Reprinted from
PHARMACEUTICAL ENGINEERING
THE OFFICIAL TECHNICAL MAGAZINE OF ISPE
NOVEMBER/DECEMBER 2012, VOL 32, NO 6

www.PharmaceuticalEngineering.org

Equipment Mix Determination for Multi-Product API Facility Planning

by Joseph R. Hettenbach, P.E.

This article presents a method of determining the major equipment set for the planning of new or revamped existing API multi-product facilities.

Introduction

At this period of time, in the changing business market, pharmaceutical companies are generally not building new Active Pharmaceutical Ingredient (API) facilities. However, companies are using a number of API manufacturing facilities both within their company, in a more dynamic less dedicated fashion, as well as utilizing API facilities of outside parties for manufacture of many of their products. Despite this trend, there may be a need at times to revamp existing facilities to be able to accommodate a number of smaller bulk volume APIs in a single facility or alternatively, to build new facilities to fill this need.

A number of years ago, a need was recognized to develop a model which could provide a basis for the planning of a major equipment list and identify the key features to be included. This tool could be considered for use in an upgrade/expansion of an existing multi-product API facility, as well as for the planning of a new "flexible" multi-product facility. It was expected that the model could have ongoing use in the planning of any facility, be it a new API facility or fine chemical plant facility. This was recognized as a challenge, since the model would have to be able to determine the number and sizes of reactors, support equipment, API product isolation devices, such as filters and centrifuges, and dryers. In addition, the Materials of Construction (MOC) of the major process equipment, piping, etc., must be compatible with the processes and chemistries to be run in the facility. One of the key elements in this exercise is determining the right number of reactors and product isolation devices and dryer combinations and a MOC "mix" to define this multi-pool type facility, designed for simultaneous manufacture of a number of processes. It should be pointed out that the scope of this article does not include incorporation of the many variables involved in running API manufacturing operations for a large pharmaceutical company into a very complex model. The focus is a single facility which will handle a small fraction of such a company's API manufacturing needs.

This proposed facility would have to reasonably accommodate the different processes expected to be made in the plant and satisfy the production volume requirements for selected product mixes from the company's "portfolio" of required APIs. In many cases, the product mix to be accommodated by these type of facilities is changing, along with variable specific product bulk volume needs.

At the same time, it would be desirable to achieve a high level of effective reactor volume utilization, which would involve the use of the reactors for reactor service, as opposed to using the reactors for support services. In some cases, reactors are used as wash pots and as vessels to hold waste streams for subsequent treatment. Further, there are times that some of the reactors are left idle during a given campaign.

The purpose of this article is to describe the methodology that was developed and utilized to develop the "optimum equipment mix" for planning these type of facilities. While it is conceivable to use this methodology to plan bioprocessing type facilities (which typically include, smaller scale reactors, product isolation devices, etc.), experience to date has only been in API, where commonly, the processing has been strongly organic synthesis based, at a larger scale. Its mode of operation is characterized mainly as batch or semi-batch in nature. For this reason, the primary focus area of this discussion is batch processing of APIs or fine chemicals.

The technique has been subsequently applied successfully on a number of other major projects. Its description will follow, concluding with a case study to illustrate the use of the model developed for use, initially, on one project.

The basis for this discussion is a "typical" generic batch process, depicted in the flow diagram in Figure 1. In such a process, one or more reactors are used with a product isolation device (i.e., a centrifuge or product filter for a solid product), a dryer (if the product is dried), and a number of auxiliary/support equipment pieces and systems. For more complex processes, additional reactors and support equipment would be added to this "picture."

Equipment Considerations

The list that follows identifies the major types of equipment and important features that typically need to be specified for a multi-product plant. Table A includes additional characteristics and design aspects that are normally related to that equipment. The equipment mix, then, includes:

- The number and sizes of reactors and the support equipment pieces directly associated with them to be provided. It is important to recognize that some processes require special heating and cooling systems, and the application of special instrumentation and controls, including Process Analytical Technology (PAT). It would be good practice to make some provisions for these features on a selected number of reactors in the mix, particularly for those reactors to be used as specialized reactors and crystallization vessels.
- The number of head tanks (for charging liquids and solutions to reactors and solid/liquid separators) to be provided.
- The number of specialty commodity liquid chemical tanks of the appropriate Materials of Construction (MOC) to be provided. Examples could be commercial grade hydrochloric acid, sulfuric acid, sodium hydroxide, others.
- The number of API product isolation devices provided, including various types of filters and centrifuges, which are used to collect/separate the API product from the crystallization slurry produced in the process. Since products have different handling characteristics and cake washing requirements, it is important to have at least a few different types of product isolation devices available.
- The number of product dryers provided. It is also important to have a few different dryer types available (Table A) to handle the different product handling and processing characteristics one would anticipate in the multi-product facility. For general information, it should be noted that a significant issue to address with the use of filter dryers is the management of the residual heels produced in the operation.
- The number of other major equipment pieces and support features as needed for the type of processes and chemistries to be encountered. Examples would be continuous extraction, filtration, and drying to be used in semi-batch processing schemes.

