Supporting the biopharmaceutical manufacturer –
A supplier’s perspective on Raw Material Management

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Regulatory Advocate

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Agenda

1. What raw materials does EMD Millipore supply?
2. Raw Material Management – Challenges and Critical Steps
3. Quality Assurance for Pharmaceutical Grade Chemicals
   3.1 EMPROVE Concept
4. Cell Culture Media– Coupling Raw Material Quality & DOE Approach
5. Filter Manufacturing Complexity – Managing Variability and Change
Access broader capabilities that span the entire drug research, development & production value chain

**EMD Millipore**

- Bioscience kits and reagents
- Process monitoring tools
- Lab & On site Services
  - Advanced lab instruments & consumables
  - Disposable manufacturing solutions
- Chromatography & Cell Culture media
- Pharmaceutical raw materials

**Biopharmaceutical Value Chain**
Creating an integrated solutions offering to biopharma customers

**Pharmaceutical Value Chain**
Enhancing EMD’s strong product offering to pharma customers

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**EMD**

**Millipore**
Process Solutions Business Unit
Innovation that transforms the way biological drugs are manufactured

Proven leader in helping customers manufacture biopharmaceutical drugs safely and efficiently and delivering transformational innovation solutions

Products & Services
- Filtration
- Chromatography
- Single-Use Manufacturing
- Cell Culture Media & Supplements
- Active Pharmaceutical Ingredients

Customer Value
- Most comprehensive solution
- Deep Applications expertise
- Engineering and Regulatory Services
- EMD’s chemistry with Millipore’s engineering expertise creates powerful R&D platform
Raw Material Management – Challenges and Critical Steps
## Challenges related to Raw Materials

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large number of components</td>
<td>Components include both chemically defined and complex ingredients, and animal/plant/bacterial derived materials.</td>
</tr>
<tr>
<td>Large number of suppliers</td>
<td>Requires considerable vendor oversight Some suppliers may have sub-suppliers</td>
</tr>
<tr>
<td>Traceability of raw materials</td>
<td>Global sourcing -- Some countries may not have very stringent quality practices. Are raw materials from different countries segregated/mixed?</td>
</tr>
<tr>
<td>Variability in raw materials</td>
<td>Even with stringent quality management in place, inherent variability in source materials.</td>
</tr>
<tr>
<td>Testing-related issues</td>
<td>Contaminants may not be homogenously distributed; therefore, detection is based on probability and low levels of virus may go undetected.</td>
</tr>
<tr>
<td>Materials impact</td>
<td>Materials may meet specifications; however, they may have a detectable impact on final drug product quality.</td>
</tr>
</tbody>
</table>
## Critical Steps in Supply Chain Management

<table>
<thead>
<tr>
<th>Area</th>
<th>Details</th>
</tr>
</thead>
</table>
| Supplier selection process   | Clearly define your requirements in terms of material specifications, quantity required  
Does the vendor have enough capacity to ensure uninterrupted supply?  
Quality and regulatory compliance  
Adherence to good distribution practices  
Procurement/cost: look beyond just cost  
Responsiveness and communication |
| Due diligence process        | Necessary for key and critical raw materials; Risk analysis; Include cross functional team; Review management history; Mergers and acquisitions; Sub-suppliers                                                                 |
| Quality Assessment           | Supplier/manufacturer questionnaire; Site-audits; TSE/BSE Assessment; Does the supplier use sub-suppliers?; cGMP compliance history; Quality agreement; Other: historical performance                                                                                  |
| Change Control               | Change control SOPs  
Mechanism for initiation of change, execution of change, review of change  
Change communication procedures |
| Supply Chain Security        | Procedures to ensure supply chain security  
Supplier changes in raw material sourcing as well as manufacturing process                                                                                                                             |
| Ongoing Monitoring and Evaluation | Review key performance indicators: delivery, audit observations, customer complaints, failures, etc, Re-audit frequency                                                                                     |
# Expected Profile of an Ideal Raw Material

