Development and Piloting of High Potent API Processes

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Topics

- Goal of Pharmaceutical Technical Development Chemical Actives (PTDCA)
- Challenges of High Potent APIs in Process Development
- HPAPI Containment Philosophy in Roche/Genentech
- Case Study
Goal of PTDCA

*Develop robust, safe, cost effective Small Molecule API processes from clinical to commercial scale (IND to NDA)*
Roche / Genentech Pipeline

Industry Leader in Oncology  =  High % of HPAPIs and ADC toxins in the Development Pipeline
HPAPI Containment within Roche /Genentech

- PTDCA groups in Switzerland (Basel) and US (Florence, SC) for Small Molecules

- A gap was recognized in bridging lab development and Piloting/Scale-up of High Potent APIs with CTM manufacture in the Supply Centers

- Facilities were constructed at both Development sites to handle laboratory process development and initial scale-up of High Potent API processes
Challenges of HPAPIs in Process Development

*Qualitative and Quantitative*

- **Quantitative**
  - Internal procedures don’t distinguish between Labs / Pilot Plant (short mfr lifetime) and regular production facilities (long mfr lifetime)
  - Little or no toxicology information available to assess compounds in Development
  - High capital investment

- **Qualitative**
  - Slow pace of development work (gowning, facility procedures, etc.)
  - Resource intensive (chemists can not work alone)
  - Chemists avoid HPAPI facilities if at all possible
Roche Health Hazard Category (HHC) Scheme Implemented

<table>
<thead>
<tr>
<th>Category</th>
<th>Applicable Airborne Concentrations</th>
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</thead>
<tbody>
<tr>
<td>HHC 1</td>
<td>&lt; 100 μg/m³</td>
</tr>
<tr>
<td>HHC 2</td>
<td>&lt; 10 μg/m³</td>
</tr>
<tr>
<td>HHC 3A</td>
<td>&lt; 1 μg/m³</td>
</tr>
<tr>
<td>HHC 3B</td>
<td>&gt; 0.05 μg/m³, &lt; 1 μg/m³</td>
</tr>
<tr>
<td>HHC 4</td>
<td>&lt; 0.05 μg/m³</td>
</tr>
<tr>
<td>HHC D (default)</td>
<td>&lt; 10 μg/m³</td>
</tr>
</tbody>
</table>
Inherent Problem of Process Development: Little or No Biological Information Known

• Assumptions made:
  – Band assignment made by the Roche Industrial Hygiene Committee, but based on limited or no information. Analogous compounds or mechanism of action often used for Band assignment, and typically conservative.
  – Biological activity (including potency) is not present until most or all the structural moieties are present in the molecule. Most process intermediates were considered Band D (control to 10 µg/m³).
  – Lab personnel were protected to some degree by scale.
Roche K1, K15 Directives

• Compounds are assigned HHCs (1, 2, 3A, 3B, 4) or OELs based on criteria established by Roche Industrial Hygiene Committee (RIHC)

• Periodic SHE Audits to confirm containment and safety practices at Roche sites

• Primary reliance on engineering controls of all unit operations contain to below the OEL for a compound without the use of (PPE)

No relaxation of exposure limits for labs or Pilot Plant
Florence Facility - HAS Mini-Plant

User Requirements

• Facility to be used for the manufacture of non-sterile Small Molecule APIs and Intermediates

• Facility to be used as a multi-product plant
  – Wide range of chemical capabilities
  – Critical unit operations:
    • Batch reaction and extraction
    • Distillation
    • Crystallization
    • Solid isolation and drying

• Composed of 2 separate work areas, a Laboratory and Manufacturing suite, both capable of GMP production

• Containment capabilities sufficient to meet $\leq 50 \text{ ng/m}^3$ (Roche HHC 3B).
Florence Facility - HAS Mini-Plant
User Requirements (cont’d)

• Containment Requirements
  – Primary
    • Closed process and transfer equipment
    • Contained handling of solids in isolators
  – Secondary
    • Separation of HAS facility from common areas by air lock
    • Negative pressure cascade leading into production area with interlocks
    • Down flow hoods
    • Single pass HEPA filter air

• Cleanability
  – Room surfaces / equipment
  – Bag-in/bag-out filter exchanges
HAS Laboratory Layout

HAS LABORATORY

MATERIAL AIRLOCK

GOWN-IN/GOWN-OUT

CORRIDOR

P5

P4

PF

PG
HAS Laboratory Process Flow

Diagram showing the layout of a laboratory process flow with various labeled areas such as P5, P4, PF, PG, chase, tray dryer, walk-in down flow booth, transfer port, isolator, bench top down flow booth, filter, under counter refrigerator, under counter dish washer, door vision panel, work station, wall cabinet, stool, window, door, decon shower, sink, waste, and corridor.
Mini-Plant Layout
Mini-Plant Process Flow
Mini-Plant Pressurization
Case Study: Basel Facility

Toxin for ADC

The Process

• 4-Step process to a macrocyclic toxin (small molecule portion of an ADC): 1) hydride reduction, 2) esterification, 3) amide formation, and 4) reductive cleavage of a disulfide.

The Issue

• Step 1: Hydride reduction step led to problematic over-reduced impurity. Alternate reduction methods/reagents needed to be evaluated.

• Substrate was classified as HHC 4 (required containment below 50 ng/m³).
Parameters of High Potent Lab Facility

• Lab personnel had to gown and enter facility through an air lock. Lab equipment was passed through a separate air lock. Limits on equipment that could be removed from the facility.

• At least two operators needed to be in the lab when facility was being used.

• When downflow hood was used, double gloved hands could not be removed from hood, so second operator would pass needed equipment to the hood.

• Lengthy procedures for cleaning, inerting gloveboxes, etc.
Case Study: cont’d
Toxin for ADC

Workflow

• Model compounds (non-macrocycles) were evaluated in a standard development lab using alternate and modified hydride reducing agents with some success, however results did not translate to the actual substrate when run in the High Potent facility.

• Enzymatic route proposed, however the size of the macrocycle eliminated using model compounds (couldn’t model the substrate in the active site).

• 96 enzymes screened, frequent breaks needed, 2 operators … estimated 3X as long to do screening in the High Potent Facility
Questions to the Audience – Industry Perspective

• How much weight does categorization carry on early clinical compounds?
• Should default containment limits be considered within the industry?
• How much consideration should be made for exposure in development (short term) vs exposure in commercial manufacture (long term)?
Doing now what patients need next
HAS Mini-Plant
HAS Mini-Plant
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