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A Holistic Analysis of Pharmaceutical Manufacturing and Distribution: Are Conventional Supply Chain Techniques Appropriate?

by Christopher J. Savage, Kevin J. Roberts, and Xue Z. Wang

This article evaluates the post-discovery supply chain to determine whether it can be evaluated by conventional analytical methods and improved by the application of supply chain techniques. It considers the impact of factors, including changes in legislation and drug delivery methods.

Introduction

The pharmaceutical industry operates globally, generates a massive amount of revenue (Table A) and affects almost everyone in the developed world. Drug treatment is the most common form of healthcare intervention and represents the highest non-staff revenue cost in the UK's National Health Service (NHS) with estimates suggesting that 70% of the UK population are taking medication on any given day.[11] The industry traditionally enjoys high profits with finished product margins as high as 30%, notionally justified by the high R&D, drug development, and marketing costs estimated at US $800 million to US $1 billion per marketed Stock Keeping Unit (SKU).[10]

Recently, these profits have come under increasing scrutiny as a result of government policies, generic competition, and wholesaler objectives. Logistics costs, as a percentage of sales revenue, tend to be lower than in other industries due to the high value of the goods.[2] Nevertheless, pharmaceutical companies are becoming more interested in optimizing their supply chains to save costs and perhaps, more significantly, gain competitive advantage. This article focuses on adopting a holistic approach in order to try to identify problems that hinder optimization of the supply chain through a collaborative project involving the *Institute of Particle Science and Engineering* of the University of Leeds and the *Division of Transport and Logistics* of the University of Huddersfield. Data was collected through discussions and workshop sessions with a number of key UK pharmaceutical production companies as well as pharmacists from the UK, New Zealand, and the USA. The work summarized in this article provides the foundation for a larger project by examining the basic premise and potential future approaches.

Country	US$ billions
United States	177.40
Canada	10.43
Germany	25.70
Italy	14.50
France	21.70
United Kingdom	15.70
Spain	10.60
Japan	59.00
Mexico	6.60
Brazil	5.30
Argentina	1.80
Total	**348.73**

Table A. Retail pharmacy sales, 12 months to March 2005.[4]

Pharmaceutical Supply Chains: A Divided Structure

Overall, the pharmaceutical industry can be broadly divided into two market segments; ethical (prescription) and "over the counter" products. This work focused on the ethical segment, where two distinct supply chain components can be clearly identified, i.e., the pre-production (Discovery) chain and the post-development (Production) chain. Both components, while clearly different in their content and magnitude, form significant parts of the overall process responsible for converting an initial idea from discovery into a usable drug and delivering it to the patient (or rather to the retailer or dispensing pharmacist). These two components intertwine to form a lengthy and complex supply chain that

is difficult to consider holistically and can lead to a protracted "time to market" for the resultant product. In addition, the overall process could offer significant scope for improved efficiency and enhanced product profitability.

In the pre-production (Discovery) chain, the process of discovering and developing a compound to produce an ethical drug in an approved format to be used by the patient (Figure 1), can take as long as 15 years although a seven year development/approval time has been achieved for some markets. As product filing usually takes place five years into the development cycle, this leaves only 10 years from the 20 year patent protection limit for the company responsible for the research to enjoy "unshared" benefit of their discovery.

As the diagram shows, for each drug successfully approved, millions of potential compounds may be screened. Then typically, of those that enter the clinical stage, only one in 10 is eventually marketed. Further failures can occur after a product is launched, e.g., when longer term side effects become apparent. This can incur major expense or delay for reformulation/approval or in the worst case the abandonment of many years' work/cost. All of these trial products have high R&D costs that must be borne by those that are brought successfully to market. Drug development also is made more difficult by the ever-increasing complexity of molecules required in drug compound formulation, which works against the need for a quicker route to market. In the post-development (production) chain, the more conventional procurement, production, delivery supply chain can range from nine to 24 months depending on the drug product form and the associated manufacturing complexity.

