Enterprise Recipe Management

ISA 88 Recipe Definitions and Exchange across the Enterprise

Presented by

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MESA INTERNATIONAL
Driving Operations Excellence

BR&L Consulting
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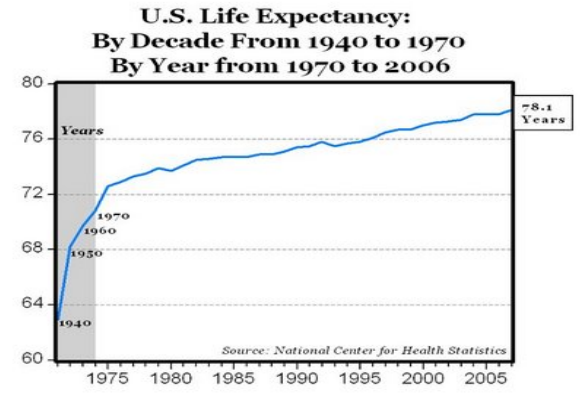
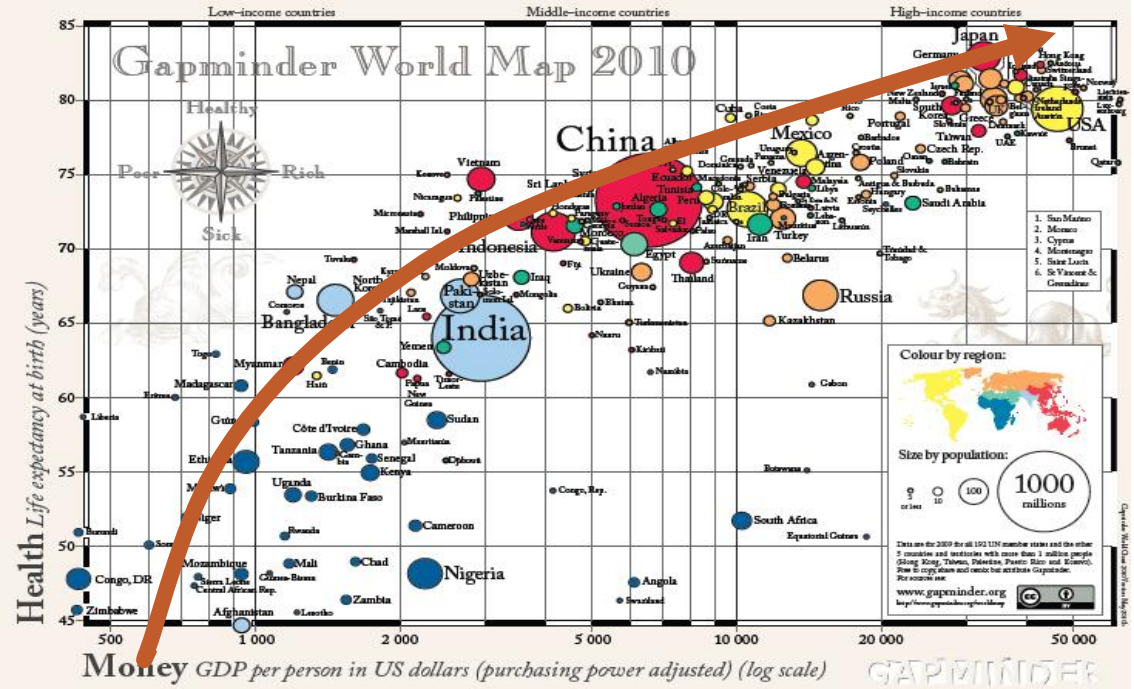
Here is our problem

- 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?

