Incremental Addition of Parenteral Capacity
Case Study for a Lyophilizer

Filling parenterals is capital intensive, with large, fixed ongoing maintenance fees to support continuous operations. There is an additional requirement to remain current with the latest innovations in equipment and best practices leading to regular upgrades and changes within a regulated environment that is generally distrusting of change and requires substantial validation of all improvements. As a case study and model, the addition of new lyophilization business will be considered.

Since removing water from drug and biological molecules significantly reduces hydrolytic reactions and thus enhances stability, lyophilization or freeze-drying is an essential marketing requirement for many biotech drugs. The injectable nature of these products also dictates aseptic processing that is slow, requiring 2 to 4 days on average, and involves substantially more equipment than just a lyophilizer. Aseptic filling and packaging will normally support multiple products that may be campaigned at different times throughout the year, but growth in pharmaceutical manufacturing is typically incremental. Therefore, it is desirable in planning for new increments to estimate the costs, understanding that the different aseptic processes involved consume variable capacity.

The following discussion is about the addition of a lyophilizer. It includes information about maximizing capacity and minimizing costs, not only cost of the new lyophilizer, but also of all support equipment and environments that are needed for a parenteral product. Obtaining the capacity of a single piece of equipment without consideration to its impact within a facility is insufficient to achieve that rated capacity. If new equipment does not smoothly interface into a manufacturing operation, one will discover unexpected bottlenecks that prevent previously planned capacity from being realized. The goal is to increase capacity incrementally, and to know in advance the magnitude and cost of the increase.

A Spreadsheet Model

Using standard spreadsheet software, one can list the various pieces of equipment that are used in a parenteral filter, fill, and lyophilize operation. Each of these units or list items may contain sub-elements with increasing detail and complexity. For example, list items should include equipment and environmentally controlled rooms and in most instances, bound combinations of the two. The list should also include major utility systems because capacity of these support systems will eventually become rate limiting to operations. The longer the list, the more complex the model becomes, which will only improve the model if the items might limit some necessary operation. The idea is to get a complete list of all the major equipment, utilities, and controlled environments needed for the task, and then matrix cost elements, such as capital, maintenance, validation, and staffing. However, one must also account for capacity and utilization of each list item. Within the operational environment, some items may be utilized less than half of the time while others are capacity bound. What can be done to smooth out the capacity so that most of the equipment can be used most of the time? Furthermore, what is the total investment in order to add, in this case a lyophilizer, and be able to use it for the intended purpose, as an incremental addition to business and without interfering with existing operations? How much of the existing plant capacity will the new operation consume?

The same spreadsheet model can be used to make financial decisions related to manufacturing within the organization, or choosing to outsource. Assembling data for the model requires considerable expertise and experience and may be delegated to a team of

managers from operational departments, as well as a cost accountant, capital acquisition personnel and equipment purchasing agent to assist with finance and pricing. While the model does not directly attempt to consider timing for the project, it does so implicitly as costs are assigned to each line item.

Parenteral Support for Unit Lyophilization

Shown in Fig. 1 is a room layout for typical formulate, filter, fill, and lyophilize operations. One might start with the preparation of rubber and steel materials for sterilization. Such materials include the stopper on the top of the vial, probably the aluminum closure to hold the stopper in the vial, and any steel parts that must be re-sterilized between filling lots. The rubber stoppers for lyophilization may also need to be aseptically dried after steam sterilization, which will usually take one shift (8 hours) of oven time. Glass washing and subsequent oven depyrogenation may be either an online process occurring with the fill, or it may be conducted as a batch, before filling. If the later strategy is to be used, then an acceptable amount of aseptic storage must be available, and the arrangement of rooms needs to be such that the vial depyrogenation process does not interfere with another filling process. Under cGMPs, one cannot be filling product A while moving glass from product B through the same room.