<table>
<thead>
<tr>
<th>Ideal Raw Material</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe</td>
<td>Known safety profile</td>
</tr>
<tr>
<td>Consistent quality</td>
<td>Lot-to-lot consistency throughout its life cycle</td>
</tr>
<tr>
<td>Well-characterized</td>
<td>Known material quality</td>
</tr>
<tr>
<td>Well-defined product interaction</td>
<td>Known physico-chemical interactions</td>
</tr>
<tr>
<td>Compliant to regulatory requirements</td>
<td>US, European Union, Japan, other regulatory authorities</td>
</tr>
<tr>
<td>Continuous supply</td>
<td>Keeping consistent quality</td>
</tr>
<tr>
<td>Supply chain transparency</td>
<td>Get to know the supply chain</td>
</tr>
<tr>
<td>Manufacturer/vendor relationship</td>
<td>Open communication, auditing</td>
</tr>
<tr>
<td>Back-up supplier</td>
<td>Appropriately qualified</td>
</tr>
</tbody>
</table>
Quality Assurance for Pharmaceutical Grade Chemicals
Quality Assurance and Analytical Chemistry Today

Darmstadt and Gernsheim Germany Sites:

- Multiple analytical and QA departments
- QC + QA Pharmaceutics
- QC + QA Chemical Production

Chemical and Pharma Quality divisions with integrated management which includes a cross-section of core competencies

- Analytical Strategic Committee
- Analytical Chemistry Management Team
- Competence circles
- Common SOP System and GMP regulations (Validation Master Plan) for all Chemical Quality-units

November 15, 2012- Regulations discussed in this presentation are as interpreted by EMD Millipore only and are not meant to give official regulatory guidance
Pharmaceutical Starting Materials
Chemical Product Overview

Approximately 1000 Pharmaceutical chemicals
- Purchased as raw materials from suppliers
- Manufactured or chemically purified at EMD Millipore

Pharma raw material product range: Process chemicals, Excipients and API’s
- Solvents, Acids, Bases, Buffers
- Excipients for semi and solid dosage forms
- Antioxidants, Preservatives, Lubricants
- Active Pharmaceutical Ingredients
- Vitamins
- Minerals
- Amino Acids, Biochemical Products
- Food Additives, Fatty acids, Components of Essential Oils
- Pigments, Dyes

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Quality Assurance and Material Qualification

Five Basic Qualification Principles

For Raw Materials in Pharmaceuticals Supply Chain

1. Qualified raw material manufacturer
   Change control contracts, special EMD Millipore supplier specifications and quality requirements

2. Incoming material control
   Quarantine within warehouses and dedicated sampling facilities

3. Analysis and release
   Multi-pharmacopoeial specifications for each batch, specified parameters validated with analytical methods

4. Filling and end-control
   Dedicated cGMP filling plants, cleaning validation and packaging control

5. Distribution & Customer support
   Comprehensive regulatory info./support, Applications services

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Supplier Qualification

Over 800 different GMP products!
Characterized by dedicated GMP Quality Markers in SAP (eg., API, EXP, etc.)
Information for Supplier Qualification

Inquiry Check-List for Suppliers:

- Specification
- Test monograph
- Technical product data
- Material safety data sheet
- Packaging materials
- Manufacturing process (Flow-Chart)
- In-Process controls
- Impurity profile
- Stability data
- Batch size, batch definition
- Location of Manufacturing site
- Quality Management Questionnaire
- Certificate of Ph Eur (CEP)
- GMO
- Biological origin
- Residual solvents
- Aflatoxins
- Kosher-Certificate
- Halal-Certificate
- Allergens (food)

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Our answer to a market need

The EMPROVE® - concept
More than just chemicals….

Do you intend to be cutting-edge?

The raw material market for pharmaceutical manufacturing has changed. Certain regulations have been implemented. More change is going to happen.

EMD Millipore has always had its finger on the pulse of the time:
- Our main focus is and will remain on patient safety
- Besides our outstanding product quality…
- … our support includes all measures which help to improve patient safety

To explain it in detail…

We can support you at our best with creative solutions:
- GMP manufacturing of salts, buffers, solutions and even more…
- Safe packaging concepts & customized solutions
- Best in class regulatory documentation

Find out more about EMD Millipore’s Emprove® concept!
EMPROVE® – Designed to fulfill customer needs

**EMPROVE®**
- The top brand for (Bio)pharmaceutical production -

<table>
<thead>
<tr>
<th>EMPROVE® exp</th>
<th>EMPROVE® bio</th>
<th>EMPROVE® api</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient</td>
<td>Special Chemicals</td>
<td>Active Pharmaceutical Ingredients</td>
</tr>
<tr>
<td>- Described as excipient in line with CTD* Format</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Complete dossier including periodical update</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special Chemicals For the biopharmaceutical production process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General product features:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Endotoxins: tested</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Microbiology: tested</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Proteases: tested (partly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ACS* Reagent Standard: tested (partly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Components for Cell Culture:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Non-animal origin: verified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cell culture tested</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Manufactured acc. to ICH/Q7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Documentation (ASMF, CEP, DMF) available for pharmaceutical approval</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## EMPROVE® Dossiers

