aqpa – Vereinstreffen
15. Okt. 2014, Wien

EU-GMP-Richtlinie
Part II – Basic Requirements for Active Substances used as Starting Materials

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History

- **ICH Richtlinie Q7** – Nov. 2000
- EU GMP-Richtlinie Anhang 18 – Juli 2001
- **EU GMP-Richtlinie Teil II** – Okt. 2005
  - Um u.a. der Richtlinie 2001/83/EC bzw. deren Ergänzungen zu entsprechen
  - Anhänge gelten nun auch sinngemäß für APIs
- **Ergänzung Quality Risk Management** – Juli 2010
  - Damit im Einklang mit der ICH Richtlinie Q9
  - Cave: Damit aber mehr Anforderungen als die ICH Richtlinie Q7
- **Eher formale Anpassungen** – Sep. 2014
  - Keine „Public Consultation“

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Änderungen – Sep. 2014

- **Mögliche Auswirkungen**
  - Kein Verweis mehr auf Teil 1, falls Anhänge noch nicht angepaßt sind
  - **Ausnahme (wie bisher): Sterile Wirkstoffe**
    - Part II gilt nur bis zu dem Punkt **unmittelbar vor der Sterilisation** des Wirkstoffs
    - Die Sterilisation und die aseptische Aufbereitung steriler Wirkstoffe werden nicht abgedeckt, hier gilt der Anhang 1 der EU-GMP-Richtlinie
- **Rein formal**
  - Verweis auf die EU-GDP-Richtlinie für APIs
  - Verweis auf QRM im Teil 3 statt auf den Anhang 20

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Definition Wirkstoff – EU-Richtlinie

- An “Active Substance Starting Material” is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is **incorporated as a significant structural fragment into the structure of the active substance**.
- The manufacturer should designate and document the **rationale** for the point at which **production of the active substance begins**.
- For synthetic processes, this is known as the point at which "Active Substance Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc), this **rationale** should be established on a **case-by-case basis**.

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Definition Wirkstoff – EU-Richtlinie

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging

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Definition Wirkstoff – EU-Richtlinie

- The term **Active Pharmaceutical Ingredient** (API) is used repeatedly and should be considered **interchangeable** with the term "**Active Substance**".
- Active Pharmaceutical Ingredient (API) (or Drug Substance)
  - Any substance **or mixture of substances** intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
- **Cave: Manche Behörden erkennen Mischungen nicht an**
  - -> Herstellung gemäß EU-GMP-Richtlinie Part I

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Definition Wirkstoff - Österreich

- **AMG**
  (4a) „Wirkstoffe“ sind Stoffe **oder Gemische von Stoffen**, die dazu bestimmt sind, bei der **Herstellung eines Arzneimittels** verwendet zu werden und bei ihrer Verwendung in der Arzneimittelherstellung zu arzneilich **wirksamen Bestandteilen** des Arzneimittels zu werden.
- **AMBO**
  (6) Die in dieser Verordnung enthaltenen Bestimmungen über die
  - 1. pharmazeutische Qualitätssicherung,
  - 2. allgemeinen Anforderungen an die Betriebsorganisation und das Personal,
  - 3. Betriebsräume und Ausrüstung, 4. Dokumentation,
  - 5. Herstellung und Qualitätskontrolle, 6. Tätigkeiten im Auftrag und
  - 7. Lagerung, Lieferung, Transport und Verkehrsfähigkeit

  gelten sinngemäß für Betriebe, die ausschließlich Wirkstoffe herstellen, kontrollieren oder in Verkehr bringen.

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2.1 Quality Management - Principles

- 2.19 To achieve the quality objective reliably there must be a comprehensively designed and correctly **implemented quality system incorporating** Good Manufacturing Practice, Quality Control and **Quality Risk Management.**

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2.2 Quality Risk Management

- 2.20 Quality risk management is a **systematic process** for the **assessment, control, communication and review of risks** to the quality of the active substance. It can be applied both proactively and retrospectively.
- 2.21 The **quality risk management system** should ensure that:
  - the evaluation of the risk to quality is based on **scientific knowledge**, experience with the process and ultimately links to the **protection of the patient** through communication with the user of the active substance
  - **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 Part III of the GMP guide**.