Overall, there may be scope for time reduction in both of these supply chain components with the concomitant potential for significant cost savings and possibly earlier relief from sickness or even prevention of death. Although both are important, this article will concentrate on the more conventional, post-development supply chain. As this project develops, a parallel article will address the drug discovery chain itself leading to integration of the two components with the aim to examine their design interdependence and give an holistic view.

Methodology

Initial work has concentrated on gathering data on specific as well as generalized pharmaceutical supply chains in order to

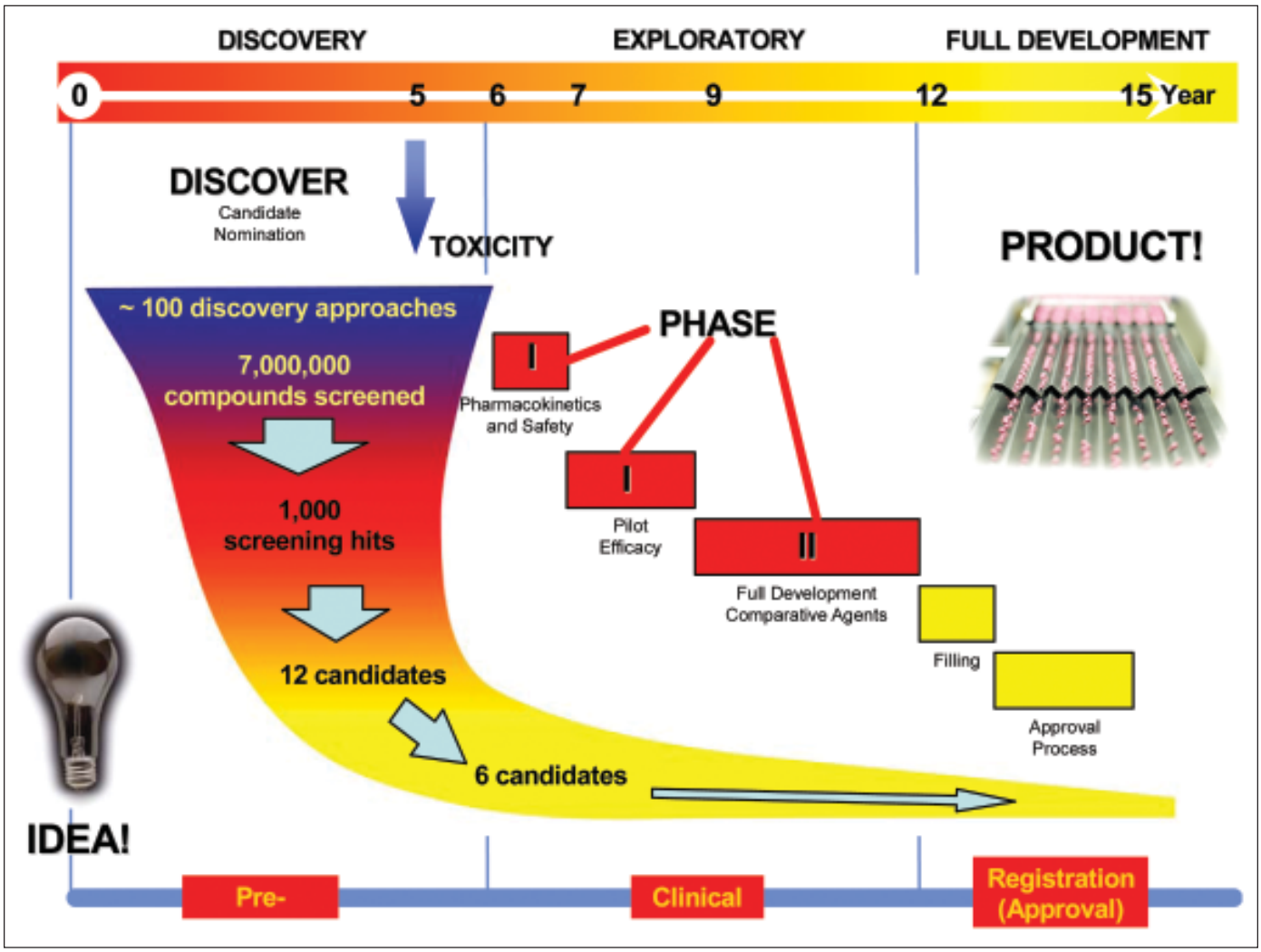

Figure 1. Schematic representation of the timescale for drug development to the marketplace with drug filing after five years into a 15 year drug development cycle.[3]

