Tools to address EMA manufacturing guidelines and hazard assessment for development and CMC timelines

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Topics

• Background for changes and expectations of regulatory guidance for GMP
• Hazard bands in early development
• CMO communications
• Collaborative industry efforts
• Summary
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)
Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

• “Outlines how the data on which the threshold value is derived should be presented in order to achieve a clear and harmonious approach across pharmaceutical industry”

• “Determination of health based exposure limits for a residual active substance is based on the method for establishing the so-called Permitted Daily Exposure (PDE)…”
  – Appendix 3 of ICH Q3C (R4) “Impurities: Guideline for Residual Solvents”
  – Appendix 3 of VICH GL 18 on “residual solvents in new veterinary medicinal products, active substances and excipients (Revision)”
Guideline for determination of health-based exposure limits: investigational medicinal products

• Difficult to derive ADE/PDE due to lack of sufficient data during Phases 1 and 2

• Some facilities may be manufacturing IMP in GMP equipment
  – Presents challenge for appropriate cleaning practices
    • Development facilities, CMOs
  – Internal policies dictate requirement for ADE if manufacturing in GMP equipment

• Guideline accepts ADE/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
- Workplace safety assessments
The ADE/PDE value is a potent tool in product quality and workplace safety.
## Health Hazard Categories

<table>
<thead>
<tr>
<th>HHC</th>
<th>Expected range of IOEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$&gt; 100 , \mu g/m^3$</td>
</tr>
<tr>
<td>2</td>
<td>$10–100 , \mu g/m^3$</td>
</tr>
<tr>
<td>3A</td>
<td>$1–10 , \mu g/m^3$</td>
</tr>
<tr>
<td>3B</td>
<td>$0.05-1 , \mu g/m^3$</td>
</tr>
<tr>
<td>4</td>
<td>$&lt; 0.05 , \mu g/m^3$; exposure target</td>
</tr>
<tr>
<td></td>
<td>$0.005 , \mu g/m^3$</td>
</tr>
<tr>
<td>D</td>
<td>$10 , \mu g/m^3$</td>
</tr>
</tbody>
</table>
Hazard Band/ADE Life Cycle

**Hazard Band**

**ESR/LSR**

Candidate Selection

**IND**

**Ph 1**

**Ph 2**

**Ph 3**

Launch

**Request band ≥3 mo prior to CS**

**Request ADE prior to Ph 3 campaign (≥6 mo)**

- Pilot tox (SMs)
- MoA
- Molecule attributes

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

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

- Ph I Data

- Post Marketing Data
What is happening before Phase 1?

- Handling large number of unstudied molecules
- Handling varying amounts/volumes of substances
- Single use or repeat use handling
- Contract manufacturing selection and utilization
- “Default” hazard bands may not be protective

Early Development Compound Groups: a potential tool for IMP
Preliminary review of available OELs

Example of EDCG based on API Class

Percent (%)

Blood Formation, Coagulation, Thrombosis
Central Nervous System
Cardiovascular
Autonomic System
Electrolytes, Caloric & Water Balance
Respiratory Tract
Gastrointestinal

EDCG D
EDCG C
EDCG B
EDCG A
# Early Development Compound Groups (EDCG): Large Molecules

<table>
<thead>
<tr>
<th>EDCG</th>
<th>Large Molecule Example Material Types</th>
<th>Handling Practice Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>• Large molecule (antibody only, including naked antibodies for ADCs/TDCs)</td>
<td>2</td>
</tr>
</tbody>
</table>
| B    | • Antibodies/fusion proteins with direct agonistic mechanism of action  
• T-cell dependent bispecific antibodies with low antigen expression on normal tissues or low number of target cells | 3A                          |
| C    | • T-cell dependent bispecifics (TDB)  
• T-cell dependent bispecific antibodies with high antigen expression and/or high number of target cells  
• Highly potent stimulatory CIT molecules | 3B                          |
| D    | • None identified to date | 4                           |
**Early Development Compound Groups (EDCG): Small Molecules**

<table>
<thead>
<tr>
<th>EDCG</th>
<th>Small Molecule Example Material Types</th>
<th>Handling Practice Categories</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>• Non-oncology</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>• Antibiotic component of ADC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Antibiotic conjugated to antibody</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>• Immune modulators</td>
<td>3A</td>
</tr>
<tr>
<td></td>
<td>• Thrombolytics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Non-endocrine hormones</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Protein kinase inhibitors (PKI) intended for non-oncology indications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Oncolytics including targeted pathway inhibitors intended to treat cancer (non-PKI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Anticipated reproductive toxicants based on MOA</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>• Oncology chemotherapeutics (alkylating agents, DNA intercalators)</td>
<td>3B</td>
</tr>
<tr>
<td></td>
<td>• Endocrine disruptor hormones</td>
<td></td>
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<tr>
<td></td>
<td>• Vitamin D analogs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Protein kinase inhibitors intended to treat cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cytokines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Antibody drug conjugates (ADC)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>• Toxin component of ADC (“Warhead”)</td>
<td>4</td>
</tr>
</tbody>
</table>
Hazard Band/ADE/SDS Life Cycle

Apply to Active Pharmaceutical Ingredients and Isolated Process Intermediates

- Product Quality Systems expectations
  - Regulatory expectations
  - In-licensed materials
Genentech CMO Communication Tool: facilitating manufacturing partnerships

- Used to communicate toxicology information to CMOs
- Replaces communication of HHC documentation to CMOs to improve protection of sensitive, confidential information in development
- Delivered at Candidate Selection with HHC and chemical-specific SDS/transportation classification
Collaborative industry effort

• Regulatory, operational, and technical aspects of setting Acceptable Daily Exposures (ADEs)
  – Workshop
  – “Teaser” article in Contract Pharma (Sept 2016) (contractpharma.com)
  – 10 peer-reviewed articles in Regulatory Toxicology and Pharmacology (special supplement-electronically available)

• Harmonization effort elucidate best practices

• Educational tool for regulators, non-experts, manufacturers

• Over 20 toxicologists from industry, academia, or consulting engaged

• Funded by Genentech Product Quality & Occupational Toxicology
Collaborative industry effort


Summary

• GMP guidelines have new focus on toxicological assessments for risk management of cross contamination and other manufacturing activities

• Assessments for IMP require creative approaches to protect workers and inform manufacturing activities

• 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