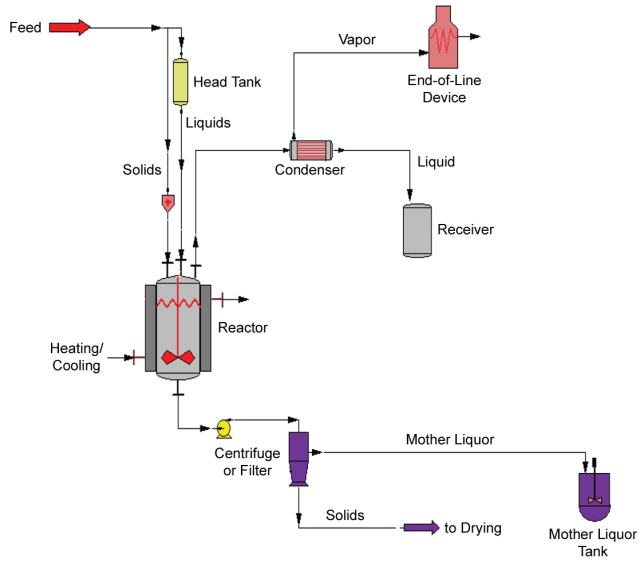

Figure 1. A Typical batch "single reactor" process train.

In addition to the major equipment considerations, there are other elements that define how the facility can operate in a flexible mode. Two examples of such features are:

- The number of process vacuum pumps which are often "shared" for reactor service
- The number of process inlet lines and process outlet lines, which typically are routed to and from process manifold rooms, sometimes called transfer stations

The Process Basis

One concept is to analyze a considerable number of products either targeted for the facility or products similar to those types of processes and chemistries reasonably expected to be manufactured/utilized in the planned facility. If one can comfortably consider these to represent a "universe of processes," averaging techniques and ranges can be used to come up with the guidelines for the equipment list development.

A flow sheet would be developed for each synthetic process step looking at some reasonable batch size and using some reactor size as the average one in your standard manufacturing practice; in the case study described below, it was 7500 liters. The reactors can then be scaled up and down to comfortably hold the respective maximum – and minimum – process volumes to be handled in each reactor at some volume utilization. In general practice, this could be 85% of the maximum volume (on the high side); and low volumes

Equipment Type	Equipment Attributes and Design Considerations
Reactors	Typical reactor design considerations that must be resolved. What material of construction they should be? How many should have solids charging capability? How many should have decanters? How many should have distillate receivers? What type(s) of distillation and heating/cooling capability should be provided? Reactor construction will be metal or glass-lined. Glass-lined carbon steel reactors will mainly have dished head bottoms with heating/cooling jackets; some could be specified as cone bottom. Metal reactors are typically 316L stainless steel (s/s), or Hastelloy®, or equivalent. The metal reactors are better suited for high temperature service and better heat transfer and can be fitted with internal coils or removable tube bundles, which inherently pose some process cleaning challenges, as a trade-off. There are a number of different impeller designs available to suit agitation requirements, which are not readily met by the standard impeller choices offered with glass-lined reactors, which are more limited. Reactors are usually fitted with overhead condensers; vertical units (typically Hastelloy® MOC on the tube side) are often preferred over horizontal for shell and tube units since they are easier to clean; plate type design units could be considered. There are also specialty reactors with their unique requirements. Examples could include hydrogenators, which could be stirred tank or loop type designs.
Process Piping	Reactor inlet and outlet process lines are general purpose, and are typically Teflon-lined (T/L) carbon steel pipe unless the vessel is a s/s MOC. In addition, s/s lines would be added to the numbers of general purpose process lines to accommodate higher numbers of solvents to be handled for the processes envisioned to be run in the facility, as well as some solvents for which the T/L pipe could be an issue, e.g., toluene.
Head Tanks	Typically glass-lined carbon steel, jacketed, with agitators. Solvent wash tanks would likely be jacketed with agitators, and stainless steel MOC. A high proportion of the head tanks would be jacketed with agitators and heating and cooling to handle miscellaneous chemicals, solvents, and solutions – to be charged to reactors with process temperature control. Some of the head tanks should have solids charging capability as well, e.g., to make up solutions such as sodium bicarbonate into water. This is preferable to using a reactor for this simple service. Stainless steel jacketed tanks, with agitators, heating and cooling can be provided for solvents used to wash product filters and centrifuges.
Commodity Chemical Tanks	Commodity tanks are head tanks, suitably sized (say 1000 to 2000 liters). They are typically g/l, but at times other MOC are provided for specific material compatibility requirements. Generally would not have jackets. Typical commodity chemicals might be 50% sodium hydroxide, 37% hydrochloric acid, and 99% sulfuric acid.
Mother Liquor Tanks	They are typically of g/l MOC with jackets, agitators, and heating and cooling capability, and are used to receive mother liquors from product isolations/filtrations and to neutralize the pH if necessary. Typically one nominal size larger than the reactors/crystallizers it would be serving, e.g., a 10,000 liters size mother liquor tank for a 7500 liter size reactor. Also used to receive extract and wash layers destined for waste/effluent treatments operations or outside disposal, at times requiring some pre-treatment. Can be used as additional distillate receivers for processes having more distillations, as well as for miscellaneous process services as holding/surge tanks, etc.
Distillate Receivers	Used to collect solvent (cuts) from atmospheric and vacuum distillation operations. Typically glass-lined MOC. Sizing should be appropriate to its related reactor (e.g., 5000 liters for a 7500 liter reactor it would serve).
Product Isolation Devices	Product isolation devices include filters and centrifuges. Filters could include candle type and plate type. There are number of different centrifuges; both horizontal basket and vertical basket are the most common for API processing.
Solids Charging Devices	Solids charging to reactors, head tanks, and product dryers would entail contained Intermediate Bulk Containers (IBCs). They are used with charge chutes or alternative acceptable contained systems, product dryers should be provided with contained discharge systems suitable for the products handled.
Product Dryers	Product dryers are generally vacuum type, ranging from tray driers to various agitated and paddle types. Filter dryers are also used quite extensively and are handy for doing “in-situ” repulps, prior to the drying operation.