determine whether conventional logistics analysis techniques and tools can be used to evaluate them and by doing so, identify the critical points for further, more detailed investigation. In addition, an evaluation has been made as to whether manufacturers of similar products structure their supply chains and respond to challenges in a similar manner. The method adopted was to gather data from a series of face to face interviews and brainstorming workshop sessions, and by telephone and e-mail with a sample population of manufacturers, intermediaries, and dispensing pharmacists. The output from these[11] was then combined, compared, and analyzed.

Results and Discussion

An Examination of the Post-Development Supply Chain

The first task was to try to determine whether pharmaceutical supply chains are "different" to such an extent that conventional techniques cannot be used. The initial response from the group of interviewees was usually that "pharmaceuticals are different; they cannot be treated as normal commodities." The most frequently stated reasons for this were the high cost and long duration for the R&D process and the possible impact on life should a drug not be available on time.

There was also a commonly held belief that the production cycle time is very short and highly reactive, a view that would be contested by many supply chain professionals from other fields. When challenged over these statements, their promulgators were unable to substantiate them convincingly. This suggests that they are perceptions rather than facts and that pharmaceutical supply chains could be modelled and optimized like any other. If one concludes that a pharmaceutical supply chain may be treated in a conventional manner, it is nevertheless important to acknowledge some factors that do make it more difficult to change existing methods or at least to do so "quickly." These include:

- a high degree of regulation at all stages of manufacture and distribution, this is arguably greater than any other industrial sector (including the aeronautical industry)
- In the case of ethical (prescribed) medicines, one must be aware that in most cases, the end user (patient) does not choose the product, and that although the patient makes a contribution (e.g., prescription charge), it is the government of the country concerned that is the main financial customer.[14]
- complexity of regulatory environment where for example, changing any manufacturing facility, even something as apparently simple as a packaging site, will require multiple approvals for each SKU for each sales territory. This can take different lengths of time for the same product, e.g., Europe three months, Middle East three years
- the complex extended supply chain with its simultaneous, interwoven discovery, and production components
- supply chain integrity, i.e., a reflection of "life impact" view mentioned above, but not an insurmountable one

The combination of these features may apply significant constraints on strategic supply chain development, often exacerbated by "within company" conflict of interest (e.g., R&D or marketing vs. manufacturing) over issues such as standardization. Similar difficulties result from the proliferation of drug and packaging variants, which some writers ascribe to pharmaceutical companies' desire to differentiate themselves.[5] It is acknowledged that proliferation takes place, but the apportionment of "blame" is disputed by the industry feeling that is frequently caused by customer and/or legal demands and not the manufacturer's whim.

A number of examples have been cited in support of the above view, notably:

Country specific regulations which are very explicit and often subtly different, e.g., packaging has to have details of the product licence holder printed on each inner carton and some regulations require that the foil portion of a blister pack covering each tablet or capsule has a small red box with warnings printed on it.

Fraud prevention where manufacturers may create artificial differences in the physical product to identify it with a specific country, e.g., GSK produce HIV drugs and sell them into African countries on a marginal cost basis. The difference between that price and the selling price in (say) the UK is so great that it is worthwhile for unscrupulous people to buy the tablets in Africa manually open them and repack the product in blister packs or jars for reselling. To prevent this, "Africa specific" SKUs of a different color to mainstream ones are produced. This is similar to the counterfeiting problem discussed by Lewis.[2]

Personalization where conventional dosages are calculated to give the statistical "best fit." This may produce a tablet of 50mgs when the patients need is for 25 or 45mgs. Modern thinking suggests that the correct dosage should be available on an individual basis (without cutting tablets). In due course, the medical practitioner may be able to prescribe an exact dose to match the patient genotype and metabolism. This will require significant legislative changes, but should be possible in the UK within 20 years and will clearly have significant implications for pharmaceutical supply chains.

