procedures
  - **Traceability** of whereabouts of the affected batch(es)
  - Written **procedures** available to organise any recall activity
  - Defined **responsibilities** for execution / co-ordination of recalls
  - **Information of competent authorities** of significant events
  - **Regular review** for any indication of specific or recurring problems

Inspection of Complaint & Recall Handling – Typical Elements

- **Availability to receive complaints at any time, by any means?**
  (phone, fax, e-mail, letter post, personal communication)
- **All complaints immediately transmitted to responsible person?**
- **All complaints captured in a list? [for regular review]**
- **Qualified Person involved in all cases of potential quality defects?**
- **Evaluation of defects promptly, conclusions adequate?**
- **Information of competent authority of considered actions?**
- **Emergency plan available / effective?**
  - e.g. information of all potentially affected wholesalers / customers?
- **Recalls completely recorded? Issue of a final report?**
- **Validity of the recall procedure regularly reviewed?**

6. Product Quality Review (PQR)

Background for PQRs

- **Legal basis**
  - EC GMP Guide part I chapter 1.4 (for finished products)
  - EC GMP Guide part II section 2.5 (for APIs)

- **Objectives**
  - **Verification**
    - Consistency of the current **process**
    - Appropriateness of current **specifications**
      - for starting materials
      - for the finished product
  - Highlighting of any **trends**
  - Identification of product and / or process **improvements**

What should be considered in a PQR?

I. **Starting (incl. packaging) materials**, esp. from new sources
II. Critical **IPCs** and **finished product results**
III. Batches that **failed** to meet specifications
IV. Significant **deviations**, incl. effectiveness of CAPA measures
V. Changes carried out to the processes or analytical methods
VI. Status of **Marketing Authorisation** variations
VII. Results of the **on-going stability monitoring programme**
VIII. Quality-related **returns, complaints, recalls**
IX. Adequacy of previous **corrective actions**
X. Post-marketing commitments (e.g. stability testing, validation)
XI. Qualification status of equipment and utilities
XII. Up-to-dateness of **contractual arrangements**

How often should a PQR be performed?

- normally annually
- deviation from p.a. basis possible but has to be justified (cf. objectives of the PQR)
  - e.g. when number of batches produced is too small for trending
- periodic or rolling - both acceptable
- previous reviews should be taken into account
- (procedure should be described in an SOP in order to ensure that:)
  - report is available soon after end of respective period
  - all batches are considered (no gaps)
  - report concludes with assessment, whether / to what extent CAPA or revalidation should be undertaken

Inspection of PQRs - Further Aspects

- where Market Authorisation Holder and Manufacturer are not identical – **responsibilities** clearly shared (via tech agreement)?
- where **grouping** of products is performed – assignments scientifically justified?
- **database** complete? (all changes, deviations, complaints, etc.)
- **integrity / audit trail** of PQR data ensured?
- **trend analyses** performed properly?
- **conclusions** scientifically sound, proposed measures adequate?
- proposed CAPA / revalidation **measures pursued**?
- **effectiveness** of CAPA measures verified, e.g. through self-inspections?

7. On-going Stability (OGS) Monitoring Programme

Background on OGS

- **Legal basis**
  - EC GMP Guide Part I chapter 6.23 ff. (for products)
  - EC GMP Guide Part II section 11.50 ff. (for APIs)

- **Objectives**
  - after market launch:
    - (timely) detection of any **stability issue**
    - verification whether product remains within specs under the **labelled storage conditions**
    - Check on impact of **special conditions** on the shelf-life
      - e.g. storage of the bulk product for a long period before being packaged
      - e.g. changes, deviations, reworking, reprocessing, recovery

Follow-up vs. On-going stability testing

- **Follow-up** stability testing
  - commitment within the frame of a **market authorisation** procedure (or a variation application)
    - where shelf-life is calculated provisionally, based on accelerated stability tests a/o. using batches of limited representativeness
  - **one-off** verification of the claimed shelf-life period
  - often the **first three** production batches

- **On-going** stability monitoring programme
  - **after** MA / VA approval
  - a **GMP** requirement
  - **continuous** verification of the shelf-life

GMP Requirements Related to OGS (1)