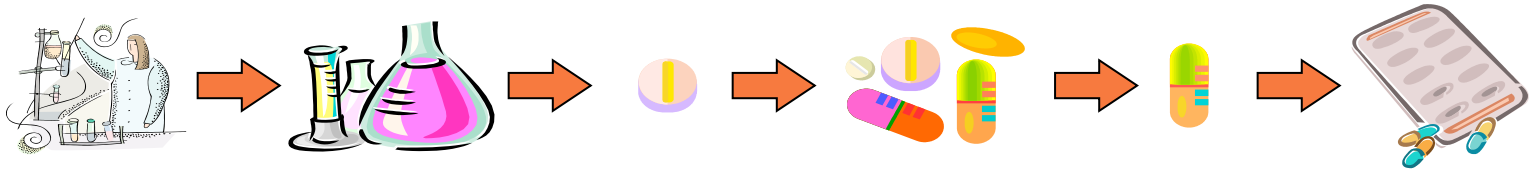


It's Happening around the World



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



Lab | Pre-Clinical Test | Clinical Trial Phase I | Clinical Trial Phase II | Clinical Trial Phase III | Full Commercial Production

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

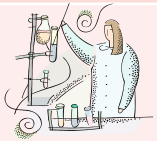
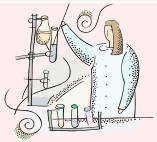
Technology Improvements

Technology Improvements

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

	Lab	Pre-Clinical Test	Clinical Trial Phase I	Clinical Trial Phase II	Clinical Trial Phase III	Full Commercial Production
Intermediate API Production						
Final API Production						
Unit Dosage Production						
Packaging						

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

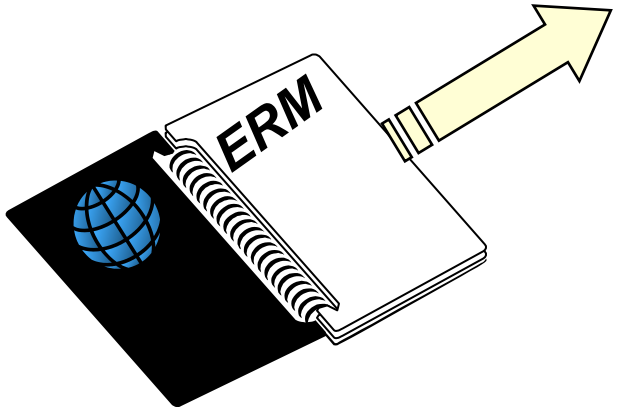
- Definition of equipment independent manufacturing processes
- Information for QbD (Quality by Design) Design Spaces
- Information for lean manufacturing studies
- Information for multi-site investigations
- Information for sustainable manufacturing
- Information for contract manufacturing
- …

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

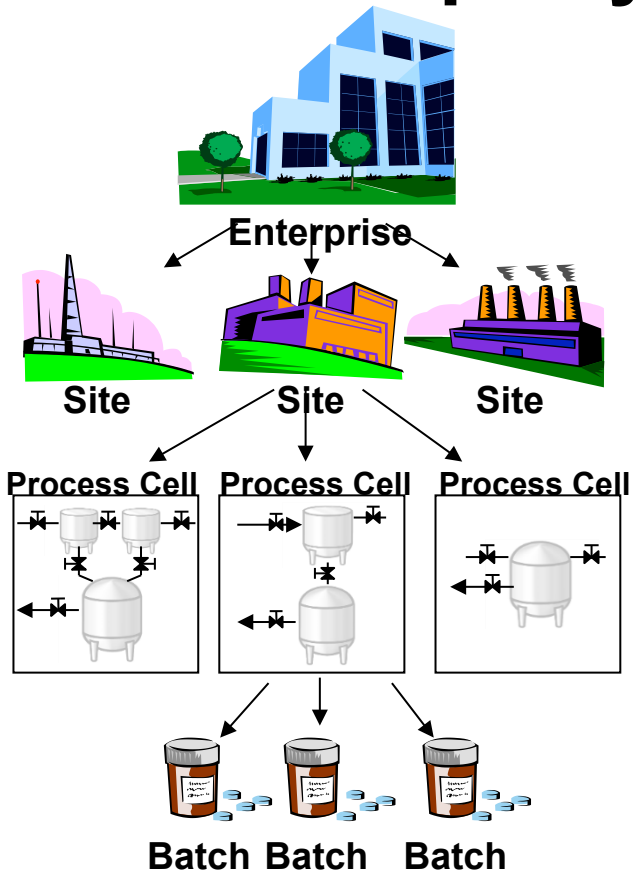
Standard Process Report Definitions

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

ISA 88 Recipe Types



One **General Recipe** per product variation, maintained at the corporate level. For example, 2000 company wide products