The above suggests that, while pharmaceutical supply chains can be broadly regarded as "conventional" in terms of their potential for evaluation, there are indications that special circumstances may modify the way in which such tools are applied to develop workable operational solutions.

Application of "Tools" to Pharmaceutical Supply Chains

During discussions, most of the population agreed that the application of supply chain tools was possible, but research to date has failed to uncover much noteworthy, documented, supporting evidence. One published example is the case of Boehringer Ingelheim's Roxane Laboratories (Columbus, Ohio) where a Supply Chain Operations Reference Model

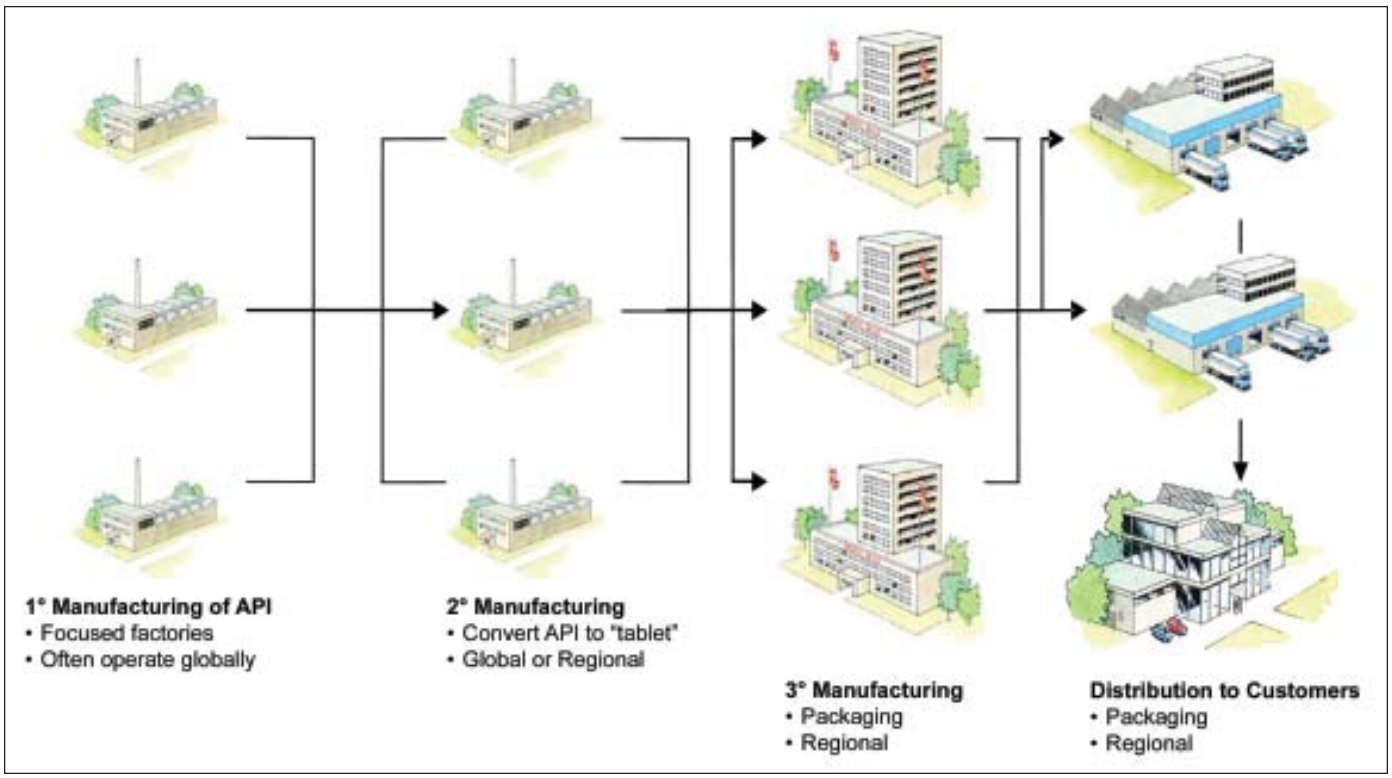

Figure 2. Schematic representation of a generic ethical pharmaceutical manufacturing network.

