Regulatory Expectations for GMP: What’s Happening

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Topics

• Background for changes and expectations of regulatory guidance for GMP

• Evaluation of European Medicines Agency (EMA) Regulatory Guidances

• US Trends and Expectations

• Challenges and recommendations

• Questions
The regulatory picture for patient protection and control of cross contamination

- “There shall be separate or defined areas or such other control systems for the firm’s separation as necessary to prevent contamination” (FDA 21 CFR.42)

- “Cross-contamination should be avoided by appropriate technical or organizational measures. The appropriate measures should be determined following a quality risk assessment...” (EU Guide to Good Manufacturing Practice)

- “Dedicated production areas....should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins. The use of dedicated production areas should also be considered when material of infectious nature or high pharmacological activity or toxicity is involved....unless validated inactivation and/or cleaning procedures are established and maintained.” (ICH Q7)

Ensure safety of human patients exposed to residual active substances via medicinal products
EMA Guidances

• EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use
  – Chapter 3: Premises and Equipment
  – Chapter 5: Production

• Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
  – EMA/CHMP/CVMP/SWP/169430/2012
  – Committee for Medicinal Products for Human Use (CHMP)
  – Committee for Medicinal Products for Veterinary Use (CVMP)
• Measures to prevent cross contamination should be commensurate with risks

• Quality Risk Management principles should be used to assess risk

• May be necessary to dedicate premises and equipment for manufacturing and/or packaging to control risks
  – Risk cannot be adequately controlled by operational or technical means
  – Scientific data from toxicological evaluation does not support a controllable risk
  – Relevant residue limits derived from tox evaluation cannot be satisfactorily determined by validated analytical method
• 17: Production of non-medicinal products should be avoided in areas of medicinal product manufacturing, but may be justified based on risk management and toxicology

• 18: Contamination of a starting material or of a product by another material or product should be prevented, i.e. accidental cross-contamination

• 19: Prevent cross contamination by attention to designe of premises and equipment

• 20: Quality Risk Management process (including a potency and toxicological evaluation) should be used to assess and control cross contamination risks

• 21: Outcome of QRM should be basis for determination of technical and organizational measures to control risks

Improve guidance on prevention of cross contamination and to refer to toxicological assessment.
EMA Guidances: Chapter 5 (Sections 27-30)

New section on qualification of suppliers to reflect legal obligations of manufacturing authorization holders to ensure active substances are manufactured according to GMP.

• 27: Selection, qualification, approval, and maintenance of suppliers of starting materials, including purchase and acceptance, should be documented as part of pharmaceutical quality system
  – Supervision aligned with level of risk including supply chain complexity and final use of material
  – Staff must have current knowledge of the suppliers, supply chain, and associated risks

• 28: Quality requirements established by manufacturer for starting materials should be discussed and agreed on
  – All aspects should be documented in a formal quality agreement or spec
• 29: Approval and maintenance of suppliers of active substances and excipients
  – Supply chain traceability for entire production cycle should be formally assessed and periodically verified
  – Traceability records should be available
  – Audits for confirmation of performance to GMP and distribution

• 30: Each delivery of starting material require containers to be checked for integrity of packaging, including tamper evident seal where relevant and for correspondence between delivery note, purchase order, supplier’s labels and approved manufacturer/supplier information
EMA Guidances: Chapter 5 (Sections 35-36)

- **35**: Manufacturer of finished products are responsible for testing of starting materials as described in marketing authorization dossier
  - Minimum: identification testing

- **36**: Rationale for outsourcing testing should be justified and documents
  - Distribution controls
  - Audits
  - Certificate of Analysis
  - Manufacturer experience with supplier
  - Periodic testing

Clarify and harmonize expectations of manufacturers regarding testing of starting materials.
• 71: Manufacturer report to manufacturing authorization holder (MAH) any constraints in operations that may also result in abnormal restriction in supply
  – Timely reporting
  – Relevant competent authorities must be notified
  – Legal obligations
Health-based Exposure Limits
“The use of arbitrary non-health-based limits is not scientifically justified if sufficient data are available to derive ADEs and compound-specific, scientifically-derived, health-based values should be established whenever possible.”
The ADE value is a potent tool in product quality and workplace safety.
• Medicinal products provide benefit to intended patient and cross contaminants provide NO benefit to intended patient

• Presence of contaminants should be managed according to risk posed which in turn are related to levels that can be considered safe for all populations

• Health-based limits through derivation of a safe threshold value should be used to identify the risks posed
  
  – Structured scientific evaluation to derive Permitted Daily Exposure (PDE) or Threshold of Toxicological Concern (TTC) using all available toxicological and pharmacological data

• Objective to recommend an approach to review and evaluate these data to determine threshold values to align with Chapters 3 & 5 of GMP guidelines
Guideline for determination of health-based exposure limits: calculation of a PDE

“Represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose for a lifetime.”