Table A. Significant consideration in the determination of the multi-product equipment mix.

may be processed by the use of special agitator/impeller designs (somewhat enhanced by using cone-bottomed reactors). The flow sheet should show all of the equipment listed above, the features required, as well as the numbers of inlet/outlet lines for each reactor. The number of reactors needed is, of course, also a function of your manufacturing practices regarding the number of vessels used for operations such as batch extractions, etc.

> *In practice, the FIR concept has provided a powerful tool to quickly characterize multi-product plants.*

A central concept in identifying the optimum equipment mix is a parameter defined as the Filtration Intensity Ratio, hereafter referred to as FIR or F/I/R in a few of the tables. The FIR is defined as the ratio of the number of reactors to the number of product isolation device and product dryer combinations. A simplified depiction of this can be seen in Figure 2. In this case, there are four reactors and one product isolation device and dryer combination, resulting in a FIR of 4. For example, in a plant having 16 reactors, 4 product isolation devices, and 4 dryers, the FIR would be 16/4 = 4.0 for the entire plant. Each product isolation device is valued at 0.5 units, and each product dryer is valued at 0.5 units, in this calculation.

A filter dryer (combining the product isolation and product drying operations in one unit) is valued at 1.0 unit. Specific process steps in which the product is kept as a wet cake (i.e., not dried before subsequent processing) would have higher effective FIRs by calculation. For processes with higher FIRs, the process "train" would require more reactors, and conversely for processes with lower FIRs. Note that the centrifuge in the diagram in Figure 2 is representative of a product isolation device, accounted for in the "Filters + Dryers" term in the FIR calculation shown for a sample process in schematic form.

The number of reactors used for a given process can be increased with the benefit of achieving lower "batch turnaround" times (TA), the period of time between batch make-ups, but with the "trade-off " of having higher FIRs and fewer reactors available for other processes run simultaneously in the facility.

The effect of having fewer reactors available, because one process train is using a higher number of reactors from the total mix available, could be underutilizing the installed number of product isolation devices and drying capacity for plants configured to have lower FIRs.

In practice, the FIR concept has provided a powerful tool to quickly characterize multi-product plants. Experience has demonstrated that the more recent processes coming down the pipeline were trending toward needing lower FIRs. This trend rendered some of our older facilities, which generally had higher installed FIRs, as not being good fits for those same processes since some significant level of reactor capacity would be "wasted." Of course, for planning purposes, one way to rectify that situation would be to install additional product isolation devices and dryers to the extent that capital funding and space were available.

Guidelines for a Multi-Product Plant Equipment Set

The data derived from the process analyzes can be tabulated for each specific process step, including the number, sizes, and MOCs of the reactors and support equipment pieces (head tanks, commodity tanks, mother liquor tanks, receivers); the number and sizes of the reactors that require solids charging capability, decanters, and vacuum pumps typically used for vacuum batch distillations; the number of process inlet and outlet lines on the reactors; and the number of product isolation equipment devices and dryers required. Note: At times, a product is isolated as a wet cake and then re-pulped or re-dissolved and recrystallized; then the product from this additional processing is isolated and dried, all as part of one distinct process train with its resulting calculated FIR. The data from all of the processes can be compiled to determine averages and reasonable ranges for FIR values. An example of one such table of results is illustrated in Table F in the case study.

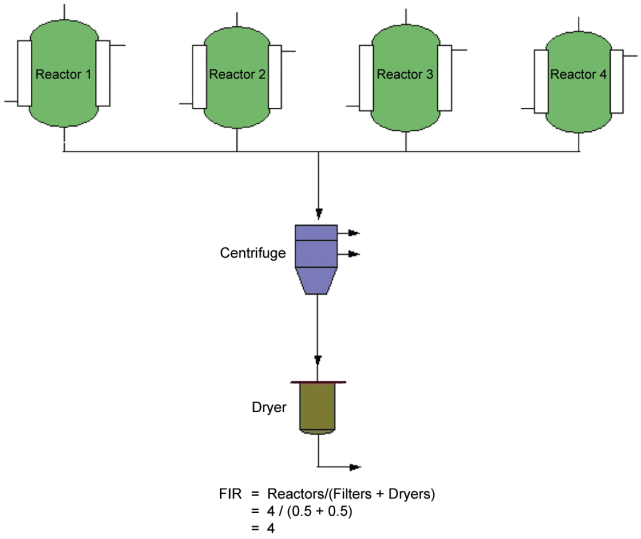

Figure 2. Filtration Intensity Ratio (FIR).