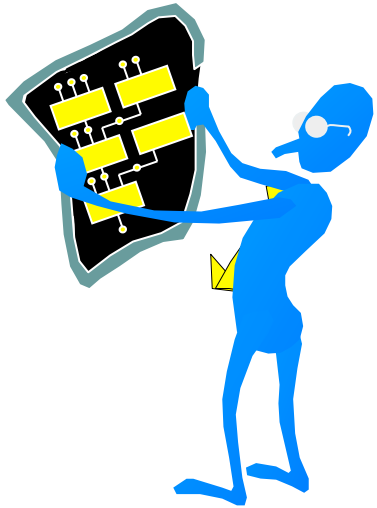
One **Site Recipe** per site and product, maintained at the site for local materials, language.
For example, 10,000 site recipes for **5** sites

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

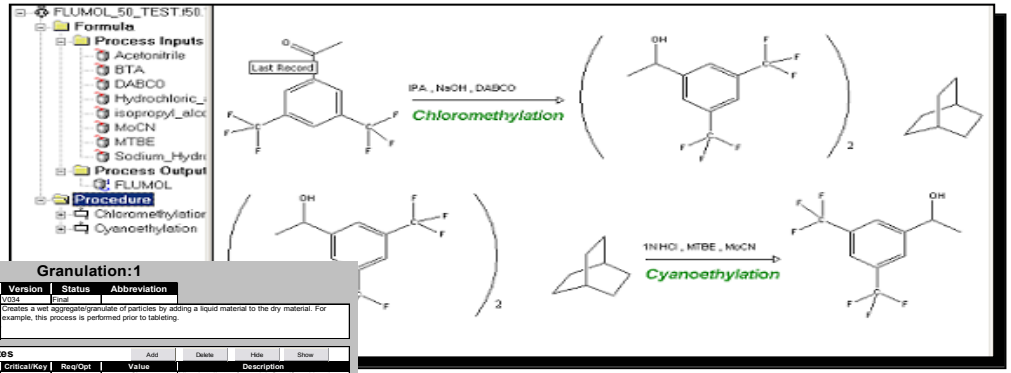
One **Control Recipe** per batch. For example, 1,000,000 batches per year. Describes the custom options and formula values for one specific batch of product.

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



Process Operation **Granulation:1**

ID	Version	Status	Abbreviation
Granulation	V034	Final	

Description 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

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 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)

Process Reports

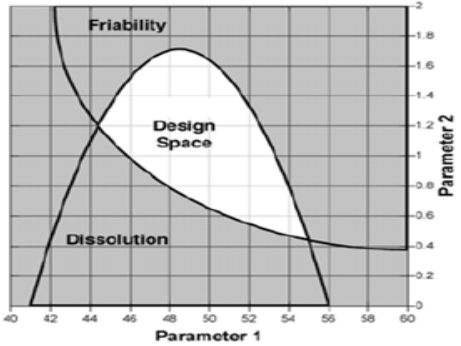
Report Name	Critical/Key	Req/Opt	Description