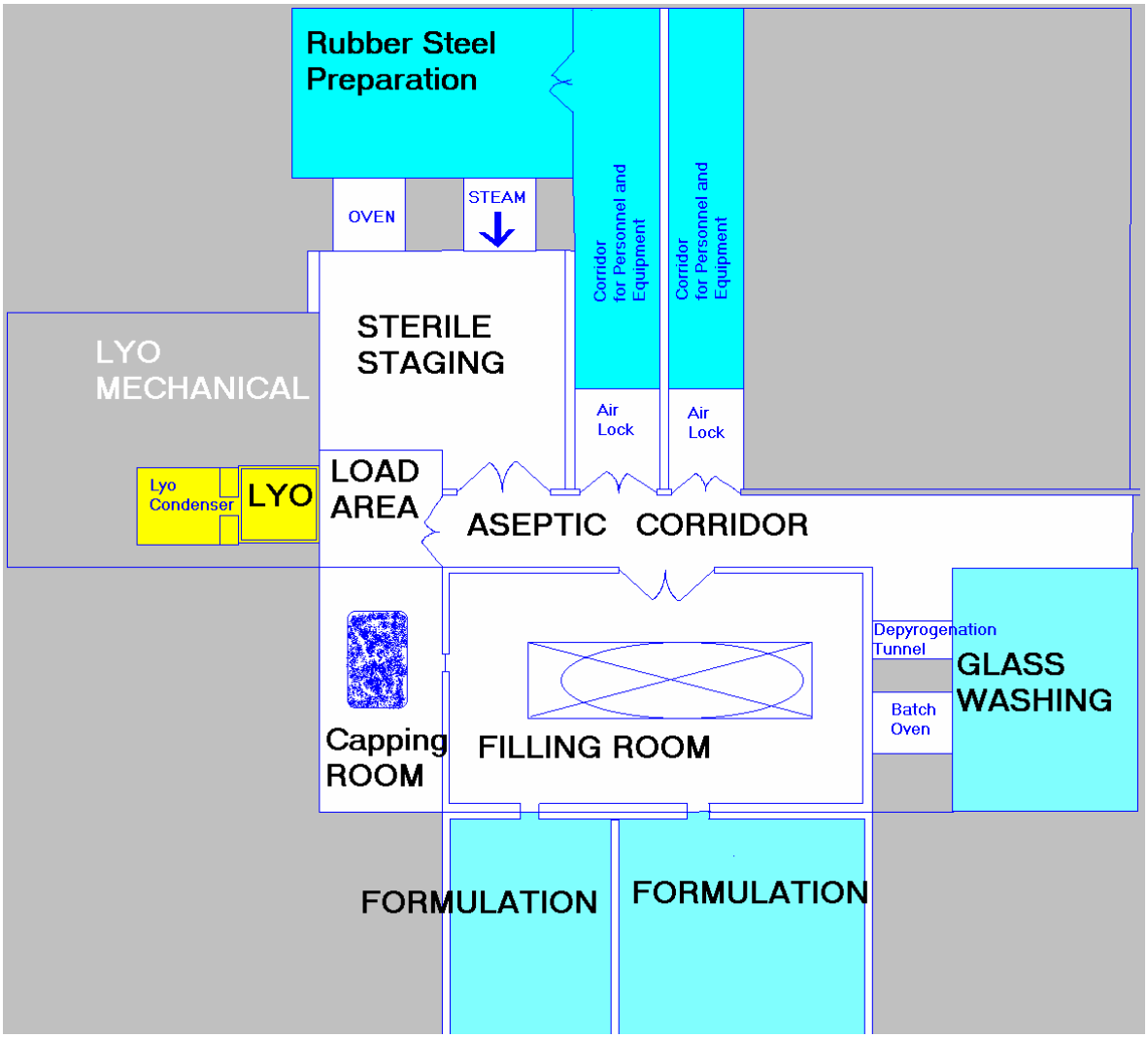
The formulation operation must also precede filling. Since we are concerned about aqueous stability, hence lyophilization, it is reasonable that formulation might have to occur immediately before the fill, allowing the smallest possible lag time between formulation and fill. Typically, that time can be 1 to 3 hours, sufficient for quality testing to assure that the formulated product meets specifications for the fill. Under cGMP, it is common that only one product at a time be permitted within a defined formulation space.