(SCOR) was said to be used in conjunction with a system of benchmarks to improve customer service level and improve inventory turn by 44%.[8]

The apparent lack of evidence may not be significant as such work is regarded as highly commercially sensitive, often kept "in house" and not published. Therefore, as the contributors were not able to provide conclusive confirmation, it was decided to seek corroboration by treating the use of a particular logistics technique within the supply chains of contributors' companies as an "indicator." In order to decide which indicator might be appropriate, it is necessary to understand the nature of modern pharmaceutical supply chains, their structure, and what drives them. There are many variants even within a given company; therefore to make a selection and illustrate the reasons for the choice, the artificial "generic" shown in Figure 2 has been derived from discussions/correspondence with members of the sample group.

Examination of the typical network structure used by a generic ethical manufacturer, e.g., for the production of tablets and capsules, reveals that three major "stages" or "levels" in the production process or network are clearly recognized.

Primary Stage

This concerns the manufacture of the Active Pharmaceutical Ingredient (API). It is technology driven, usually taking place in "focused factories" that tend to operate globally, producing material for many countries and is often outsourced ~ frequently dual sourced. The processes are multi-staged, usually with stages occurring on different sites depending on the APIs concerned. Process control is often weak, which combined with scheduling issues, leads to proliferation of safety stock, poor asset utilization, and high levels of Work In Progress (WIP) capital.

Secondary Stage

This is where the intermediate formulation processes such as blending, granulation, drying, compaction, and coating leading up to and including the production of the "tablet" take place. These factories also may be considered as focused in that they tend to specialize by physical product type, e.g., sterile, topical, tablet, or capsule. The preferred location would be physically near to the market to serve regions consisting of one or more countries that are close to one another, but this may be overridden by political and/or economic factors. Units tend to be global, where the technology is *difficult,* but regional where the technology is *less critical* or *well established*. Products may be moved from global to regional factories as they mature (i.e., later in their life cycle) or when some specific "local formulation variants" can be produced. Localized secondary manufacture may tend to increase should personalized prescribing become a reality.

Tertiary Stage

This is where packaging takes place and is divided into three significant component types each of which may entail different manufacturing sub-stages, including:

- Drug product environment, i.e., packaging closest to the tablet (the blister pack or bottle) which is often critical as it provides immediate protection for the product and helps maintain its stability.

- Drug packaging, i.e., the carton that holds the blister packs or bottle together with the associated leaflet.

- Product identification, i.e., printing or labeling of a carton with specific information such as date, price, and license holder. It is also where customer (retailer) specific additions are made, e.g., the addition of Radio Frequency Identification (RFID) tags to packs.

In general terms, the shape of the bigger companies' networks are influenced by the principle of continuous improvement and a continual tension between the desire to have common global supply and the need to satisfy specific local needs. Networks are evolving and simplifying by reducing the number of nodes, e.g., GSK reduced from 120 manufacturing sites worldwide four years ago to current 80 (as of May 2005).

The traditional manufacturing approach has been that of a "push" of production against forecast. This is changing and companies are moving towards more "leagile" networks where lean and agile paradigms are combined within a total supply chain strategy to respond to volatile demand downstream while providing level scheduling upstream.[9] This is usually accomplished by means of a de-coupling point so that the later (secondary and tertiary manufacturing stages) are made to order (pull) while the primary (API) manufacture is effected via a controlled push to meet forecast. This push process is often managed using Kanban. The latter is a Japanese term used to signal a cycle of replenishment for production and materials to maintain an orderly and efficient flow of materials throughout the manufacturing process with low inventory and work in process. The key to successful "leagility" may be said to be "decoupling" the supply chain by making use of postponement where possible.[13] Although postponement has been proposed as a logistics and manufacturing concept for a long time,[1] and its use has led to improved supply chain performance,[15] its use in the ethical pharmaceutical area is less and documented. Therefore, the use of postponement was selected as a specific indicator of the application of a conventional logistics tool to pharmaceutical supply chains.