Process Fit Analysis Results (for the 52 steps)			Existing API Plant (for comparison) (13 reactors)	Case Study Plant (tentative) (17 reactors)
Size (liters)	Counts	% of Total	% of Total	% of Total
4,000	21	13	15	19
7,500	77	48	54	44
10,000	39	24	15	12
12,000	20	12	15	19
16,000	5	3	-	6
	162			

Table B. Reactor sizes/counts analysis.

Case Study

In order to illustrate the method described above, the following is a summary of the results for analyzes performed for the first project in which this method was applied, which involved the revamp and upgrade of an older API facility. This existing plant did not have an equipment mix very suitable for a multi-product facility, was overcrowded, had outdated process transfer station rooms, and needed different product isolation and drying equipment to replace older, outdated units.

Definition of a Process Basis

Ten new emerging products to be considered for manufacture in a revamped 17 reactor plant involving varying numbers of process synthesis steps, different chemistries, etc., were analyzed, including drawing up detailed flow sheets, scaling, etc., as described above. The scope of the analyzes included a total of 52 synthetic process steps as follows:

Product #1 – 7 steps
Product #2 – 3 steps
Product #3 – 6 steps
Product #4 – 9 steps
Product #5 – 4 steps
Product #6 – 5 steps
Product #7 – 4 steps
Product #8 – 5 steps
Product #9 – 4 steps
Product #10 – 5 steps

To characterize these processes, the number of steps from this group having distillation operations was 25, which represents, on average, approximately one out of every two processes with this attribute. Approximately one out of every three of these process steps (18 in number) used reflux operations, and about one half of the process steps (23 in number) used batch extraction.

Case Study Results

The details of the analyzes performed and the results of the study are summarized in the tables with qualifying notes.

Size (liters)	Existing API Plant (4 "Pools")	Case Study Plant (5 "Pools")
4,000 7,500 10,000 12,000	2 4 2 1	3 4 3 2
Totals --->	2	12
Note: number of metal charge reactors included in the totals	2	2

Table C. Solids charging capable reactors listing.

Reactors Analyzes

The process flow diagrams for the 52 process steps were analyzed and scaled to give the number of reactors of different sizes which are needed. These total counts for each size were tabulated and percentages by size were tabulated, shown as Table B. For comparative purpose, a size breakdown for an existing plant is shown, alongside the tentative size breakdown for the planned 17 reactor plant. The breakdown for the proposed plant includes both existing reactors and new ones (replacements or additional ones). The breakdowns will also illustrate how the plants stack up against the Process Fit Analysis results for the new product mix studied.

So, it can be seen that the reactor size mixes for each of the facilities shown here for comparison roughly reasonably match the profile dictated by the process steps considered in this case study.

Reactors with Solids Charging Capability

Solids charging capability is a significant attribute of the reactor mix tabulated above. For the referenced existing API multi-product plant (again, for comparative purposes), 9 out of the 13 reactors have solids charging capability (68%). The process analysis for the case study plant determined that 12 out of 17 reactors would have solids charging capability (71 %). The breakdown by reactor size for solids charging

Product No.	Average Numbers per Process Step	
	M.L. Tanks / Receivers (does not include treatment operations)	Header Vessels (includes commodity bead tanks)
1	2 (1 to 3)	2 (0 to 4)
2	1	2 (2 to 3)
3	3 (2 to 3)	3 (2 to 4)
4	3 (1 to 5)	2 (1 to 6)
5	2 (1 to 5)	3 (1 to 5)
6	4 (1 to 5)	4 (1 to 9)
7	3 (2 to 4)	4 (0 to 6)
8	2 (2 to 3)	2 (1 to 4)
9	3 (1 to 8)	2 (1 to 5)
10	2 (1 to 4)	2 (1 to 3)

Table D. Mother liquor tanks/receivers and header vessels analyses.

capability is shown in Table C. The term "pool" designates a set of equipment, including reactors, and support equipment to isolate and dry a product from one distinct process. The use of the term (4 "pools") in Table C means that up to four (4) processes could be manufactured simultaneously in the facility, provided that the equipment is available (a function of process scheduling, etc.), whereas the term (5 "pools") means that up to five processes could be manufactured simultaneously.

The number of metal reactors (included in the totals in Table C) is significant and important to consider since some processes needing solids charging cannot be performed in the standard g/l reactors, due to some specific chemical, solvent, or solids incompatibility. There have been some problems with certain high temperature alkali (high pH) solutions and other specific liquid chemicals in glass-lined reactors. Certain solvents such as hexane and hexane can produce static discharge (a significant safety hazard) in non-metal (conductive) vessels. Some solids, such as metalcatalyst particles and others, can be very abrasive to the glass lining. Beyond material capability considerations, glass-lined reactors also have limitations regarding heat transfer, particularly when very low process temperatures are required.