• Hazard identification by reviewing all relevant data

• Identification of “critical effects”

• Determination of a no-observed-adverse-effect level of the findings that are considered to be critical effects

• Use of adjustment factors to account for various “uncertainties”
Guideline for determination of health-based exposure limits: calculation of a PDE

\[
PDE = \text{NOAEL} \times \text{Weight Adjustment} \times F1 \times F2 \times F3 \times F4 \times F5
\]

- **F1**: Extrapolation between species (factors between 2 and 12)
- **F2**: Variability between individuals (factor of 10)
- **F3**: Repeat-dose toxicity studies of short duration (<4 weeks) (factor of 10)
  - Factor value may vary based on individual company practice
- **F4**: Severity of toxicity (e.g. non-genotoxic carcinogenicity, developmental tox) (factor of 10)
- **F5**: Availability of no-effect level (factors between 1-10)
Guideline for determination of health-based exposure limits: adjustment factors of a PDE using non-clinical data

• Choice and use of adjustment factors should be justified
  – Deviations from default values may be accepted if adequately and scientifically justified

• Additional “modifying” factors to address additional “uncertainties” may be applied
  – Must be supported by literature or testing data
  – Adequate (and scientifically appropriate) discussion to support use of the additional factor(s)

Ensure that all rationale/justifications for conclusions and assessments are scientifically justified, cogent, easily understood by non-toxicologist, and well documented.
Guideline for determination of health-based exposure limits: adjustment factors of a Permitted Daily Exposure (PDE) using clinical data

- Good quality human clinical data very relevant
- Clinical pharmacological data should be considered to identify critical effect
- Adverse effects as reported in clinic or commercial use should be assessed and applied to the assessment if appropriate

If most critical effect identified to determine health-based limit is based on pharmacological or toxicological effects based on human, not animal, data use of the PDE formula may be inappropriate and a substance-specific assessment of the clinical data may be used.
Guideline for determination of health-based exposure limits: special considerations for bioavailability & genotoxicity

- Differences in bioavailability among routes of administration
  - Respirable fraction important (e.g. large vs. small molecules)

- Genotoxicity potential
  - Non-threshold related genotoxicants: Pre-defined levels of acceptable risk using TTC (Threshold of Toxicologic Concern) of 1.5 μg/person/day
  - Genotoxic active substances with sufficient carcinogenicity data: compound-specific risk assessment required
  - Genotoxic pharmaceutical substances with sufficient evidence of threshold-related mechanism: use PDE approach
Guideline for determination of health-based exposure limits: special considerations for highly sensitizing materials

- Dedicated facilities required for manufacture of active substances and medicinal products with high sensitizing potential for which scientific data do not support an acceptable level of exposure or risk associated with the handling of the product at the facility cannot be adequately controlled by organizational or technical measures.
  - High frequency of sensitizing occurrence in humans
  - High probability of high sensitization rate in humans based on animal data or other validated studies
  - Severity of reactions should be included in weight of evidence

Adverse Event reporting, clinical experience, and occupational physicians/health staff are good sources of data for this end point.
Guideline for determination of health-based exposure limits: special considerations for reproductive and developmental toxicity

- Lack of animal data limits power of assessment for early development materials
- Lack of animal data may also exist for authorized medicinal products
- Use of read-across data may be useful
- Application of additional adjustment factor may be required with justification
Guideline for determination of health-based exposure limits: therapeutic macromolecules and peptides

• Known to degrade or denature when exposed to heat and/or extreme pH rendering molecule inactive
  – What is knowledge of degradants?
  – Does degradant profile change with each molecule or within each molecule process?
  – Do these products carry different toxicity profiles than the active?

• Determination of health-based limits (PDEs) may not be required
  – What is your monitoring target?
ADE/PDE Life Cycle

**Hazard Band Category**

- **Early/Late Stage Dev**
  - IND
  - P1
  - P2
  - P3
  - LAUNCH

**Workplace Safety**

- Pilot tox (SMs)
- MoA
- Molecule attributes

**Occupational Exposure Limit**

- GLP Tox & PK (1-3 mo)
- GLP Safety pharm
- MoA
- Molecule attributes

**Acceptable/Permitted Daily Exposure**

- Ph 1 Data
- Clinical safety & PK
- GLP Tox (3-6 mo)
- Repro Tox (if needed)
- MoA
- Molecule attributes

**Product Quality**

- Post Marketing Data
Guideline for determination of health-based exposure limits: investigational medicinal products

- Difficult to derive PDE due to lack of sufficient data during Phase I/II, but still making GMP material

- May set PDE-like value using alternative strategies or default values (e.g. tiered TTC)

- As datasets develop PDEs should be established as soon as feasible
Challenges: investigational medicinal products

- Lack of data can render very low limit values
- Availability of analytical methods may be limited
- Programs change quickly
- Quality needs to be part of the process
  - Acceptability of limits
Summary: reporting the PDE determination

- Complete comprehensive literature search (e.g. handbooks, literature, internal data, monographs, electronic scientific databases)
  - Search strategy and results must be clearly documented
- Provide clear discussion of critical endpoints of concern and rationale for choice of endpoints and adjustment factors
- Pivotal animal and human studies used in derivation should be sourced to original reference (not summary documents) and reviewed regarding quality
- Provide overview of assessment for GMP inspectors
  - Initial page of each assessment should have summary/abstract
Implementation of guidance: in accordance of Chapters 3 and 5 of GMP Guide

- Medicinal substances introduced first time into shared manufacturing facility
  - 6 months from publication of guideline
  - 1 December 2015

- Medicinal products already produced in shared manufacturing facilities
  - 1 year after publication of guideline for facilities of human products where both human and veterinary products produced
  - 2 years after publication of guideline for facilities solely producing veterinary products
FDA Activities

• Implementation of Acceptable Daily Exposure (ADE) for control of cross contamination/cleaning validation evident
  – Inspection driven

“Please provide the information on the risk categorization of the ‘X’ Drug Substance with respect to toxicity in accordance with the ISPE Baseline Guide: “Risk-Based Manufacture of Pharmaceutical Products”, volume 7 (2010).”
Summary

• GMP guidelines are focusing on toxicological assessments for risk management of cross contamination and other manufacturing activities

• Toxicological assessments require professionals with strong expertise to perform these types of hazard/risk assessments

• Implementation of the use of PDE/ADE requires
  – Strong business process and plan
  – Cross functional teams
  – Documented processes
  – Training and education of all involved, including the regulatory professionals
Doing now what patients need next