Biopharmaceutical Multi-Product Facilities: the Challenges and the Solutions.

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Agenda:

• The Past
• The Business Case & Future.
• The Challenges:
  • Technical;
  • Regulatory.
• Approaches to Meet those Challenges:
  • Quality Risk Management;
  • Single Use Approaches;
  • EBE Multi Purpose Use Concept Paper.
• Conclusions.
• Questions.
The Past:

- Dedicated, Stainless Steel rich Facilities for Block Buster Drugs.
- Typically Single Host Cell Type eg CHO or, *E. coli* but not both.
- Typically Dedicated Single purpose Suites where Product Change over is slow and Individual Products fully temporally segregated.
- Cost not a Core Issue!
The Business Case for MPF:

- Bringing new medicines faster to the patient.

- Less Capacity Needed:
  - Increasing Titers;
  - More Products but less Blockbusters;
  - Personalised Medicine.

- Cost Issues:
  - Cost Pressures throughout the Supply Chain;
  - The High cost of Biopharmaceuticals;
  - The Introduction of Biosimilars.

- Technology Issues:
  - Flexible, Modular Facilities;
  - Disposable Components & Facilities.
Long-standing facility design paradigms are changing -

• Host cell changeovers, multi-host and/or biohazard levels in same facility;
• Non-dedicated suites where product changeovers can occur more often and more rapidly;
• Sharing of suites to manufacture different products concurrently in closed systems;
• Sharing of suites between clinical and commercial manufacturing;
• Rolling changeovers, changeover out-of-place.
The Technical Challenges:

- **Operational Complexity:**
  - Multi Product;
  - Multi Phase;
  - Multi Platform.

- **Engineering Complexity:**
  - Hardware Issues;
  - Software & Automation Issues.

- **Toxicological Complexity of Contaminants:**
  - Pharmacological Reactivity;
  - Immunological Reactivity.
The Regulatory Challenges I:

- Focus on EU Requirements for simplicity.... but...
- Key Objective in all jurisdictions is to ensure the quality of each product is not compromised by the other(s) being co-manufactured in the facility.
- Definition: Draft Annex 2 - Multi-Product Facility: A facility that manufactures, either concurrently or in campaign mode, a range of different biological medicinal substances and products and within which equipment train(s) may or may not be dedicated to specific substances or products.
- Manufacture in a multiproduct facility may be acceptable where the following, or equivalent, considerations and measures are shown to be an effective part of the control strategy to prevent cross-contamination....see later.
- Dedicated Facility requirements under review at moment.
A Regulatory Perspective…..Dr Lorcan Allen of IMB Member of the EMA Safety WP re the review of Dedicated Facility requirements….Great Summary.

Dedicated Facility Review commenced in 2005 and a 2009 Update from EMA states:

- “for other products, manufacturers introducing a product into shared facilities should carry out an assessment of all relevant product and process characteristics to evaluate whether it is suitable for production in shared facilities. This assessment should include input from a toxicologist. Where the product has known sensitizing potential, or is highly potent or toxic, the Supervisory Authority should be consulted to discuss the manufacturer’s risk management measures.” (EMA/INS/GMP/809387/2009).

- Dr Allen described the Toxicologist’s approach in more detail: Formula for defining acceptable residue level for different product classes….”no longer one size fits all”.

- Generic NOT Specific to Biopharmaceuticals but see new Annex 2
The Regulatory Challenges III:

- **Draft Annex 2 is Very Informative:**
  - Provides a **definition** of a Multi-Product Facility.
  - **Emphasises** the central role of **Quality Risk Management** under the Principles section where it states: *quality risk management principles are particularly important for this class of materials and should be used to develop their control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.*
  - **Provides Specific Criteria** (a) – (f) that: *Manufacture in a multiproduct facility may be acceptable where the following, or equivalent, considerations and measures are shown to be an effective part of the control strategy to prevent cross-contamination*

- But must also consider Annex 18 which has a number of relevant Sections.
- Complex….needing cross functional detailed planning.
The Regulatory Challenges IV - Specific Criteria:

**When Manufacture in a multiproduct facility may be acceptable:**

(a) Knowledge of key characteristics of all organisms in the same facility;
(b) Live organisms and spores are prevented from entering;
(c) Control measures to remove the organisms and spores before the subsequent manufacture of other products. Cleaning and decontamination for the organisms and spores should be validated including the HVAC system;
(d) EM specific for the organism conducted in adjacent areas during manufacture and after completion of cleaning and Decontamination;
(e) All items only moved within and removed from such areas in a manner that prevents cross contamination;
(f) Campaign-based manufacturing.
The Importance of QRM:

- Making multiple products in one facility requires QRM….if it did not exist you would have to invent it.
- QRM allows you to systematically evaluate all the issues (the RA step) and come up with specific customised solutions to those potentialities that you consider unacceptable (the Risk Mitigation step)
- It provides a framework for presenting those risks to the Regulatory Agency
- ICH Q7a Fermentation 18.38 “Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.”
II.4: QRM for facilities, equipment and utilities

Facility Needs: Risk Acceptance profile

<table>
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<th>Increasing Severity (Intrinsic Physiological and Biological API Properties)</th>
<th>Increasing Probability of Occurrence (product and process factors)</th>
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<tr>
<td>Normal multi-product facility with campaigning</td>
<td>Dedicated Building</td>
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<td>Most Appropriate ‘Minimisation and Containment’ Solution</td>
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<td>o Containment Isolators in conventional area</td>
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<td>o Dedicated suite (controlled dedicated access, HVAC, and technical area)</td>
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Disposables:

- Internal Project within Pfizer’s “Bio-process Plant of the Future” initiative:
  - “Evaluate cost/benefit as well as compliance (quality and regulatory) and technical feasibility of disposable equipment for commercial bio-processing”.

