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General Recipe: Multiproduct Facility Design; Technology Transfer

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ABSTRACT

The crucial task for engineers, involved in designing manufacturing facilities, is to determine the most efficient way to dimension process cell equipment to achieve the required production capacity when beginning with general recipes.

In case of technology transfer, the challenge is the assessment of facility production capability to perform the process requirements, being defined in the general recipe.

This paper suggests the method, which is found useful for determining the process cell equipment and equipment functionality, based on number of products, their quantity and general recipe data.

In case of technology transfer to other sites or cells, it is suggested how to assess available production capability, based on general recipe data and installed equipment capability.

The suggested method can be useful during multiproduct facility dimensioning and, in case of technology transfer, the assessment of existing facilities. The result of implemented method is the best way to optimal price/performance ratio, in case of investment decisions, and reduction of life-cycle engineering efforts.

INTRODUCTION

Multiproduct facility assumes a facility suitable for the manufacture of several products, but limited to a single technology [4].

The way towards a multiproduct facility starts with gathering information on number of products to be manufactured in one year's production, their identification, quantity, units of measure, and product production rules: general recipes.

Required total quantity of materials to be produced during one year will be realized in production performances. A production performance will be a collection of production responses. The possible maximum number of production responses per year is dependent on batch time duration. The number of production responses is also dependent on batch size. A batch size can be influenced by the business decisions: time-to-market and investment cost, what will influence the choice of the way of production: campaign or concurrent. Campaign production reduces the number of production responses per year due to turnaround time (product change over).

Input data generate directions, constraints and level of freedom for designer. The possibilities generate variants. The owner wants to have variants in the early stages of the project to be able to evaluate them and to determine what variables need to be modified. Conceptual design time is manpower low intensity time, but impact to investment price high intensity time. Timesaving in that "cheap" time will give possibility to stay with the whole project in the contracted time frame. The designer should satisfy owner's expectations. Knowing the organized way to variants, designer will do it effectively.

After information gathering, the path to an optimized multiproduct facility will continue with product definition assessment of how to make (what must be defined to make) a product. A result of such an elaboration will be a resource specification (in this case, equipment specification, only), but without quantities.

Based on production information of what should be made during one-year production, resource specification properties will be varied, and then optimized in several iterations.

The result of implemented method will be a production capability, which collects personnel capabilities, equipment capabilities, material capabilities, and process segment capabilities (in this paper a collection of equipment capabilities and process segment capabilities), that are committed to production of intended quantity of products during one-year period.

Models and terminology of S88 and S95 are used as support in this article, wherever feasible.

FROM PRODUCT DEFINITION TO EQUIPMENT CAPABILITIES CLASSES

A production rule defines how to produce a product.

Although production rule model definition is not in the scope of S95, several relationships of production rule, coming from S95 Product definition model, Process segment capability model, Process segment model and Object model inter-relations, are considered important to be highlighted, due to further exposition.

A production rule is made up of one or more product segments.

A product segment:

- may be made up of other product segments
- specifies the values needed to quantify a segment for a specific product, such as specific equipment capability, associated with the identified product segment
- from business system point of view, is the most detailed process view to control material, labor, resource usage, cost, and quality in order to control the production
- must correspond to an identified process segment.

A process segment:

- is related to a product segment that can occur during production
- is a logical grouping of personnel resources, equipment resources, and material required to carry out a production step
- is defined as the collection of capabilities needed for a segment of production, independent of any particular product. This may include material, energy, personnel, or equipment capabilities
- may relate to one or more products.

A production rule, in case of batch processes, is defined by general recipe (or site or master recipe), whose model definition is described in S88.01.

General recipe identifies raw materials and their relative quantities requirements, equipment requirements, but without specific regard to the equipment, and processing requirements.

General recipe procedure defines the strategy for carrying out a process. It describes process in non-equipment specific terms. Therefore, general recipe procedure uses structure of Process Model: Process Stages, Process Operations, and Process Actions.

A product segment corresponds to process segment, which, in case of batch processes, may be process stage and process operation for general and site recipe (unit procedure and operation for master recipe), what is shown in the table below:

Product dependent	Product independent	Process Model
Product segment	Process segment	Process stage Process operation
Production step: crystallization of substance to achieve product X	Process step: crystallization	

There is no 1:1 relationship between process stage and unit procedure or process operation and operation, since process stages and process operations are not constrained by equipment boundaries in any specific facility.

Shortly, general recipe segmentation to product segments, identification of process segment, which is related to product segment, leads to recognition of equipment capabilities, needed for a segment of production.