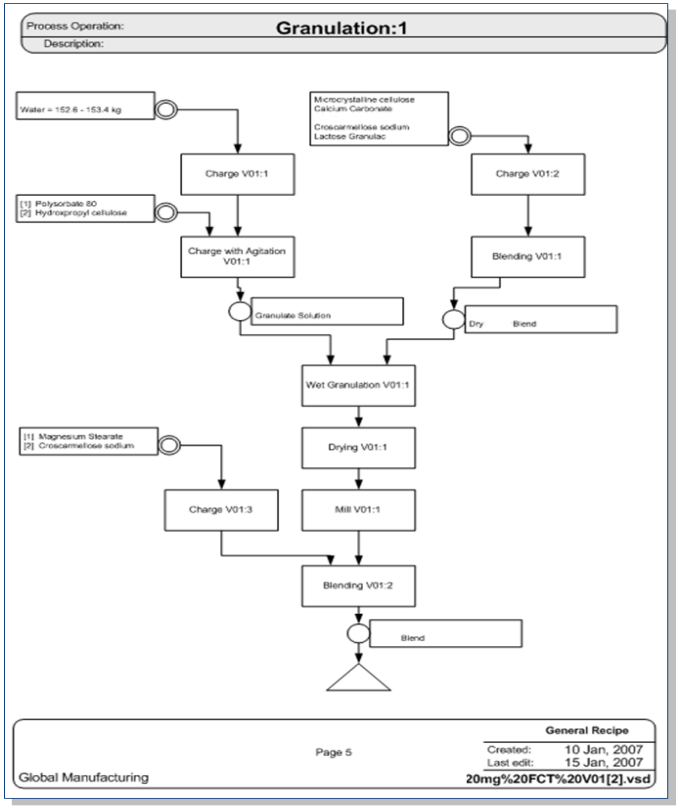
Constraints

Constraint Name	Critical/key	Req/Opt	Range	Description

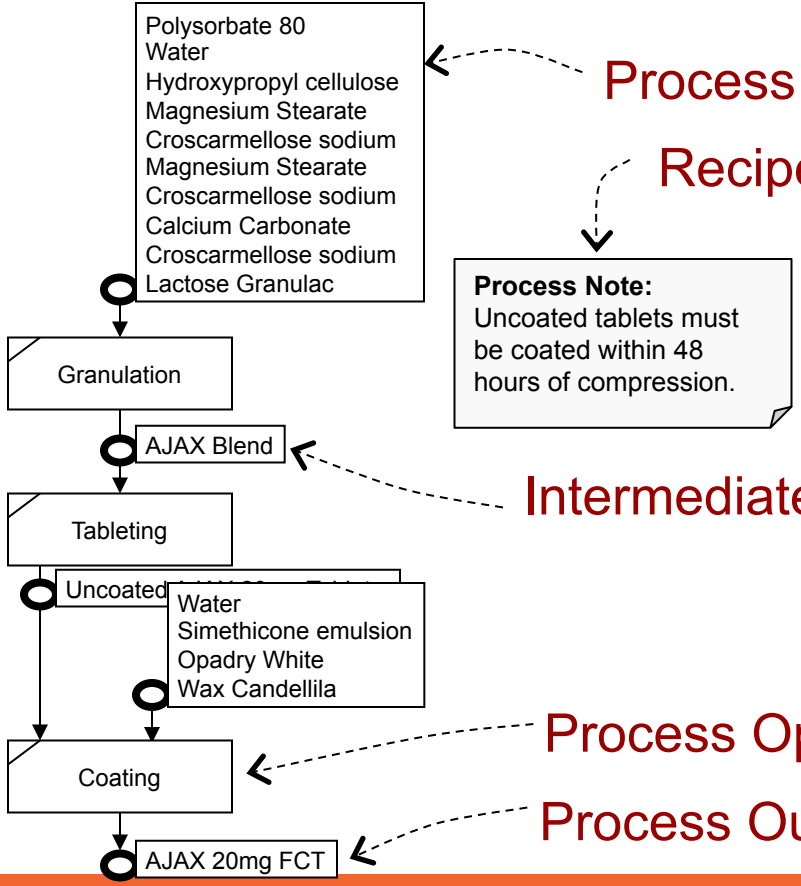
Other Information

ID	Interpretation	Type	Category	Value
Control Space	Reference	MathML	Design Space	\\SRV00345\Curelt\All\V034\Granulation\ControlSpa
Clumping Risk	Reference	SVG	Risk Assessment	C:\ABC