- Multidisciplinary internal team for period Dec 08 to Dec 09.

- Key Objectives were around better understanding of:
  - Our current usage of disposables?
  - Opportunities for a coordinated disposables approach in Company
  - The challenges (technical, regulatory, quality, procurement, engineering etc)

- Key themes included increased operational flexibility and reduced cost.
Single Use Time Line in Bio-Manufacturing Industry

Storage
- Up To 750L
- Up To 10,000L

Connections
- Tubing Welders
- Sterile Connectors
- Steamable Connections

Solid/Liquid Separation
(Centrifugation, Normal Flow or TFF)
- Sartorius Pall
- Millipore
- Unifuge

Mixing
- Hyclone
- HyNetics
- Levetech

Cell Culture
- Roller Bottles
- WAVE

Chromatography
- Xcellerex Hyclone
- GE Healthcare
EBE Multi-Purpose Use of Plants:

Published July 2010

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EBE Concept Paper - Table of Contents:

• References
• Purpose
• Scope
• Regulatory Aspects
• Methodology:
  • Segregation of Products
  • Risk Assessment:
    • Material
    • Environment
    • Equipment
    • Methods
    • People
• Cleaning
• Change-Over
EBE Concept Paper – References:

• References include EU GMPs, CFR and ICH.

• Therefore Scope of Applicability is Global.

• Scope states: “….applicable to any (bio)pharmaceutical manufacturing facility manufacturing commercial APIs in which additional API (commercial or, clinical) manufacturing processes are introduced.”
EBE Concept Paper – Purpose:

• Guidance on design and operational requirements to be considered when a new product enters the facility, in particular transition from a single product operation to a Multi product operation.
• A methodology described to control the associated risks.
• The risks will be unique to each transfer and “governed by the specific combination of product(s), process(es) and site design features…”
• Therefore, approach is to describe “all the points that should be considered…”
EBE Concept Paper - Regulatory Aspects:

• Complex, consider Early Communication.
• Consider Manufacturing AND Marketing Authorisations:
  • May be a Major Change (Type II in EU/CBE 30 in US);
  • May trigger Pre-approval GMP inspection.
• Type and Scope of Variation depends on:
  • Current Operating model for Facility (Single V Multi Product/Host);
  • Nature of new Product/Process;
  • Any Facility/Equipment Changes Being made.
• Must consider MAs of all products in Facility not only New Product.
• Generally no Comparability Exercise required.
1. Segregation of Products:
   - “…..appropriate controls to prevent cross contamination…”
   - Segregation is due to a combination of Soft (ie Procedural Controls) and Hard (ie Physical controls) Boundaries which together minimise risk of cross contamination.

2. Risk Assessment
3. Cleaning
4. Change-Over
EBE Concept Paper - Methodology II:

• 1. Segregation of Products:
• 2. **Risk Assessment:**
  • Risk Assess Overall Operating Model:
    • Campaign/Parallel Processing
  • Select appropriate Operating Model
  • Risk Assess Each of the Operating Steps
    • Consider Categories of Materials/Environment/Equipment/Methods/People
• 3. Cleaning
• 4. Change-Over
EBE Concept Paper - Risk Assessment - Equipment I:

• Closed Systems:
• Single Use/Disposable equipment:
• Dedicated Vs Shared Equipment
• Shared Equipment qualification/maintenance/calibration
• Automation
• Equipment Identification Practices

• NOT an Exhaustive List.....Should trigger further thinking relevant to your facility.
• 3. Cleaning:
  • Risk Assess Cleaning Processes/Validation
  • Cleaning Validation Strategy for New product based on data with this product.
  • Intervals for monitoring of cleaning and revalidations reassessed

• 4. Change-Over:
  • Clearly document processes and Procedures.
Conclusions:

- The Future is Flexible Multi Product Facilities;
- Requires experienced, skilled staff at all levels with broad understanding;
- QRM is a proven tool in documenting that all concerns have been adequately controlled;
- EBE Concept Paper provides an effective framework for using QRM as a Central Tool for achieving biotech manufacturing facility flexibility.
- Level of achieved flexibility is a function of:
  - The rigor of your risk management;
  - The effectiveness of your prospective engagement with BoH;

- Single Use Systems offers major benefits but with challenges around assuring consistent quality.
Questions:
Acknowledgements & References:

- **EBE Concept Paper – Multi Purpose Use of Plants (2010).**

- **Kristin Murray & Stephen Reich (Pfizer):**

- **Paul McCormac (Pfizer):**

- **Lorcan Allen (IMB):**

- **Stephan Ronninger (Roche):**

- **ISPE Risk Based Manufacture of Pharmaceutical Products – A Guide to Managing Risks associated with Cross Contamination (2010).**