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QRM - International Conference on Harmonisation

On the ICH Q9 document slides are available on:

Executive summary for regulators and industry
Background
History
Content
Tools - overall notes
↳ Basic Risk Management Facilitation Methods
↳ Failure Mode Effects (Criticality) Analysis (FMEA & FMECA)
↳ Fault Tree Analysis (FTA)
↳ Hazard Analysis and Critical Control Points (HACCP)
↳ Hazard Operability Analysis (HAZOP)
↳ Preliminary Hazard Analysis (PHA)
↳ Risk Ranking and Filtering
↳ Supporting Statistical Tools
↳ Combination of Tools

http://www.ich.org/products/guidelines/quality/q9-briefing-pack/briefing-pack.html

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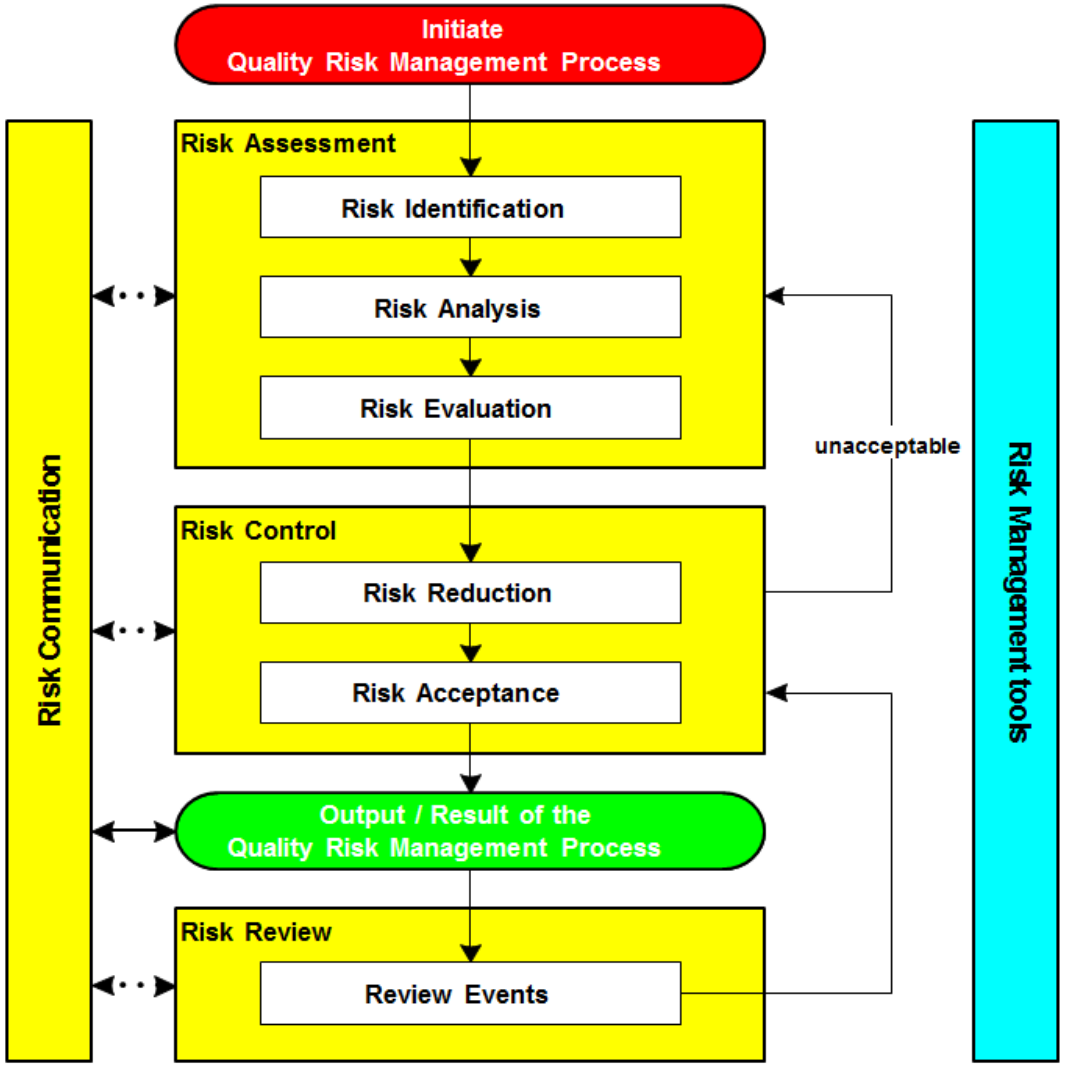
QRM – Anwendungen

- Empfehlung der ICH zur Anwendung von QRM
  - Documentation
  - Training and education
  - Quality defects
  - Auditing / Inspection
  - Periodic review
  - Change management / change control
  - Continual improvement

QRM - Prozess



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QRM – Auswahl der Methoden

- Supports **science-based decisions**
- A **great variety** are listed but other existing or new ones might also be used
- **No single tool is appropriate** for all cases
- Specific risks do not always require the same tool
- Using a tool the **level of detail** of an investigation will vary according to the risk from case to case
- **Different companies**, consultancies and competent authorities may promote use of **different tools** based on their culture and experiences

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Diskussion

- **Fragen?**
- **Ergänzungen?**
- **Anmerkungen?**

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