Before vial filling can begin, the lyophilizer must also be prepared. Upon completion of a product lyophilization, particularly if a different product is to follow, the lyophilizer must be cleaned and then tested to assure that it meets a cleaning specification. Next, it must be sterilized, usually by steam, and then leak tested to assure that it will hold vacuum. Any leak after product is introduced may be determined to have come from a non-sterile environment and thus cause the entire product lot to be rejected.

The filling and tray-loading operation can begin, only after materials are washed, sterilized and staged, the lyophilizer is made ready, the filling machine is aseptically assembled and the formulation is completed and tested. After each tray of vials are filled, they must be transported to the lyophilizer, which has been located outside the filling room by design, so that the filling machinery can be used to service another lyophilizer, or perform liquid fill over the period when the lyophilizer is running. In most operations, filling machines can be used to perform at least one lot every 24 hours, while a lyophilizer can rarely exceed one lot every 48 hours. The shortest lyophilizer cycles are about 20 hours, and it takes slightly more than 1 shift to clean, test, sterilize and leak test a lyophilizer to get it ready for use again.

Post filling operations, placing the crimp onto the vial, visually inspecting each unit, and finish packaging must also be carefully considered, since the equipment to be used is probably multi-use and thus subject to capacity constraints. One may assume that any equipment that is dedicated to one product (in this case study, the lyophilizer) will be purchased at an optimal size and thus define 100% capacity.

The figure does not include everything that might be rate limiting to different organizations or specialized products. For example, warehousing of both the incoming glass and the finished, packaged product has been omitted, as has any specific formulation equipment. Personnel requirements for the case study are included, but are clearly unique and will differ for each



situation.

Figure 1: Facility room layout, showing position of added lyophilizer and loading area within a parenteral fill unit.

Lyophilization Capacity and Cycle Length

Lyophilization capacity is defined by the number of vials that will fit into a load, thus defining a lot size. It may also be defined by the number of vials that can be produced per year within a single operation, which could be more than one lyophilizer. Obviously, vial size is a factor in calculating capacity, since more small vials will fit into a lyophilizer chamber than larger ones. However, it is sometimes not obvious as to how dramatically different the numbers are. In table 1, it can be seen that for a lyophilizer with total shelf area equal to 23.4 m^2, one can get as many as 107,000 each 2cc vials or as few as 7,200 each 100 cc vials. Clearly, large vials will have proportionately greater cost coming from lyophilization. Capacity may also be

limited by the size of trays, and tray size may be limited by the dimensions of an existing tray loader on the filling machine. Thus, there may be additional expenses to maximize lot size within a lyophilizer. In the example of table 1, although the total shelf area is 23.4m^2, the total tray area is only 21.3m^2.

Next, it can be seen in table 1 that two vials of nominally the same size, "5cc" have meaningfully different outer diameters and thus different capacities per lot. In the case shown, the 21mm vial (51,840 units equal 1 lot) will produce 6840 units per lot more than the 22.5mm vial (45,000 units equal 1 lot), an increase of 15%.

Finally, cycle length will greatly affect annual capacity. For most operations, staggered shifts are impractical and thus filling events with subsequent lyophilization events will occur at a set time of day, whether it is every day or once a quarter. Thus the shortest turn around time (start-to-start) for a lyophilization is 2 days. Matching annual sales capacity to lot size and number of lots produced is both a science and an art. Operating close to maximum capacity is efficient, but failing to meet market demand is catastrophic. Figure 2, shows annual capacity for the case study lyophilizer, based on 50% utilization, and varying sizes of vials. In each vial size instance, a 3-day cycle turn is assumed. Since lyophilization is often a rate limiting step, this is a very important graph to consider when setting up a manufacturing operation.