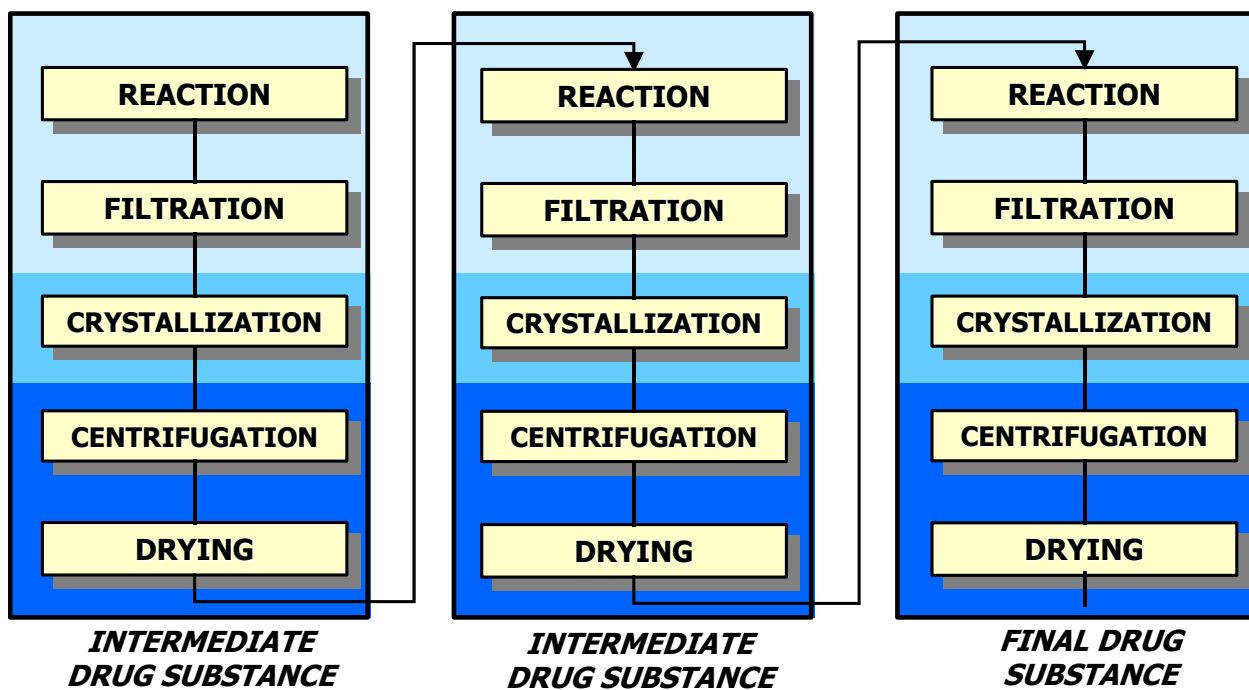
Several segmentation examples are mentioned below.

In case of microbial biotech processes commonly recognized process stages are: fermentation, recovery, and purification, while for cell culture processes they are: cultivation & harvest, pre-inactivation purification, and post-inactivation purification.

In case of active pharmaceutical ingredients processes, it is often possible to recognize the following process stages: reaction, crystallization, and isolation.

Examples of process steps in active pharmaceutical ingredients production are: dissolution, reaction, distillation, crystallization, evaporation, sublimation, absorption, filtration, and centrifugation [5].

A figure below illustrates active pharmaceutical ingredients process [6]. Since a process is made up of process segments, every drug substance process is considered as process segment. Further, every of mentioned process segments are made up of process stages: reaction, crystallization, and isolation.



The formula, as part of general recipe, through process inputs, gives identification and quantities of raw materials, required to make a product. Quantities of raw materials, which are consumed in the batch process segment, for the production of specific quantity of material in related product segment, imply equipment size for the particular product segment. In other words, the formula gives product dependent ratio of product segment yield size and equipment size.

The general recipe gives also product segment duration time.

The production rule assessment should give elements, important during equipment specification optimization.

The way to that goal will be:

1. segmentation

- segment general recipe into product segments, and general recipe procedure into process segments: process stages and process operations, respectively
- recognize process stages and process operations, which may define constraints to the target equipment, when the equipment characteristics may influence the chemistry or physics of the process [7]

2. identification of elements inside of segments

- identify equipment capability property to process segment
- identify approximate product segment yield size / equipment size ratio
- identify approximate time duration, associated to product segment.

CONSOLIDATION OF REQUIREMENTS, COMING FROM DIFFERENT PRODUCTION RULES

Above described strategy should be implemented for every production rule.

Results of assessment should be consolidated.

Equipment capability will be grouped per process segments, based on similar characteristics.

	Product 1	Product 2	Product m
Process segment name	reaction	reaction	reaction
Equipment capability	dissolution	dissolution	dissolution
	reaction	hydrogenation	reaction
	distillation	-	-
Process segment name	crystallization	crystallization	crystallization
Equipment capability	crystallization	crystallization	crystallization
Process segment name	isolation	isolation	isolation
Equipment capability	centrifugation	centrifugation	centrifugation
	drying	drying	drying

Result of grouping will show special equipment and equipment classes, or, better to say, potential for multipurpose equipment usage.

PRODUCTION INFORMATION VS. EQUIPMENT CAPABILITY

General recipe describes *batch process that leads to the production of finite quantities of material by subjecting quantities of input materials to an ordered set of processing activities over finite period of time using one or more pieces of equipment* [2].