Manufacturing Representation



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

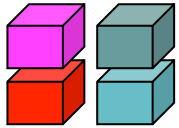
Adding Material

Finalizing Material

Removing Material

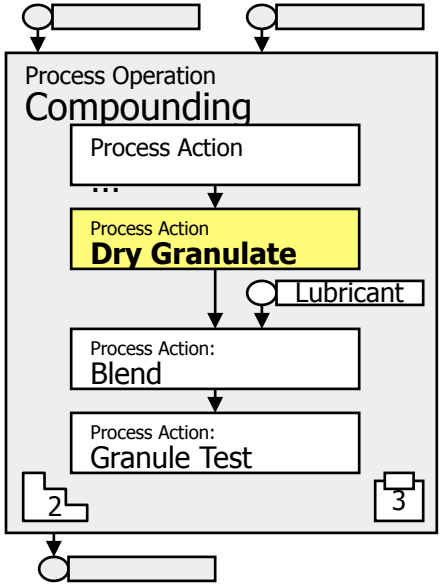
- Fill Vial
- Filtration
- Freeze Dry
- Inspect
- Metal Check
- Mill
- Mix
- Print Vial
- Steam Sterilize
- Testing
- Water Wash
- Wet Granulation
- ----------
- Equipment Finalize
- Equipment Initialize
- Equipment Shutdown
- Equipment Startup
- Material Input
- Material Output
- Material Transfer
- Procedure Complete
- Procedure Abort
- Procedure Resume
- Procedure Startup

Testing or Analyzing Material



Preparing 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

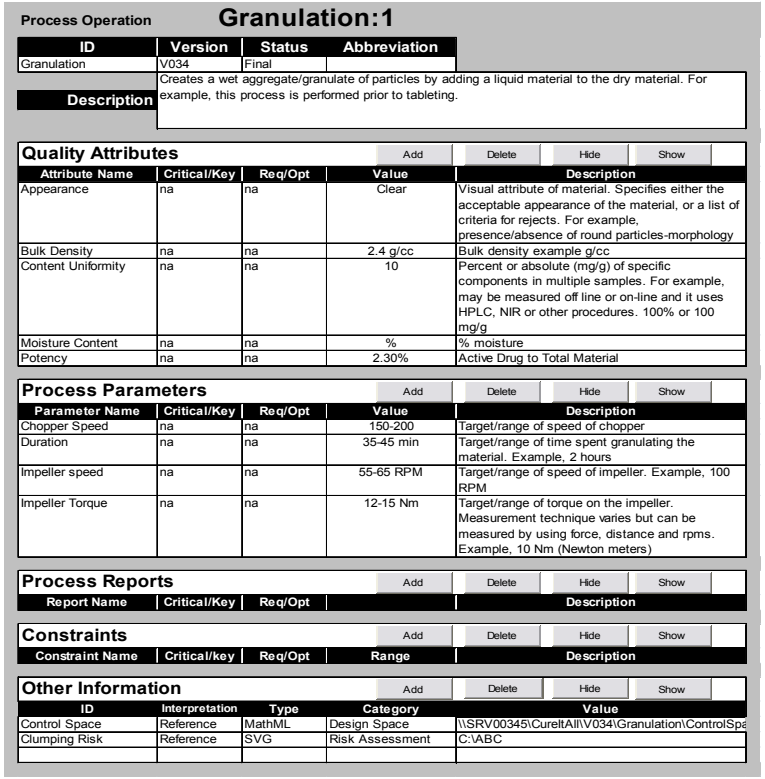
- Operate in Inert Environment (Yes, No)
- Operator Exposure Band (Level 1 through 5)
- Water Cooling (Yes, No)

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



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Process Reports (Add | Delete | Hide | Show)

Report Name	Critical/Key	Req/Opt	Description

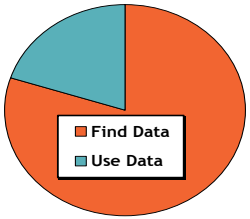
Constraints (Add | Delete | Hide | Show)

Constraint Name	Critical/key	Req/Opt	Range	Description

Other Information (Add | Delete | Hide | Show)

ID	Interpretation	Type	Category	Value
Control Space	Reference	MathML	Design Space	\\SRV00345\CureItAll\V034\Granulation\ControlSpa
Clumping Risk	Reference	SVG	Risk Assessment	C:\ABC

