Enterprise Recipe Management
ISA 88 Recipe Definitions and Exchange across the Enterprise

Presented by
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Chairman, MESA Americas Board
“Something’s just not right—our air is clean, our water is pure, we all get plenty of exercise, everything we eat is organic and free-range, and yet nobody lives past thirty.”
Here is our problem

• We are living longer than ever before!
• We are healthier than ever before!
• We have more doctors, nurses, medical technicians, scientists, … than ever before!
• We have more medicines and health products than ever before!

• Why is this a problem?
It’s Happening around the World
How do we keep improving?

• It takes too long to get medicines and medical devices from lab to patient.
• We are still using stone age tools to move from laboratory to full production!
• And we use the same tools six or more times for every medicine and device
Information Transfer

• How do we get the right information transferred at each step in the process?
  – Fly engineers to the appropriate site
  – The equivalent of wandering minstrels or sitting around the campfire and exchanging stories
There is a Better Way

• Common Language to define how to make a drug or biotech product
• Common meaning and structure for the information
• From Laboratory to Pilot Facility to Production Facility
• Between production facilities for technology transfers
• Across production stages
# Common Language Across the Complete Product Life Cycle

<table>
<thead>
<tr>
<th></th>
<th>Lab</th>
<th>Pre-Clinical Test</th>
<th>Clinical Trial Phase I</th>
<th>Clinical Trial Phase II</th>
<th>Clinical Trial Phase III</th>
<th>Full Commercial Production</th>
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<tbody>
<tr>
<td>Intermediate API Production</td>
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<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
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<td>Unit Dosage Production</td>
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Enterprise Recipe Management

• Standard Process Descriptions for products for:
  – Technology Transfers
  – Investigations & Studies
  – MES and Batch Startup
  – Co-development
  – Sustainability

• ERM is a STRATEGY not a tool
  – It is a method for faster technology transfers
  – It is a method to support faster investigations and better production data collection
  – It is a method to reduce the time and effort required to build Manual Batch Records (MBR) and Electronic Batch Records (EBR)
  – Provides a consistent EBR and MBR presentations for similar production tasks
ERM Information

• Definition of equipment independent manufacturing processes
• Information for QbD (Quality by Design) Design Spaces
• Information for lean manufacturing studies
• Information for multi-site investigations
• Information for sustainable manufacturing
• Information for contract manufacturing
• …
Why ERM

- Faster recipe approval
  - Quicker review Times
- Increased Regulatory Agency confidence with our processes
  - Same structure / format across all sites
- EBR development down to weeks instead of months (or years!!!!)
- Consistent approach to recipe development across sites for product transfer
- Reduce (eliminate) investigations due to doc errors
- CpKs compatible across sites
- Faster / More RFT Development

- Will achieve a higher level standardization of manufacturing process
  - Following industry standards & learning from others
- Improving site to site knowledge of processes (sharing)
- Supports basis for site to site supply chain evaluation (standardized processes)
- Enable quicker development of MBRs
- Achieve enhanced strategic alignment between API & Secondary Processing
- Drives consistency in MBR/EBR reducing operator error
The ERM Concept

Standard Process Descriptions for Products

based on

Standard Definitions of Manufacturing Operations

using

Standard Quality Attribute Definitions (CQA, KQA)

and

Standard Process Parameter Definitions (CPP, KPP)

and

Standard Process Report Definitions
Enterprise Recipe Management

- Based on relevant IEC/ISO and ISA standards
- IEC/ISO 61512 (ISA 88) Recipe Standards
- IEC/ISO 62264 (ISA 95) Material, Equipment, Personnel standards

- Proven in multiple industries, including pharmaceutical and biotech
One **General Recipe** per product variation, maintained at the corporate level. For example, 2000 company wide products.

One **Site Recipe** per site and product, maintained at the site for local materials, language. For example, 10,000 site recipes for 5 sites.

One **Master Recipe** per Process Cell and product variant. For example, 50,000 master recipes for 5 process cells per site.