Current Application of Postponement in Current Pharmaceutical Supply Chains

When asked about the concept of postponement (or late stage customization as it is sometimes referred to in the industry), the response was often positive but varied. The degree to which it has been adopted or is perceived to be able to be used differed greatly across countries and companies as well as within them. The restriction often cited was legislation, but it appears that the degrees of inventiveness and/or risk-taking that management were prepared to utilize were also major factors.

The following responses to the question "Do you use postponement?" give an indication of the range of reaction:

- **Very positive:** we are trying to make as much use of postponement as possible to decouple the supply chain, reduce stock holding/costs, while maintaining/improving customer service.

- **Positive (conditional):** the simple answer is yes, we would like to meet specific customer needs as late in the supply chain as possible because we would consider that there is more mileage in demand driven supply. It is easily dismissed and while patient specific supplies, personalized medicines or 'lot size 1' are often discussed as concepts, the traditional methods of manufacture (big, push driven, batch sizes) are often used to block changes.

- **Neutral (or confused?):** there are two basic inventory management approaches more pharmaceutical companies are moving toward to demand forecasting.

- **Negative:** "this might happen somewhere in industry, but I doubt it."

To seek clarification, more positive respondents were asked to give some examples of postponement as used in their company. The following is a sample of the responses:

- **Common cartons:** facilitated by attaching the leaflet to the outside of the carton rather than inserting it.

- **White box printing technology:** by using high quality, limited color printing, "vanilla" cartons can be used for a number of lower demand countries.

- **Blister pack customization:** is possible using "on-line" foil printing, but is much more difficult due to technical issues, country specific variations, and the associated cost. It is probable that pre-printed foils will continue to be preferred, and that manufacturers will concentrate on developing packaging lines with faster changeover times. Thus, trading-off line-operating speed (less important as batch sizes reduce) against set up/changeover time (becoming more important as batch sizes become smaller and changeovers more frequent)

- **Two stage packing:** one factory would pack bulk blister strips or bottles of tablets/capsules. These would be printed only with common data, such as the brand, generic name, strength, batch number, expiry date. This factory could utilize efficient high speed packaging equipment as it would be packing for several markets. At a later date, the same factory (or a different one) would complete the packaging by printing any market specific data onto the pack using on line printing equipment and would add a market specific leaflet to the pack. Typically, these packaging runs would be smaller and utilize semi-automated equipment – again this is "under development."

Future Scope for Application of Postponement in Pharmaceutical Supply Chains

It must be noted that most examples given above are of possibilities or developments rather than "current practice." Therefore, respondents were asked what their views of the future scope for postponement were and whether they were aware of any likely constraints.

Technology Developments

There are a number of technology developments that will have a significant impact on the supply chain and could lead to a need for decoupling much closer to the end-user. For example, the possibility of remote prescribing by medical or nursing practitioners via internet or sophisticated computer enabled telephones. In addition, developments in knowledge based systems combined with the availability of genotype and complimentary information will enable greater tailoring of drugs, and combined with the above technology, will permit remote diagnosis and prescribing. Note, currently, all new UK-issued prescriptions (excluding repeat prescriptions) should be issued "face to face." Although not yet legal in the UK, the use of such approaches would enable patient specific prescriptions to be sent directly to the dispensing pharmacists who are already assuming a greater role in the management of drug treatment. This would have a significant impact on the supply chain and could even lead to in-pharmacy formulation. In general larger companies will listen to customer requirements and try to meet them where appropriate. Specific requirements may increase supply chain complexity so they need to be evaluated (usually against a two-year development/approval horizon) to decide if they add sufficient value.

Inventory Policy

This factor may be seen to override postponement benefits for which a number of key reasons emerged. First, medical criticality, i.e., the failure of drug availability, could cause patient harm and damage to the company's image. Second, the balance of business financial risk reflecting the fact that the cost of the API is frequently much less than 25% of the final price and so the risk of revenue loss through failure to supply, a "stock out" situation, is perceived as outweighing the cost of stockholding. Finally, there is a clear need to maintain safety stocks:

- Normal: to cover minor "blips" and irregularities in production or the supply chain
- Strategic: to cover a major disaster such as a factory fire or raw material supplier failure

Parallel Importing Issues

Common pricing across Europe does not apply to pharmaceutical products; which means that customers may import at lower prices from non-manufacturing countries, which, in turn, frustrates the manufacturer's inventory stock holding, production, and packaging plans making postponement more difficult.