Support Equipment Analyzes

The average number of mother liquor tanks (also serving as larger volume solvent receivers) and head tanks (for miscellaneous solutions and commodity type chemical solutions) were determined for each product (which includes a number of different, distinct synthetic process steps).

Table D shows the averages for each product, and the range of the counts determined from the process analyzes (flow diagrams) that were developed (as done for the reactors). This is included to show the wide range of variability expected in a multi-product plant using this type of equipment. A number of distinct process steps is included in each of 10 products listed in Table D. The "Average Numbers per Process Step" of "M.L. Tanks and Receivers" and "Header Vessels," show the range of the numbers of each type of vessel for all of the process steps of that product in parentheses, as well as the rounded off average for all of those specific process steps. For example, for Product No. 4, the numbers of M.L.Tanks and Receivers for the 9 distinct processes steps ranges from 1 to 5 with a rounded-off average of 3, for all of the 9 process steps of that particular product.

Not surprisingly, processes needing more of these equipment pieces (the higher end of the ratios shown) would not generally be a good fit for the facility "designed" using the average ratios. Alternatively, reactors could be used for other services to supplement the apparent "count" deficiencies for certain products, resulting in a drop in the effective capacity based on reactor count utilization.

Support Equipment Ratios (per Reactor)	Proposed Design Guideline	Existing API Plant (for comparison)	Case Study Plant (tentative)
Head Tanks	0.5 - 0.7	0.67	0.5
Mother Liquor Tanks	0.8 - 0.9	0.83	1.1
RR's (Reactor Distill. Receivers)	0.3 - 0.4	0.33	0.14
Commodity Tanks	0.2 - 0.3	0.6	0.29

Table E. Support equipment ratios.

Mother liquor tanks or reactors can be used to treat mother liquors and other waste streams prior to disposal, or subsequent treatment, or recovery for re-use. Of course, the number of mother liquor tanks available can affect the production scheduling and the effective reactor capacity utilization.

The support equipment ratio (expressed as the number of specific equipment type pieces/the number of reactors) is shown in Table E.

The Filtration Intensity Ratio (FIR) Analyzes

This brings us to the key characteristic parameter for multi-product plants, introduced in this discussion. The filtration intensity ratios were calculated for all of the processes, using the process flow diagrams. The incidence of the FIRs (i.e., the number of processes having that ratio) were compiled for each product. Product averages and totals were calculated to give a good feel for what the "average" situation looks like. The use of averages is basic to implementation of this method. Table F lists the filtration intensity ratios that an analysis of the processes determined. To clarify the number entries in this table, and to show how the calculations are performed:

Product 9, for example, includes four specific process steps: 2 steps have a F/I/R = 1.0, 1 step has a F/I/R = 2.0, and 1 step has a F/I/R = 6.0. The average then for Product 9, shown in the last column on the right = $(2 \times 1 + 1 \times 2 + 1 \times 6) / 4 = (10 / 4) = 2.5$

Note: N/A: There are no FIRs for these process steps since a solid product is not isolated.

For the 49 data entries for the specific process steps for FIR values (not including those listed in the N/A column in the table above):

- 32 had FIRs Less Than 3.0
- 17 had FIRs Equal to or Greater than 3.0

- 8 had FIRs Equal to 4.0 or Greater

As a means for a comparison, a similar, existing highly functional multi-product API plant has 14 reactors in total including 13 reactors and 1 mother liquor tank, similarly outfitted; 3 filter dryers, 1 centrifuge (for product isolation), 1 pan dryer, and 1 rotary dryer; and the calculated FIR (from the definition above) for that equipment mix = 14/4.5 = 3.1.

For the case study plant, the proposed FIR for a configuration (allowing for planned future additions) was 3.40 (= 17/5).

This FIR (3.40) was used to develop the equipment set for the case study plant; future additions of one reactor, one product isolation device, and one dryer (in spaces reserved for this equipment) could reduce the FIR to 3.0 (18/6), which is the proposed guideline value.

It should be emphasized that the FIR is intended to identify the major equipment, in total, for a facility. If multiple products are run simultaneously, there could be different FIR configurations for individual process steps/equipment trains. The assumption here is that any and all of the product isolation devices and drying equipment is accessible to any and all of the reaction vessels.

Of course, for scheduling product mixes, the FIR requirements for specific processes could restrict the total utilization of the reaction vessels and product isolation devices and drying equipment for a given "product mix" campaign.

Capacity Determinations and Checking the Facility for Accommodating Product Mixes

In addition to the process basis (i.e., having the right equipment set), another important consideration is the process fit with regard to product bulk volume requirements. One can test a given equipment set by analyzing a number of product mix scenarios. This, of course, would involve some iteration with the goal of maximizing effective installed total reactor volume (capacity) utilization.