Table 1: Chamber capacity for vials

Vial Size	Outer Diameter	Units in Chamber
2cc	14.8mm	107,640
3cc	17.0mm	81,600
5cc	21.0mm	51,840
5cc	22.5mm	45,000
10cc	24.0mm	38,640
20cc	30.0mm	23,760
50cc	38.7mm	14,280
60cc	41.6mm	12,480
100cc	52.4mm	7,200

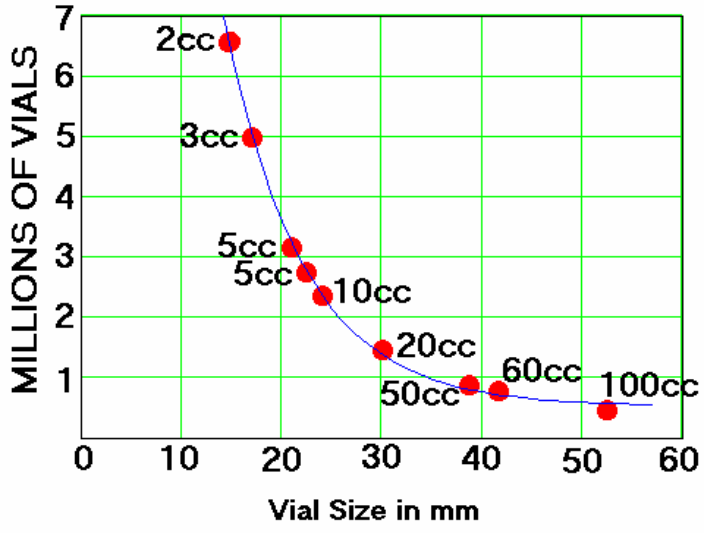


Figure 2. Annual production capacity from one lyophilizer at varying vial sizes. The computation assumes 50% utilization (operating 180 days/year) and a 3 day cycle from start to start.

Incremental Capital Costs for Equipment

Every project has its own unique needs for capital. It is rare, however, in a pharmaceutical setting to incrementally add a major piece of equipment without a large impact on other operations, as a consequence of using capacity that was previously available for those other activities. In table 2 for the project of this case study, the equipment and capital outlays for support activities have been presented. Besides the lyophilizer and lyophilizer loading room, these include a fill machine with class A space for operation, vial washer, autoclave, class B preparation area, incremental upgrade for water for injection (WFI), depyrogenation tunnel, vial capper, and automated inspection station. The selected budget is modest, and based on experienced purchasing and engineering personnel able to source a combination of new and used equipment at very competitive prices. Class air space is priced at the lower end of the spectrum, based on no included equipment. It would be easy to spend twice the budget for the same equipment list.

What is most clear is that the lyophilizer alone would be inadequate to incrementally add a product to the existing operation. It is important to add sufficient infrastructure to achieve new capacity without crippling capacity that is already in place.

Table 2: Equipment List

Equipment	Purchase Price
Lyophilizer	$900,000
Load Room (class A)	$37,500
Filling Room (class A)	$325,000
Fill Machine	$800,000
Prep Room (class B)	$162,500
Vial Washer	$75,000
Autoclave	$250,000
WFI System (upgrade)	$300,000
Depyrogenation tunnel	$250,000
Vial capper	$125,000
Inspection Station	$300,000

Support Systems and Estimated Utilization

Full utilization of the lyophilizer probably does not mean 100% utilization of the various support functions thus far considered. Depending on the length of the lyophilization cycle, one filling room may support several products. Since the lyophilizer is assumed to take 3 days from start-to-start, and the filler can be used for a new lot each day, it might be possible to take on two additional products. Table 3 summarizes the estimated capacity draw on each support system from the new project lyophilizer running a three-day start-to-start cycle and operating at 100% capacity (about 48 weeks/year). Immediately, it is seen that the area in front of the lyophilizer is only used 50 to 60% of the time, during the load and unload operations. Worse still, a new filling and capping area put in just to support this machine is only expected to be used 33 to 50% of the time, and a new equipment preparation area is estimated for only 30 to 40% usage. Use of an existing sterilizer, WFI, and steam plant are truly minimal at <10% each, but both the autoclave and WFI system were assigned budgets because it was estimated that they were near

100% capacity before incremental expansion. If either of these were rate limiting, it would seriously hinder operation of the new lyophilizer.

