EU GMP Requirements

- Quality Systems -

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Biodata of the speaker

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- 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
  - 2\(^{nd}\) focus on real-life (EU inspector’s life …) **interpretations**
  - (3\(^{rd}\) 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


- 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 at 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 

- **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

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
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 significant 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 Requiring 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 occurrence

- **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
  - incl. 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 management** 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