One formula that can be used to determine the capacity utilization for a given process at a scale (average reactor size) suitable for anticipated product volumes, and utilizing an equipment pool chosen is (Equation #1):

$$\text{Capacity (days)} = (\#) \times (1 / 24) \times (TA) + (C) \times \{(CT - TA) \times (1 / 24) + (CO) + (CU)\}$$

Where:

- **#** = the number of batches at the batch size (product output) determined to meet the annual production volume needs.
- **TA** = the batch turn around time in hours (also called the "bottleneck time") which is the period of time between subsequent batch make-ups, using the number of reactors specified in your flow sheet. (Again, using additional reactors can reduce the TA).
- **C** = the number of campaigns run per year (typically 2, perhaps 3).
- **CT** = the overall batch cycle time in hours. The (CT - TA) term represents the "tail" of the last batch, finishing up the campaign.
- **CO** = the changeover time in days between campaigns for the particular pool used and incorporating the peculiar process particulars involved.
- **CU** = the cleanup time in days for the equipment used for that process.

Performing the process fit studies provide a reality check on the size/scale/number of equipment pools ("average" process trains) to be provided in a new facility, and can identify some of the operational constraints inherent in the upgrade/expanded existing facility.

Product Analyzed	Incidence of F/I/R (Rounded) in the Process Steps								Product Average
	N/A	1	2	3	4	5	6	9	
1	1	1	4	1					2.71
2		1	2						1.67
3		2	2			1			2.03
4		2	3	1	1	1	1		2.9
5		1	2	1					2.06
6	2			1	1			1	5.33
7				2	1		1		4
8			5	1					2.16
9		2	1				1		2.5
10		2	2	1					1.8
Totals:	3	11	21	8	3	2	3	1	2.716

Table F. Filtration Intensity Ratio (FIR) Analysis (FIR) for the process steps analyzed.

Conceptual Model Calculations Results and Proposed Guidelines

The results generated for the case study analysis were compiled into a design guidance document for a multi-product organic synthesis facility. Table G summarizes some key aspects of the guidance document, showing the results of the process analyzes described above in the column labeled "Process Based

Conceptual Model Results" and the derived guidance in the "Proposed Design Guidelines" column. Regarding the data in the third column, "An Existing API Plant for Comparison" has been included to show the actual equipment mix factors for a relatively new API plant located in the same production site, which was completed about four years earlier than the case study. The existing, relatively new API plant had been planned with a product mix basis that was similar to, but somewhat different than the product mix utilized in the case study project for the upgrade of the older API plant, i.e., involving older (in-line) products.

Multi-purpose Facility Summary Table			
	Proposed Design Guidelines	Process Basis Conceptual Model Results	An Existing API Plant for Comparison
Reactor Quantity	15	15	14
Reactor Sizes (% of Total)			
<4000 liters	0%	0%	0%
4000 liters	10 - 15%	13	15
7500 liters	40 - 50%	48	55
10000 liters	20 - 30%	24	15
12000 liters	10 - 20%	12	15
16000 liters	0 - 5%	3	N/A
Reactor MOC Ratio (metal ones/ total ones)	< .25	< .25	< .23
Reactors w/ Solids Charging Capability	60 - 70%	35%	69%
Support Equipment Ratios (per Reactor)			
Head Tanks	0.5 - 0.7	0.67	0.5
Mother Liquor Tanks	0.8 - 0.9	0.83	1.1
Reactor Distillate Receivers	0.3 - 0.4	0.33	0.14
Commodity Tanks	0.2 - 0.3	0.6	0.29
Overall Equipment Mix			
Filtration Intensity Ratio *F/I/R*	3	< 3.0	3.1
Simultaneous Process Trains	5	5	4

Table G. Model results and proposed guidelines for equipment set and features.

The actual equipment set was developed using this table as a guide, and the new equipment was installed while allowing space for future additions to improve the FIR for the longer term. The ranges delineated in the "Proposed Design Guidelines" column were accepted by management as a viable tool to be carefully applied, still with an eye towards the evolving product pipeline, subject to adjustments.

Of course, it should be recognized that the overall project time schedule for a new API plant – from the time the Equipment List is "frozen" for the design to the time that the construction is completed and the facility is approved and ready for actual production startup – can be on the order of two to three years, depending on the size of the facility and other factors. During this time period, product mixes and capacity utilizations can change due to production volume requirements, as well as the actual processes utilized, due to process changes, optimization, etc. A good, flexible design will provide a facility that can better meet the changing product profile, recognizing that the model used for planning has its limitations and cannot always ensure that the variable needs can be met in a given facility.

Note that while the proposed guidelines follow the results from the conceptual model (case study), they are not an exact match. Some areas were adjusted in the interest of greater flexibility. Admittedly there is some "feel" involved here, based on the designer's familiarity with the historical performance of similar facilities. For example, in the category of reactors with solids charging capability, the values were slanted toward the existing plant with which we had a lot of operating experience.

It should be emphasized, again, that these guidelines are appropriate for use in planning facilities utilizing similar chemistries and manufacturing practices.

Product Mix Details and Capacity Calculations Results

An initial example product mix was chosen to check the suitability of the equipment set determined for the case study plant, utilizing the "equipment set" dictated by the factors in the proposed guidelines from Table G. This involved specific process steps chosen for five of the products, which had been analyzed as part of the model development. A calculation showed a good fit with reactor count utilization > 90%; 16 of the 17 reactors of the facility would be utilized for this product mix (16 /17 × 100% = 94%).

Table H is included to give a feel for the production cycles and output volumes for this same product mix that might be expected of an equipment "pool" in the size range, as discussed earlier in this article.