- pre-defined **programme**
- **all marketed products** covered (each strength, each primary packaging)
- at least **one batch** of finished product per year
- (selection of a **representative** batch)
- **further batches** if indication that stability performance may deviate
  - e.g. as a result of deviations in the manufacturing process
  - Intermediate / bulk batches should be taken into account, too
- pre-defined **storage conditions, scope of testing, acceptance criteria**
  - + justification if different from stability studies for market authorisation
- use of **qualified equipment** (incl. storage chambers, alarm system)
- correct **labelling** of samples (→ no risk of loss or mix-ups)
- **period of storage** long enough to cover end of shelf-life

GMP Requirements Related to OGS (2)

- **monitoring** of storage conditions
- use of validated **test methods**
- adherence to predetermined **points of time** for testing
- **documentation** standards same as for routine QC
- continuous **trend evaluation**
- **Investigation** of atypical trends, out of spec / trend results
- **Communication** of atypical trends, OOS, OOT
  - íncl. qualified person
  - incl. supervisory authority (if significant)
- **Formal reporting** of study results
- If done at **contract laboratory**:
  - tech agreement (quality standards, delimitation of responsibilities)
  - controlled transport of samples

Permitted **Facilitations** for OGS Monitoring

- **Bracketing**, e.g.:
  - only smallest and largest pack size
  - only lowest and highest strength
- **Matrixing**
  - not every factor combination tested at all time points

- Applicability of **reduced designs** (i.e. bracketing a/o matrixing):
  - where **justified** (e.g. closely related formulae, by prior knowledge)
  - matrixing designs **statistically balanced** (cf. ICH Q1D)
  - design should have ability to adequately **predict shelf life**
    - a.o. dependant on variability of applied test methods
  - generally not for **drug substances**

8. ICH Q10 – Pharmaceutical Quality System (PQS)

ICH Q10 – current legal status in EU

- Harmonised version **adopted** (stage 4 of formal ICH process) by EU, US, and JP in June 2008
  [*in EU: cf. EMEA/CHMP/ICH/214732/2007*]

- **Implementation** in EU initiated, way still under discussion
  - e.g. revision of chapters 1 and 2 of EC GMP Guide Part I?

- Will **not** become **mandatory**
- **Optional** use should facilitate innovation and continual improvement
- No specific Q10 **inspections** nor **certification** intended

ICH Q10 – What is novel? (1)

- Proposal of a **model** for a pharmaceutical quality management system (**PQS**)
- Based on **ISO 9000 series** QM thinking
- PQS designed for entire **product lifecycle**
  - can be applied to APIs *and* products
  - incl. development, use in clinical trials, tech transfer, discontinuation, etc.
- **Knowledge management** recognised as enabler
- **Quality risk mangement** recognised as enabler
- **Quality manual** – specification of (minimum) contents
- Specification of **management responsibilities**, e.g.
  - Quality policy, quality planning, resource management
  - Internal communication
  - Outsourced activities and purchased materials
  - Change of product ownership

ICH Q10 – What is novel? (2)

- Specification of the **system elements** of the PQS:
  - Process performance and product quality **monitoring** system
  - Corrective and preventive action (**CAPA**) system
  - **Change management** system
  - **Management review** of process performance and product quality
- **Level of effort, formality** and **documentation** dependent on lifecycle stage (e.g. development ≠ commercial manufacturing)
- Obligation to **continually improve** the quality system

ICH Q10 - Objectives

- Complement and serve as a **bridge** between regional GMP regulations
- Promote consideration of **all stakeholders** for product realisation
- Enable use of ICH Q8 and Q9 → facilitate **innovation**
- Promote a **state of control** for process performance + product quality
- Facilitate **continual improvement** across entire product lifecycle
- Facilitate appropriate levels of **regulatory scrutiny**, dependent on:
  - Product and process understanding (ICH Q8)
  - Results of quality risk management (ICH Q9)
  - Effectiveness of the pharmaceutical quality system (ICH Q10)

Potential Opportunities by Establishing an Effective PQS according to ICH Q10

- PQS (Q10) alone
  - Increase of risk based approaches for regulatory **inspections**
- PQS + process understanding (Q8) + Quality Risk Mgt (Q9)
  - Increase of risk based approaches for regulatory **inspections**
  - Facilitate science based pharmaceutical quality **assessment**
  - Optimise science and risk based **post-approval change** processes to maximise benefits from innovation and continual improvement
  - enable innovative approaches to **process validation**
  - establish **real-time release** mechanisms

Up for discussion
Have you got any …?

- … questions?
- … remarks?
- … recommendations?

Teşekkür ederim!

- … for your attention
- … for your contributions