### EMPROVE® Dossier (exp, bio)

#### Basic (Complete)

<table>
<thead>
<tr>
<th>General information</th>
<th>Characterization</th>
<th>Reference standard materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Nomenclature</td>
<td>▪ Elucidation of structure and other characteristics</td>
<td>▪ Stability summary and conclusions</td>
</tr>
<tr>
<td>▪ Structure</td>
<td>▪ Impurities</td>
<td>▪ Post-approval stability protocol and comment</td>
</tr>
<tr>
<td>▪ General properties</td>
<td></td>
<td>▪ (Stability data)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manufacture</th>
<th>Control of drug substance</th>
<th>Container closure system</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Manufacturer</td>
<td>▪ Specification</td>
<td>▪</td>
</tr>
<tr>
<td>▪ Description of the manufacturing process</td>
<td>▪ (Analytical procedure)</td>
<td>▪</td>
</tr>
<tr>
<td>▪ Control of materials</td>
<td>▪ Validation of analytical procedure</td>
<td>▪</td>
</tr>
<tr>
<td>▪ Control of critical steps and intermediates</td>
<td>▪ Batch analysis</td>
<td>▪</td>
</tr>
<tr>
<td>▪ Process validation and/or evaluation</td>
<td>▪ Justification of specification</td>
<td>▪</td>
</tr>
</tbody>
</table>
EMPROVE® – Main Benefits

Convenience – Time saving

- Dossier is in line with the Common Technical Document part 3 "Quality" (CTD format)
- Ideal for worldwide product approval
- Clear dossier structure enables efficient working
- Highest possible security with EMD Millipore know-how
- Avoid development of analytical test methods

Simplify your processes, make them faster, more efficient and thus, above all, more cost effective
Assuring product quality in a globalized world

EMD Millipore is member of:

Rx-360 Consortium
Rx-360 is an international consortium of pharmaceutical and biotech companies and suppliers to the industry, incorporated in 2009, that aims to develop and implement a global quality system to help members ensure product quality and authenticity throughout their supply chain to enhance patient safety.
Cell Culture Media—Coupling Raw Material Quality & DOE Approach
Scalable and Consistent Milling and Blending

Ball Mill
- For high hardness materials
- Circular product shape
- Easy and stable technology
- Capacity adjustments easy

Pin Mill
- Fine grinding of materials
- De-agglomerating
- Wet or dry materials
- Tight particle size control

Jet Mill
- For heat sensitive material
- For low melt point material
- Low particle size possible
- High investment

Most commonly used
Best in class
Smallest Particle Size
Scalable and Consistent Milling and Blending

<table>
<thead>
<tr>
<th>lab</th>
<th>pilot</th>
<th>production</th>
<th>batch size</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>&gt;10</td>
<td>&gt;2000</td>
<td></td>
</tr>
</tbody>
</table>

- Non-animal origin production lines
- Controlled particle size and production temperature
- Full GMP (several FDA and EMEA audits)
- Humidity control and inert process
- High flexibility and customized packaging
Consistent Particle Size Distribution

Particle size distribution analyzed by laser diffraction

Consistency of particle size distribution of independently produced batches
Cell Culture Media Consistency
Amounts of Selected Critical Raw Materials

Evaluating Amino Acid content:

Amino Acid profiles have been evaluated by NMR for batch-to-batch consistency.

The outcome demonstrated equal amounts of single components in several media production lots.

Confirmed batch-to-batch consistency for single components
Cell Culture Media Consistency Growth Profiles

Consistency of cell growth

Comparison of production powder lots:

Raw material consistency in several powder lots was evaluated resulting in consistent growth profiles.

Cells were seeded into 3 independent powder lots of Cellvento™ CHO-100 in shaker flasks (in triplicate) and sampled daily for cell counts.

Equal growth profiles of three independent production powder lots
Cell Culture Media Consistency Production Profiles

Consistency of cell production

Comparison of production powder lots:

Growth and production profiles confirm min risk of process variability attributable to cell culture media raw materials and processing

Cells were seeded into 3 independent powder lots of Cellvento™ CHO-100 in shaker flasks (in triplicate) and sampled daily for cell counts.