The process turnaround times (TA) and batch sizes from the process analysis were used in the capacity formula de-

Process Step	TA (hrs) Lot Frequency	KG/ Batch	KG/ Week/ at TA	FG Conversion Equivalent (KG)
Product #7 – Step 3	24	188	1316	1877
Product #10 – Step 4	24	240	1680	1400
Product #5 – Step 2	36	697	3253	2954
Product #8 – Step 1	29	638	3696	4228
Product #6 – Step 5	20	300	2520	2520

Table H. Product output for the example product mix.

scribed above (Equation #1) to calculate the number of operating days needed in that specific pool to produce the desired annual output of product. The F.G. (Finished Equivalent (Finished Goods, Final API product, from the multi-step synthesis), numbers listed in the last column on the right side of Table H are the amounts of the finished product that would be produced from the particular intermediate step listed (for the specific product), assuming standard yields are met for all of the remaining sequential process synthesis steps for that product.

The total numbers for the head tanks, commodity tanks, mother liquor tanks, and distillate receivers also were consistent with the ratios (to the number of reactors) as specified in the proposed guidelines.

Outcome of the Case Study Plant Project

The case study plant project was completed with the revamp work and new equipment additions implemented, closely following the guidelines developed in Table G, except that a FIR of 3.4 was used (suggested to be = 3.0). The facility was operated successfully for a number of years, before it was shut down due to a business decision involving downsizing of worldwide capacity.

An Illustrative Example of the Use of the Guidelines

Say a company which has the same chemistries and manufacturing practices as those used to develop the guidelines from the detailed process analyzes described above (i.e., assuming that the guidelines in Table F are applicable) wants to get a feel for the approximate level of investment needed for a new 15 reactor API facility to manufacture a number of promising new products.

Applying the FIR of 3.0 from Table E, then 15 / 3 = 5 filter and dryer combinations would be needed. A good mix of these units to handle variable product characteristics could be 2 filter driers, 1 pressure filter, 2 centrifuges, 1 cone dryer, and 2 pan dryers. The facility would be nominal "5 pool" one – meaning up to 5 processes could be run simultaneously.

Applying the % factors in Table E for reactor sizes, metal reactors, and solids charging features, the breakdown could be 2 @ 4000 L, 7 @ 7500 L, 3 @ 10,000 L, 2 @ 12,000 L, and 1 @ 16,000 L. Two of these would be metal reactors with the rest being g/l vessels and 10 of these would be set up with solids charging capabilities. Using the factors in the table for support equipment, the major process equipment list would round out as 9 head tanks, 4 commodity chemical tanks, 13 mother liquor tanks, and 5 distillate receivers.

A ball park cost for the facility could be estimated by using a factor of 6 to 8 times the total equipment cost (from the company's experience) or by using a factor of $X / installed reactor liter (again from the company's experience). If this factor is pegged at $1850 / liter of installed reactor capacity based on the company's current cost experience, then for this facility with 130,500 liters of reactor capacity, the ball park (off the top of the head) estimate would be $240 million (to be used for discussion purposes only).

"Reduced Scope" Approaches

If there is a need to reduce the scope/cost of a new or upgraded/expanded facility project, the following are suggestions for alternative approaches. In some respects, these changes or reductions to the "full blown," more flexible facility could be considered a "semi-dedicated" approach. Since it is widely accepted in the project engineering/management domain that the capital cost of a project is very much a function of the process and support equipment list/cost included in the scope, there are some significant cost reductions that could be achieved by the "semi-dedicated" approaches, which could include:

- Use of only a few different reactor sizes – planning to run smaller process volumes at times (reiterating a few points made above), aided by the installation of the appropriate agitation system, including impeller designs, speed control, etc., to appropriately "manage" these low volumes. A number of coned bottom vessels, both g/l and metal, also could be used to help manage the low volumes.
- Installation of fewer reactors, but reserving ample space, and the planning of the infrastructure, and consideration of the people and materials flows, utilities services, etc., to accommodate the future additions. This would, of course, translate into fewer potential "process trains" in the shorter term.
- Although not recommended strictly, one could install an overhead condenser that could be shared by two reactors, while reserving ample space, local utilities services, etc., for future additions.