Table 3: Utilization of Support Equipment/systems

Equipment	% Utilization
Lyophilizer	100%
Load Room (class A)	50-60%
Filling Area/Capper	33-50%
Depyro tunnel	33-50%
Prep Room (class B)	30-40%
Steam Autoclave	<10%
WFI System	<10%
Clean Steam System	<5%

Hardly anything except the lyophilizer is used at greater than 50% of its capacity. One possible change would be to put in a second lyophilizer fronted to the same load area and capable of producing lots in a staggered fashion with the first. Alternatively, liquid fill products (non-lyophilized) could be added to the operation to consume the excess capacity. Such products might be contracted in from other organizations or consolidated from older facilities. Often there are small products that need a home, but cannot justify capital outlay in isolation.

Significant Others

Certain activities consume a meaningful and additional percentage of the capital budget. Plainly, the spending does not end when the equipment has been acquired. Four activities, commissioning, validation, maintenance, and operations, constitute significant additional cash.

Commissioning is an engineering activity in which the equipment is set into its final location, fitted with utilities, and operated on a limited basis to assure that it meets minimal purchasing specifications from the vendor. Some activity certainly can occur at the vendor's location, but most activities must be repeated when the equipment is relocated to the operational site. Commissioning activities can be budgeted at about 20% of the cost of equipment. It may also be true that dollars spent on equipment, especially used or refurbished equipment, are inversely proportional to dollars spent on commissioning.

Validation, including IQ/OQ and especially product/equipment performance qualification will add to between 20 and 30% of the cost of equipment. Expense matters because as the equipment gets larger, performing the same tasks require more automation. For example, a small tank would not need the clean in place systems and load cells required of a large tank. Since these additional systems must be validated, it is common to see the validation costs proportional to the cost of the equipment.

At only 2 to 4% of the cost of equipment, revalidation costs seem trivial. However, they are an annual and ongoing event. Consequently, over the amortization period of the equipment and the product, these costs should be added in. Similarly, maintenance costs are estimated at 5 to 8% of the equipment cost but are repeated annually forever. It is also worth asking if the additional burden on these departments might require additional personnel. Since these costs are mostly attributed to labor hours, if no additional personnel are required, then the current personnel must be underutilized.

Money and Personnel

The cost of money is a subject onto itself, but is always considered significant. Accountants generally try to capitalize everything. Consequently, the commissioning and validation labor, which is a one time event in the project, may likely be capitalized. However, there is a budget cost associated with the decision to capitalize dollars. For the purpose of this case study, simple interest compounded monthly at 8% and structured as repayment of a loan has been assumed. By translating capital expense plus interest into monthly payments with an 8 year amortization, it is possible to both avoid the accounting game of hiding the project costs and simultaneously get a good idea for the actual monthly outlay associated with the activity. In addition, it becomes irrelevant whether the equipment is purchased or leased, since the cost is stated as a constant monthly obligation.

The need for additional personnel is implicit in the assumption that new activities will be performed as an incremental addition rather than an exchange for prior activities. Although some personnel may have been underutilized and thus by taking up slack the expected personnel increase may be reduced. Even if operations can get by with less than a totally new shift, any additional business with personnel increases can impact other departments and lead to unexpected requests for still more personnel. In this case study, it was assumed that 4 or 5 additional employees were needed, and a budget was accordingly set.

Budget

The complete capital project budget is shown in table 4. The expected product lifetime is assumed to be 8 years, and although the equipment may last beyond that period, most products do not remain in continuous manufacture with the same equipment for longer than that time. From the column labeled "Size / Capacity" in the table, one can obtain the gross capacity requirements for the equipment. Installation and validation, one time costs, can be capitalized and added to the equipment prices. Installation costs are added to class air areas even though those areas are normally quoted with installation. Consider the values to be contingency fees. Due to the inherent error in these types of estimates, and due to the way these data will be used, it is unnecessary to add inflation factors to the annual costs. Monetary inflation is accommodated by price increases on the sales side of the product, and do not need to be estimated on the cost side.