Cellvento™CHO-100 can be used confidently with min risk of process variability
Media Development Workflow

Scientific Approach:
- Balance and harmonize media components
- Waste and energy control analysis
- Metabolic monitoring of culture
- Early consideration of protein quality
- Impact of media formulations on DSP

Identify components contributing to performance, then optimize their concentrations
Raw Materials – The Essential Bricks for a Consistent Performing Media

- Quality of raw materials used in cell culture process development and media formulation can cause variability in cell growth, titer and product quality.
- Country of origin has become a major quality parameter for media and ingredients.
- Quality auditing and AOF audits extend back to the suppliers of ingredients, not just the media itself.

EMD Millipore established a qualification process based on its pharmaceutical knowledge to control raw material impacts

Raw Materials from EMD Millipore are comprehensively qualified
Analytics, QC Support and Documentation

Our responsibility:

• Employ raw material qualification process for consistent product quality based on media specific requirements
• Identification by CAS-No as unique identifier
• Non-animal origin certificate
• Comprehensive dossier for EMPROVE® components
• Change control or change notification agreements with suppliers

You receive for Cell Culture Media:

• Certificate of Analysis
• Non-animal origin certificate
• Cell culture test
• Regulatory documentation package (incl. GMP certificate)
• Product Information
Filter Manufacturing Complexity – Managing Variability and Change
Filter Characteristics

**Polymers**
- Cellulose Acetate
- Nitrocellulose
- PVDF
- Nylon
- Polysulfone
- Polyethersulfone
- PTFE - Teflon
- UHMW Polyethylene

**Pore Size and Architecture** – relates back to ability of membrane to filter out particles of a certain size

**Surface Modifications**
- Laminates and Composites (increase strength)

**APPLICATION**
# Filter Manufacturing

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Requirements</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Managing polymer types and requirements</td>
<td>• Available in industrial scale quantities and dissolvable in a solvent that allows it to be formed into a membrane</td>
<td></td>
</tr>
<tr>
<td>Controlling molecular weight variation of polymers</td>
<td>• Extensive engineering of equipment and processes</td>
<td></td>
</tr>
<tr>
<td>Confirming polymers are free of contaminants that adversely affect application</td>
<td>• Rigorous testing of resins, chemicals and resulting polymers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Expertise in polymer chemistry, specifically derivatizing and putting different chemistries onto the membrane</td>
<td></td>
</tr>
<tr>
<td>Maintaining reproducibility of precipitation</td>
<td>• Experience in continuous phase processes on casting machines</td>
<td></td>
</tr>
<tr>
<td>Achieving level of uniformity in polymers</td>
<td>• Ability to make equipment modifications needed to make an effective product</td>
<td></td>
</tr>
<tr>
<td>Making the entire structure integral</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EMD Millipore uses three different methods for making membranes. All three are controlled precipitation processes.

Air casting:

Solvent or emersion casting:

Thermal casting:
Polymers, Solvents and Casting Process Selection

• Polymer selection and solvent/polymer compatibility determine which casting process is employed in the creation of the membrane.

• Since most polymers used in membrane filtration are being designed for process streams that tend to be chemically aggressive, manufacturers select polymers that are essentially inert.

• Identifying solvents in which these polymers dissolve is difficult.
Added Complexity - Surface Modification Methods

Membranes are often treated chemically after they are cast.

Except for nylon, the polymers used to produce membranes are hydrophobic, which means they are water-repellent.

There are many applications that require the filtration of aqueous liquids through the membrane, thus requiring conversion of the surface of the membrane from a hydrophobic to a hydrophilic, or water-wettable, state.

Millipore accomplishes this by either modifying the surface chemistry of the membrane or applying a secondary chemistry coating over the base polymer.
Validation and Qualification

VALIDATION AND QUALIFICATION PROGRAM IS CLEARLY DEFINED:
1. Several lots of membrane are generated to the required specifications
2. Each cast lot is thoroughly analyzed to determine consistency within each lot and reproducibility between lots. (A single cast lot can total several thousand feet of membrane.)
3. Resulting data is statistically analyzed to determine the appropriate sampling plan on finished product and ensure the predictability of membrane performance in a variety of applications.

DURING PRODUCTION:
On casting lines, in-line cameras are used to look for pinholes in the membrane as it moves through the manufacturing system. The cameras detect transmission of light through a pinhole or gap, indicating a defect in the membrane.