- Where charge chutes and IBCs cannot be accommodated, alternative contained solids charging systems could be employed. One example is an approach which involves use of vacuum and air/nitrogen to remove material from drums/containers in a contained room – the preferred method – or in a booth and charging the material to the reactor or head tank. Although this could be setup somewhat remotely from the reactor, it is preferred that the distance between the two be practically minimized.
- A higher FIR could be used by providing fewer product isolation devices (i.e., centrifuges and product filters) and dryers for the number of reactors to be set up. Ideally, one would want to reserve space for the future additions of some additional product isolation devices and dryers, if future needs dictate that. Of course, this would translate into fewer potential effective "process trains" in the shorter term.
- Fewer head tanks could be provided by setting up a "contained" room or a booth to transfer liquid raw materials in a controlled fashion directly to reactors. In addition, some smaller, portable vessels on wheels could be used for this service, on an "as-needed" basis. These typically would be non-jacketed, but could have air-driven portable, typically "propeller type" agitators, if needed, and must be docked securely in a "safe" location. Of course, the portable vessels inherently afford a lower degree of containment in their design and operation.
- Fewer process lines to and from reactors and selected equipment and solvent lines could be installed in the shorter term, while reserving space on racks, etc., for pipe routing; and installing additional spools in the process manifold room walls to be piped to in the future. All future piping should be included in the detailed design to a reasonable extent (to suit foreseeable needs – preferably in 3-D), including pipe routing studies and isometric drawings of future lines to improve the chances of doing the future piping installation with minimum issues/interferences in the field.
- Fewer commodity tanks, distillate receivers, and mother liquor tanks can be installed in the shorter term with full provisions for future additions reasonably anticipated.
- It is good practice to have transfer pumps and agitators on all process vessels and support equipment to facilitate process cleaning by allowing closed-loop re-circulation type techniques and better sampling.
- Some degree of semi-dedication can be incorporated by setting up some reactors as solids charging capable (typically used at the beginning of a process) and other reactors as "crystallizers" (for the "isolation" of the product) with perhaps a mother liquor tank and a stainless steel solvent wash pot "semi-dedicated" to the product isolation device (be it a centrifuge, filter, or filter dryer) used for collecting the product and washing the cake, and drying. An alternative way to set up a solvent wash for a product isolation device is to utilize a pump and an in-line heat exchanger with temperature and flow control systems thereby reducing the need for the solvent wash pot.

Conclusion

There are a number of ways to develop an equipment list for a multi-product plant. One method to achieve this has been described here which involves extensive analyzes, but provides a workable model to determine the list. It should be emphasized that the ratios and percentages shown here regarding equipment pieces, etc., are very much a function of the manufacturing practices we employed and are sensitive to the type of processes and chemistries with which we have had experience. The Proposed Design Guidelines, based on our chemistries and processes, proved to be quite useful for a number of our applications. The FIR concept allows one to come up with a good starting point for development of the equipment list for a new facility, or an expansion/revamp of an existing one, provided that one analyzes at least a good number of processes expected to be manufactured in the facility. We used this model successfully for projects based in a number of locations worldwide and generally found that the facilities "fashioned" using these guidelines were versatile enough, while achieving reasonably good, effective installed reactor volume capacity utilization.

Of course, the use of "averages" as an acceptable analytical technique in the development of this "tool" (model) inherently can lead to some issues, particularly in dealing with "outliers" – specific processes which require much different ratios of the number of major process equipment and support equipment pieces to the number of reactors provided. There are also other variables involved in the API manufacturing business operations, which could challenge the basic assumptions used in the model development. The model does not include any factors to account for these variables, as its scope is a single API multi-pool flexible facility, intended to manufacture a carefully selected product mix to best utilize the facility capacity. It can be assumed that pharmaceutical companies manufacturing large numbers of API products would use a number of API facilities in their manufacturing network, including, when needed, outside parties to handle variable bulk volume requirements, conflicts between products for scheduling, etc.

The methodology described in this article is also of value as a screening measure for proposed expansions or new multi-product facilities. Proposals with FIR values as significant "outliers" to the values shown in table G might suggest that a more detailed process review is warranted (nearly two thirds of our processes had FIR values in the 2-4 range).

The same methods described here can be used for any process type/product mix, recognizing that the model will

predict approximations which must be reviewed and likely adjusted based on additional considerations. This model also provides a means to plan facilities for cases when available capital investment is limited, while improving the prospects for more expeditious expansions and product specific additions, as the needs for the facility change. In our experience, we were able to make product specific additions fairly readily to the base facilities in a number of cases, as the needs for new/different products developed, because we had planned for those eventualities.

Acknowledgement

Much thanks is to given Gregory Jack Hounsell, P.E. for his help in technical reviews and detailed editing of this article. Gregory and I worked together over a period of 30 years on a wide variety of process and environmental engineering initiatives, new facility designs, and revamps of existing facilities. We also collaborated on a number of innovations involving new technologies and novel equipment and systems applications, as well as alternative approaches for process engineering problem solving at Pfizer Inc. throughout the US and internationally. His input on this article, including some of the tables and the graphics, is greatly appreciated.

About the Author

Joseph R. Hettenbach, P.E. has more than 35 years of process engineering and environmental engineering experience, spending 33 years at Pfizer Inc., servicing manufacturing and research facilities in many US locations, Puerto Rico, Ireland, England, and Singapore. He has managed the detailed process design of a number of projects for laboratory development, kilo plant, pilot plant, and commercial scale manufacturing API facilities. He has made presentations on the subject of "Improving the Process of Process Design of Multi-Product API Facilities" to a number of E&C, A&E, and CM companies throughout the US and in Ireland, to ISPE, and to the AICHE. He has Masters Degrees in chemical engineering and environmental engineering from Manhattan College. He is a licensed Professional Engineer in New York State. He is currently an adjunct professor in the Graduate Environmental Technology Program at the New York Institute of Technology. He can be contacted by email: tjchett@optonline.net.

Process Engineering Works P.C., 155 Centershore Rd., Centerport, New York 11721, USA.