Table 4: Capital Project Budget

Item	Cost to Purchase	% Utilized	Size Capacity	Cost to Install 20% of Purchase	Cost to Validate 25% of Purchase	Annual Revalidation Costs 3% of Purchase	Annual Maintenance 6% of Purchase
Lyophilizer	$900,000	100	23 m^2	$180,000	$225,000	$27,000	$54,000
Load Area Class A	$37,500	100	7.5 m^2	$7,500	$9,375	$1,125	$2,250
Fill Area Class A	$325,000	33	65 m^2	$65,000	$81,250	$9,750	$19,500
Fill Machine	$800,000	33	$\leq$ 300/min	$160,000	$200,000	$24,000	$48,000
Prep Area Class B	$162,500	30	65 m^2	$32,500	$40,625	$4,875	$9,750
Vial Washer	$75,000	30	$\leq$ 300/min	$15,000	$18,750	$2,250	$4,500
Autoclave	$250,000	8	2 m^2	$50,000	$62,500	$7,500	$15,000

WFI System addition	$300,000	8	6 liter/min	$60,000	$75,000	$9,000	$18,000
Depyrogenation tunnel	$250,000	33	≤ 300/min	$50,000	$62,500	$7,500	$15,000
Vial Capper	$125,000	33	≤ 300/min	$25,000	$31,250	$3,750	$7,500
Automated Inspection	$300,000	33	≤ 300/min	$60,000	$75,000	$9,000	$18,000
Column Sums	**$3,525,000**			**$705,000**	**$881,250**	**$105,750**	**$211,500**

In addition to the capital budget, included in table 4 are estimates for re-validation and maintenance, annual recurring costs. These estimated numbers are derived from experience with similar pharmaceutical equipment and each individual piece can be expected to have significant variance. Overall, it is likely that the summations will be reasonable. They include labor rates fully burdened with corporate overhead.

Adding in the cost for money, and 4 or 5 employees to operate the new lines, the total comes to over 10 million dollars in 8 years, amounting to 1.4 million per year in cash payments. Furthermore, it is unlikely that any pharmaceutical product will be produced during the first year, since construction, installation, commissioning, and validation will take at about 12 months.

Table 5: Model Annualized Investment (8 years)

	Invested Dollars	Proportioned to one Lyophilized product*
Capital Repayments	$867,073	$405,064
Re-Validation	$105,750	$49,403
Maintenance	$211,500	$98,805
Employees	$220,000	not estimated
Total	**$1,404,323**	**$553,272**

*Proportioning is done based on the percent utilization of each piece of equipment or classed area within the expansion project.

Impact to Product Cost

The apportioning of cost to a vial of product will vary with the number of vials produced. Further, it has already been shown that the number of vials produced depends on the size of the vial and the size of the lyophilizer chamber, and the length of the lyophilizer cycle, start-to-start. Capital costs are not deductible from gross income in the year they occur and may be "recovered" (expensed) through depreciation, amortization or when the asset is sold, but such tax relief does not forgive the need to recover (be paid back) the expenditure from the price of the product. There is no defensible reason related to tax structure for holding aside capital cash outlays from inclusion into product costs.

Recalling that the discussion concerns the incremental addition of a lyophilizer into an existing pharmaceutical aseptic filling operation, what the market is for the incremental product? Typically (hopefully), market estimates are not flat. Reality is that market volume for a product is not smooth, but modeling and production plans need logic, so it is best to plan with typical market estimates. Table 6 shows a chosen product and the timeline for making it in through use of the investment. By product maturity in the sixth year, the lyophilizer is at a maximum, but of course, other portions of the invested dollars remain unused toward this one product. In determining cost to the product, it is necessary to estimate the percent utilization of the multipart investment that can be attributed to the one product. Since the lyophilizer essentially dedicated

to the product, all of its investment can be counted. However, other portions of the support facility, necessary to make the product are only utilized a small portion of the time for this product. Their investment costs are thus rightly shared by other products that may be produced when efficiently using the equipment.