TESTING PERFORMED AFTER THE MEMBRANE IS PRODUCED:
Visual tests – to detect defects by eye that cannot be detected by camera
Physical tests – to evaluate thickness, flow rate, bubble point, tensile strength, elongation, and other tests specific to the membrane involved
Application tests – to determine performance in specific applications that the membrane will be used
Supply Chain Management for Filter Manufacturing – Follow the Resin

Raw Material Supply Chain

- Chemical Supplier
- Plastic Supplier
- Resin Compounder
- Filter Membrane Factory
- Molded Part Manufacturing
- Finished Good Factory
Validation and Qualification of Raw Material Change that Impacts Filtration Device

<table>
<thead>
<tr>
<th>Tier</th>
<th>Details</th>
</tr>
</thead>
</table>
| 1    | **Resins/Plastics/Chemicals Meet Requirements:**  
|      | • Purchase Specification (Plastic Supplier)  
|      | • Traceability by lot number (CoA and CoQ)  
|      | • Chemical Supplier (CAS-No as unique identifier) |
| 2    | **Physical Testing of Membrane:**  
|      | • Thickness, flow rate and bubble point (3 main parameters to make a consistent membrane time after time)  
|      | • Tensile strength and elongation (membrane manufacturing process fabrication scheme)  
|      | **Compatibility:**  
|      | • Wettability (very important – aqueous versus organic streams)  
|      | • Biocompatibility (extractables, endotoxins, USP Class VI classification)  
|      | • Sterilization (ethylene oxide, gamma irradiation and autoclaving) |
| 3    | **Performance Qualification**  
|      | • For example, Bacterial Retention for sterile filter. |
## Qualification Test Results - Example

**Qualification of use of Supplier 2 for R1 in Durapore Membrane**

### Durapore 110605XCVGL Cartridge Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification/claim</th>
<th>Qualification Lot Results</th>
<th>Historical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Min</td>
</tr>
<tr>
<td>Bubble Point $^1$ (psi)</td>
<td>$\geq$ 50</td>
<td>54.3</td>
<td>52.2</td>
</tr>
<tr>
<td>$\Delta P^2$ (psi)</td>
<td>$\leq$ 3.0</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Bacterial Retention $^3$</td>
<td>Pass</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>WFI Oxidizables</td>
<td>Pass</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>Hydraulic Stress $^4$</td>
<td>Pass</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>30X Multiple Steam $^5$</td>
<td>Pass</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>Gravimetric Extractables (mg/10&quot; device)</td>
<td>$\leq$ 20</td>
<td>15.9</td>
<td>14.1</td>
</tr>
<tr>
<td>Mouse Safety</td>
<td>Pass</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>USP Endotoxin (EU/ml)</td>
<td>$&lt;$ 0.5</td>
<td>$&lt;$ 0.03</td>
<td>$&lt;$ 0.03</td>
</tr>
</tbody>
</table>

### Lot Results

- **Conforms to Specification**
- **Qualification results fall within historical ranges**

*Note: Qualification lot max value for gravimetric extractables 0.6% above historical max*

$^1$ Air pressure required to eliminate water from a membrane pore. Inversely proportional to pore size.

$^2$ Pressure drop across a device for a given flow rate of water.

$^3$ No passage of *B. diminuta* at challenge volume of 1 liter per 10 in. element and challenge conc. of $1 \times 10^7$ organisms per ml.

$^4$ Hydraulic Stress: Device remains integral after 50 psi hold; 45 pulses@ 50 psi; 80 psi hold; 45 pulses @ 80 psi; reverse pressure @ 50 psi

$^5$ Device remains integral after 30 live steam cycles at 135 °C
Change management and customer notification

SUPPLIER QUALIFICATION

SUPPLIER QUALIFICATION

CHANGE MANAGEMENT

Incoming QC and Inventory Control

Manufacturing Process Changes

Product and Packaging Changes

Customers and Change Management

Inventory Management

Change Control

Re-Validation

Change Notification

Inventory Management

Change Control

Calibration

Re-Validation

Performance Validation

Customer Notification

Inventory Management

Performance Validation

Notification Key Contacts

Regulatory Notification
Important Elements for Implementing a Change Imposed by a Supplier

• Updated list of Notification Key Contacts

• Providing Data and Validation Information

• Define the steps that should be followed to accept and manage the change

• Provide materials, resources, and data to help implement the change
Questions?