General recipe describes one process, which is referenced to one production response. Now it is time to quantify equipment capabilities, based on production information of what should be made during a one-year production cycle.

For the simplification, batch time per batch process is considered to be constant for particular product. Batch time defines theoretical maximum of production responses per year.

In the very simplified equation, which is referenced to one batch process:

$$\text{batch size} = f(\text{equipment capability capacity})$$

and, accordingly, $\text{production performance for particular product} = n \text{ batch size}$

where n is number of responses.

Represented means that expected result could be achieved by variation of two elements: number of responses and equipment capability capacity, taking into consideration their limitations.

Limitations to equipment can arise from process scale up factor limitations. Namely, from the beginning of the process development ingredients are processed in equipment of different scale: kilo lab, pilot plant, commercial facility, and that scaling factor can guarantee reproducibility of process and thus, required product quality.

Also, equipment on the market is offered in standardized sizes, not in linear sizes. Standardized sizes and scale up factor limitations can call for equipment paralleling (two times, three times), i.e. multiple-path or network structure.

Above mentioned is valid for every process segment.

Additional challenge origins from business decision: campaign or concurrent production. This means that two or more products in the same manufacturing space are produced sequentially in campaign production or simultaneously in concurrent production [4].

Campaign production, comparing to concurrent, anticipates lower capital cost, smaller facility, less but larger equipment, single operating crew [8, 9], and longer time to market response.

In case of active pharmaceutical ingredients products, where products are composed of two or more intermediate products, it is frequent requirement to produce several different intermediate products simultaneously.

Taking into consideration above-mentioned constraints, the way to multiproduct, campaign based facility equipment specification will be achieved in several iterations of capacities and number of responses. The point is to identify equipment class capability property: capacity for process segment type, related to similar process segments, which will be able to realize expected segment, coming from required production performances, knowing that all performances should be realized during one-year period.

The way to multiproduct, concurrent based facility equipment specification is slightly easier. Based on result of product definition assessment and production information for every product, equipment capability properties will be generated.

TECHNOLOGY TRANSFER

A technology transfer for new products is considered from R&D facility to manufacturing facility, while for marketed products from manufacturing facility to manufacturing facility [3].

The way towards the technology transfer for products to be produced in existing manufacturing facility (in this case multiproduct facility), in terms of design, starts with gathering information on product production rules: general recipes, from the sending site, and production capability information (in this case equipment capability), from the receiving site.

To be able to answer the question if receiving site has production capability, sufficient for production of intended products, or it requires adding or modifying the capability, it is suggested to perform:

- product definitions (general recipes) assessment to identify equipment capabilities types, needed to carry out process requirements
- receiving site equipment capability assessment, to identify available equipment capabilities types, if mentioned identification is not on disposal or properly documented
- mapping of required equipment capabilities types, with available types
- verifying or complaining, if adding or modifying is needed.

Consider process scale up factor limitations, to be sure in process reproducibility and thus, required product quality!

This paper also shows differences in information flow, when technology transfer is intended to existing facility, comparing to facility, which should be designed.

CONCLUSION

S88.01 gives models for one batch process, which leads to production of finite quantities of material over a finite period of time. It also elaborates process cell classification, by number of products or by physical structure.

When requirement is related to design of multiproduct production facility capabilities, which considers multiple batch processes to produce required quantity of products over defined period of time, S88.01 indicates lack of models.

S95 terminology and information flow, described in models, was found useful during multiproduct facility design or technology transfer. What makes them even more useful is a link to S88.01 models.

It is important to highlight that there is a big difference between designing for variants, identifying, and quantifying of production capability, comparing to designing systems, intended to connect business systems and process control systems, although they can use the same models. This paper elaborates designing for variants, identifying, and quantifying of production capability.

Design of an efficient multiproduct facility will start with production and product definition information gathering. It will continue with product definition assessment to reach equipment capabilities types, then with consolidation of requirements, coming from different production rules, based on similar characteristics. Resulting in a grouping that shows potential for multipurpose equipment usage. Based on investment cost and time to market business decisions, which can be recognized in campaign or concurrent type of production, and taking into consideration constraints, coming from process scale-up factor limitations and standardized equipment capacity on the market, production capability (in this case equipment capabilities and process segment capabilities), that is committed to production of intended quantity of products during one-year period, will be achieved in several iterations.

A technology transfer, either from R&D facility or manufacturing facility to manufacturing facility, will start with gathering information on product production rules: general recipes, coming from sending site, and production capability information (in this case equipment capability), coming from receiving site.

Efforts will be concentrated on evaluation of receiving site equipment capabilities, comparing to requirement, coming from sending site. Result will be verifying of receiving site equipment capabilities as sufficient or identifying which adding or modifying is needed.

The result of implemented method is the easier way to optimal price/performance ratio, in case of investment decisions, and reduction of life-cycle engineering efforts.

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