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

Process Reports Add Delete Hide Show

Report Name	Critical/Key	Req/Opt		Description
Defects	na	Optional		Number of sample defects. For example, are ideally 0.
Yield	na	Required		Yield. For example, are ideally 100% but most often 98-100%

Sustainability Attributes

Process Action

ID	Version
Blending	V01

Save (Default Name) | Reformat

Description: Blend dry materials to an optional specified homogeneity. Examples of equipment: Blenders (Low Shear) - BIMS, Ribbon mixers

Add | Delete | Hide | Show

Author	Date	Change ID	Version	Description

Quality Attributes

Add | Delete | Hide | Show

Attribute Name	Critical/Key	Req/Opt	Value	Description
Content Uniformity	Key	Optional	na	Typically measured as a percent or absolute (mg/g) of specific components in multiple samples. For example, it may be measured off line or on-line. Uses HPLC, NIR or other procedures
Actual % of active to total	na	Optional	na	Actual percentage of active ingredient to total material
Density	na	Optional	na	Density of material. For example, 2 g/mL
Particle Size	na	Optional	na	Average and medium particle size. For example, 50 microns - 200 microns
Moisture	na	Optional	na	LOD/KF. For example, 5% LOD

Sustainability Attributes

Attribute Name	Critical/Key	Req/Opt	Value	Description
Vapor Emissions	Critial	Required		Maximum emission by weight
Aqueous Waste	Key	Optional		Maximum waste by weight
Energy Use	na	Required		Amount of energy used to blend

Process Parameters

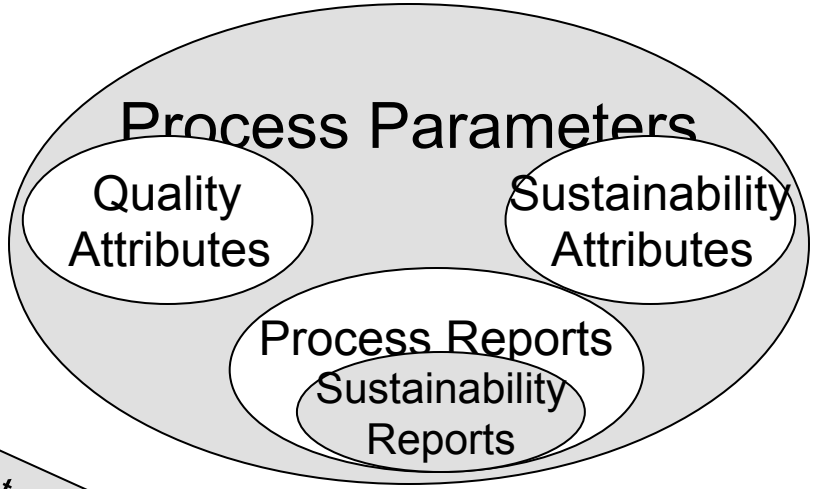
Add | Delete | Hide | Show

Parameter Name	Critical/Key	Req/Opt	Value	Description
Blending Time	na	Optional	na	Blending time to reach target uniformity. For example, 1 minute - 1 hour
Blending Speed	na	Optional	na	Speed of blender. For example, 10 - 20 RPM
Rotations	na	Optional	na	Number of blending vessel rotations. For example, 10-12 RPM (could be faster or slower)
Directions/Time	na	Optional	na	Direction of blending and time for direction. For example, Direction: clockwise or counterclockwise Time: 2 min - 30 min

Process Reports

Add | Delete | Hide | Show

Report Name	Critical/Key	Req/Opt		Description
Actual Vapor Emissions	Critial	Required		Actual emission by weight
Actual Aqueous Waste	Key	Optional		Actual waste by weight
Actual Energy Use	na	Required		Actual energy used to blend
Actual % of active to total	na	Optional		Actual percentage of active ingredient to total material
Density	na	Optional		Density of material. For example, 2 g/mL



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
- Its 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

Into The Future!