One **Control Recipe** per batch. For example, 1,000,000 batches per year. Describes the custom options and formula values for one specific batch of product.
General Recipes

• General recipes are the repository of corporate definitions that specify how to manufacture a product
• This includes
  – Identifying information (header)
  – The materials (formula)
  – A description of the manufacturing process
    • Ordering of material addition and extraction
    • Ordering of energy addition and extraction
    • Ordering of physical changes
    • “Chemistry Happens”
  – Independent of any specific production equipment
    • But it may specify constraints on target equipment, personnel, material, environment, and the supply chain
Common Data Representation and Task Specific Views

Granulation: 1

Process Parameters

Parameter Name | Critical/Key | Req/Opt | Value | Description
--- | --- | --- | --- | ---
Chopper Speed | na | na | 150-200 | Target/range of speed of chopper
Duration | na | na | 35-45 min | Target/range of time spent granulating the material. Example, 2 hours
Impeller speed | na | na | 55-65 RPM | Target/range of speed of impeller. Example, 100 RPM
Impeller Torque | na | na | 12-15 Nm | Target/range of torque on the impeller. Measurement technique varies but can be measured by using force, distance and rpms. Example, 10 Nm (Newton meters)

Quality Attributes

Attribute Name | Critical/Key | Req/Opt | Value | Description
--- | --- | --- | --- | ---
Appearance | na | na | Clear | Visual attribute of material. Specifies either the acceptable appearance of the material, or a list of criteria for rejects. For example, presence/absence of round particles-morphology
Bulk Density | na | na | 2.4 g/cc | Bulk density example g/cc
Content Uniformity | na | na | 10 | Percent or absolute (mg/g) of specific components in multiple samples. For example, may be measured off line or on-line and it uses HPLC, NIR or other procedures. 100% or 100 mg/g
Moisture Content | na | na | % | % moisture
Potency | na | na | 2.30% | Active Drug to Total Material

Process Reports

Report Name | Critical/Key | Req/Opt | Value | Description
--- | --- | --- | --- | ---

Constraints

Constraint Name | Critical/key | Req/Opt | Range | Description
--- | --- | --- | --- | ---

Control Space

Control Space Reference | MathML | Design Space
--- | --- | ---

Clumping Risk

Risk Assessment Reference | SVG | Risk Assessment
--- | --- | ---

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Intermediate Material Representation

**Recipe Annotation**

Process Input Representation (Material)

**Process Note:**
Uncoated tablets must be coated within 48 hours of compression.

Manufacturing Representation

**Granulation**
- Polysorbate 80
- Water
- Hydroxypropyl cellulose
- Magnesium Stearate
- Croscarmellose sodium
- Magnesium Stearate
- Croscarmellose sodium
- Calcium Carbonate
- Croscarmellose sodium
- Lactose Granulac

**Tableting**
- AJAX Blend

**Coating**
- AJAX 20mg FCT

**Process Operation Representation**

**Process Output Representation (Material)**

**Uncoated AJAX 20mg Tablets**
- AJAX Blend
  - Water
  - Simethicone emulsion
  - Opadry White
  - Wax Candellila

**AJAX Blend**
- Uncoated
A Contract Between R&D and Manufacturing

- A jointly developed description
- Requires knowledge of the basic manufacturing capability of the company and ranges of available equipment

- A general recipe tells manufacturing how to make a product
- It must do this in both a complete and unambiguous method
- It must be understood by all parties (R&D and all manufacturing sites)
- It must be consistent across sites
Why It Works

• Because for any type of production there are about 50 to 70 basic actions that define a company’s basic production capability

• Everything done in the laboratory and in production facilities can be defined using these basic actions

• Half of actions common across industries

• Half of actions unique to production types
Standard Unit Dosage Process Actions

- Adjust Temperature
- Band Capsule
- BFS
- Blending
- Blending with High Shear
- Capping Sterile Vials
- Charge to Adjust pH
- Charge to Adjust Viscosity
- Charge
- Charge with Agitation
- Chemical Sterilize
- Coat Particles
- Coat Tablet
- Compress BiLayer Tablet
- Compress Coat
- Compress Single Layer Tablet
- Cure
- Dedust
- Drill Tablet
- Dry Encapsulation
- Dry Heat Sterilize
- Drying
- FFS
- Fill Ampoule

Adding Energy

- Fill Vial
- Filtration
- Freeze Dry
- Inspect
- Metal Check
- Mill
- Mix
- Print Vial
- Steam Sterilize
- Testing
- Water Wash
- Wet Granulation

Adding Material

- Equipment Finalize
- Equipment Initialize
- Equipment Shutdown
- Equipment Startup
- Material Input
- Material Output
- Material Transfer
- Procedure Complete
- Procedure Abort
- Procedure Resume
- Procedure Startup

Finalizing Material

Preparing Material

Removing Material
Roller Compaction Example

Dry Granulation Process Action

**Dry Granulate - Attributes:**
- Granule Size Distribution
- Granule Density
- Gross Granule Appearance

*Note: Most critical process parameters are not defined, but must be determined for each target unit to meet the Critical and Key Quality Attributes.*

**Dry Granulate - Parameters:**
- Mill Screen Size – Required
- Milling Speed
- Milling Press (knives or hammer)
- Roller Speed – Required
- Roller Pressure – Required
- Roller Surface Shape – Required
- Roller Gap
- Vertical Screw Speed
- Horizontal Screw Speed
- Ribbon Appearance

**Equipment Requirements**
- Operate in Inert Environment (Yes, No)
- Operator Exposure Band (Level 1 through 5)
- Water Cooling (Yes, No)
Where Can It Be Used?