Table 6: Market Estimates vs. Capital Utilization				
Lyophilizer (Years)	**Marketing Product Year**	**Estimated Number of Units**	**# Of Lots**	**% Utilization**
Year 1	Clinicals		0	Validation
Year 2	Regulatory Filing Year	150,000*	3	3.1%
Year 3	First Year	1,900,000	38	39%
Year 4	Second Year	3,000,000	61	63%
Year 5	Third Year	3,700,000	75	78%
Year 6	Fourth Year	4,150,000	83	87%
Year 7	Fifth Year	4,400,000	88	92%
Year 8	Sixth Year	4,600,000	91	95%
	Totals =	**21,750,000**		
*Conformance lots produced at year end.				

The lyophilizer can produce 2 lots per week with a 50,000 unit lot size for the chosen 5cc vial. Scheduled shut down and maintenance are 4 weeks.

What cost per vial are appropriate as a consequence of the incremental investment to bring in a new lyophilizer? Table 6 has the estimated number of units that will be produced through the lyophilizer in the first 6 years after product launch. Interestingly, the investment to add equipment had to begin 2 years prior to product launch. Table 5 also has the annual costs that are appropriate to only the one lyophilized product. Personnel costs not estimated with the annual costs of the investment because it is collected as direct labor to each of the projects on which they work. These annual costs ($553,272) assume that one would want to recover the investment for this product over exactly the 8 year depreciation period. In reality, there may be business reasons to accelerate or defer the recovery period. Over eight years, the cost/vial attributable to the 5cc lyophilization product by way of the investment needed to incrementally add a lyophilizer is $0.20 = ($553,272 x 8) / ($21,750,000).

Other costs associated with the vial production are usually quite significant by comparison with the project investment. These ongoing costs elements include

- Components – glass / stopper / cap
- Contents – API / excipients
- Packaging – label / carton / shippers
- Distribution , Sales and Marketing activities
- Royalties or associated obligations
- Corporate overhead.

In order to apply this model to some other particular project, it is necessary to have market and timing estimates. Alternatively, it could be applied for each size vial by assuming a percent utilization and a level annual production, as shown in figure 3.

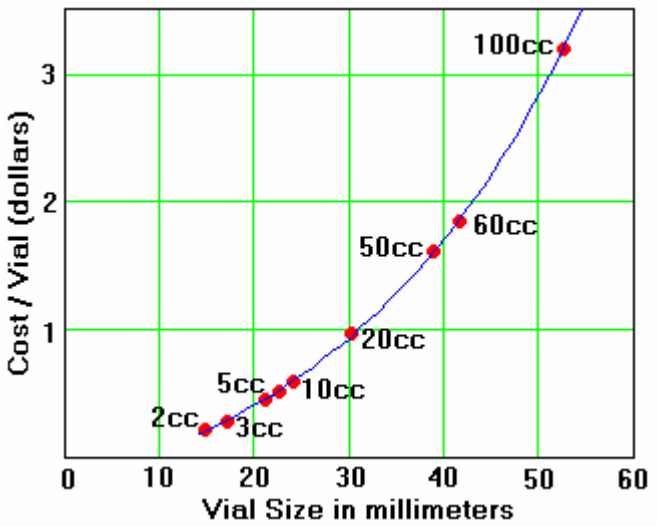


Figure 3: Investment cost per vial with 50% utilization.

Points to Consider

The addition of incremental business into a parenteral facility is straightforward, but not as simple as just adding a major piece of equipment and expecting revenue to follow. Unless a careful study is done to follow the progress of the new business and the impact that it may have on old business, it is likely that one may merely exchange for old.

- Identify all equipment and space needs, thereby permitting accurate cost estimates.
- Include costs for validation, re-validation, and maintenance.
- Evaluate the impact to ongoing operations and structure to the new business to not interfere with those operations.
- Proportion capacity for multi-use equipment so that the new business does not bear an unreasonable amount of cost. By understanding the available capacity, it is possible to intelligently search for projects that use the capacity.
- When assessing investment cost versus return, be careful to compare apples with apples. The return is going to be composed of more than just the revenue from a single product, or the revenue from a single product must be compared only to a portion of the overall investment.