• QbD – Quality by Design – Design Space documentation
• Lean Manufacturing Initiatives
• Multi-Site Investigations
• Sustainable (Green) Manufacturing Initiatives
QbD Details for an Operation

- Process operation details with associated design space and risk analysis information shown in a form
- The last two rows reference design space and risk assessment information
- The detailed format for the external information files will usually be based on the tools used to generate and store the data

### Process Operation

**ID**: Granulation  
**Version**: V034  
**Status**: Final

- Creates a wet aggregate/granulate of particles by adding a liquid material to the dry material. For example, this process is performed prior to tableting.

### Quality Attributes

<table>
<thead>
<tr>
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<th>Critical/Key</th>
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</thead>
<tbody>
<tr>
<td>Appearance</td>
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<td>na</td>
<td>Clear</td>
<td>Visual attribute of material; specifies either the acceptable appearance of the material, or a list of criteria for rejects. For example, presence/absence of round particles-morphology.</td>
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<tr>
<td>Link Density</td>
<td>na</td>
<td>na</td>
<td>2.4 g/cc</td>
<td></td>
</tr>
<tr>
<td>Contact Uniformity</td>
<td>na</td>
<td>na</td>
<td>10</td>
<td>Percent or absolute (mg/g) of specific components in multiple samples. For example, may be measured off line or online and it uses HPLC, NIR or other procedures. 100% or 100 mg/g</td>
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<tr>
<td>Moisture Content</td>
<td>na</td>
<td>na</td>
<td>%</td>
<td>Moisture</td>
</tr>
<tr>
<td>Potency</td>
<td>na</td>
<td>na</td>
<td>2.30%</td>
<td>Active Drug to Total Material</td>
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<td>Chopper Speed</td>
<td>na</td>
<td>na</td>
<td>150-250</td>
<td>Target range of speed of chopper</td>
</tr>
<tr>
<td>Duration</td>
<td>na</td>
<td>na</td>
<td>30-45 min</td>
<td>Target range of time spent granulating the material. Example, 2 hours</td>
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<td>55-65 RPM</td>
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<td>Impeller Torque</td>
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<td>Target range of torque on the impeller. Measurement technique varies but can be measured by using force, distance and rpms. Example, 10 Nm (Newton meters)</td>
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### Process Reports

| Report Name | Critical/Key | Req/Opt | | |
|-------------|--------------|---------|| |

### Constraints

<table>
<thead>
<tr>
<th>Constraint Name</th>
<th>Critical/Key</th>
<th>Req/Opt</th>
<th>Range</th>
<th>Description</th>
</tr>
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</table>

### Other Information

<table>
<thead>
<tr>
<th>ID</th>
<th>Interpretation</th>
<th>Type</th>
<th>Category</th>
<th>Value</th>
<th></th>
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<tbody>
<tr>
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<td></td>
<td>OsIsoft. USERS CONFERENCE 2013 @OSIsoftUC</td>
</tr>
</tbody>
</table>
Standardized Information for Investigations

• Process reports define the information that must be collected and reported on during execution of the process
• Process reports are to be collected regardless of the equipment layout or level of automation
  – They provide the raw material used in investigations
  – The most time consuming part of an investigation is the collection of the process data, measured at over 80% and tens of thousands of man hours
  – Formalizing the minimum amount of information that must be collected and made available will significantly reduce the time and effort required to perform investigations
Sustainability Attributes

Process Parameters
Quality Attributes
Sustainability Attributes
Process Reports
Sustainability Reports

Sustainability Attributes (targets, maximum, minimum, etc ...)
(Critical/Key, Optional/Required)
Proof of ERM Benefits

- Goal: To significantly reduce the time and effort required to construct MES and Batch recipes.
- Pilot projects exceeded goals
  - Using the ERM standard definitions and method allows for recipe assembly from predefined reusable parts in a matter of days.
  - The sites are using approximately 50 standard process actions for unit dosage production and packaging.
  - About 150 reusable recipe segments have been created at … and ...
  - Approximately 35% of these can be reused across the sites, over 50% of the recipe segments can be used in at least two regions, and the rest are all reusable at the site level.
Conclusion

• There is a better way than “tribal knowledge” to speed new product introduction
• It's up to you to decide to when to take this next step
• This is how we can keep improving our products and speed of delivery