Drug Delivery Change Constraints

Most companies are aware of the possibility (probability) of changes in methods of drug delivery (i.e., moving away from tablets); therefore, current supply chains could become obsolete in time. This means that any significant change to the supply chain has to be assessed for potential advantages against a possible relatively short time-frame (say 10 years?). Active companies are conducting research into methods to suit alternatives. This is ongoing, but confidential.

Conclusions and Forward Look

The observations discussed in this article are from a small, sample population intended as a pilot for the extended project. Any findings based on them will require confirmation, but they do suggest that conventional supply chain analysis methods can be used to evaluate ethical pharmaceutical chains with a view to moving them toward optimum performance, despite perceptions of "difference." There are factors that may restrict developments based on such evaluations and there are also valid differences between countries due to legislative and valid cultural issues. Additionally, there seems to be a general move from the traditional "push" operations to more of a demand-led market-pull response model often leading to attempts to decouple the supply chain to create "leagility." Some companies are aware of shortcomings in their supply chains and are actively trying to improve them, and of these, some understand and already try to use techniques such as postponement. There is a clear awareness of possible developments in alternative methods of prescription and of drug administration that both stimulate and restrict willingness to invest in supply chain development. However, the innate conservatism of the drug companies causes apparently unnecessary proliferation of inventory to avoid stocking out and being "beaten to a market" even though such stock can and does degrade over time. Overall, differences between the manufacturing companies suggest that analysis to date requires development. Further, conclusions on the feasibility of the "holistic approach" can only be safely drawn when the above findings on the "Post-Development" supply chain are combined with the output from similar and related studies on the "Discovery Chain" component.

For the future, it will be important to investigate the scope for applying supply chain strategic philosophy in an integrated manner covering both up and down stream process sectors to bring efficiency to the whole discovery and production supply chain. It also may be useful to compare pharmaceutical supply chains with those of commercial products with a high Intellectual Property Rights (IPR) product such as the semi-conductor industry. The first steps in this process should be to map in detail a significant number of supply chains for similar products in different companies. These can then be used as a basis for more detailed analysis and comparison including determining a method of measuring the effectiveness of these chains, as well as the impact of any changes that might be suggested. The present work looked at ethical products that are in

patent. In the future, once a viable methodology has been established, it would be interesting and useful to look at other aspects such as:

- ethical products in different stages of their life cycle (e.g., after patent expires)
- generic ethical products
- non-prescription pharmaceutical products (e.g., aspirin). Interestingly, these are often subject to more frequent changes in pack style, etc., than ethical products. They are subject to less stringent regulations, but all changes still need approval.
- the downstream part of the delivery chain, including the role of wholesalers, hospitals, and governments
- what impact alternative drug delivery methods (e.g., patches, inhalation, parenteral) would have on supply chain design
- the potential for remote and "personalized" prescribing, especially following individual genomic profiling
- how the design of individual supply chains could be influenced by and/or influence the drug development process

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Operational Considerations of Thermally Sensitive Healthcare Products

by Sanford L. Cook

This article discusses the need for special procedures starting at receipt of sensitive components/ ingredients, through operations and distribution, including requirements and new packaging supplies for temperature sensitive medical products.

Introduction

The rapid pace at which new medical products are being tested and coming to market has become a challenge that product managers, logistics and engineering professionals are confronted with at an accelerated rate. Technologies that protect these precious materials from potential environmental assault should be understood in their respective portfolios. A growing awareness of the degrading effects to products resulting from exposure to temperature and humidity has caused special considerations throughout all phases of operations. There are some basic and salient points that the plan leader should bear in mind - *Figure 1.*

This article describes the special considerations operations personnel and clinical project managers are tasked with when designing a cost efficient strategy to facilitate the safe acquisition of raw materials, formulation processes, manufacture, packaging, storage, and distribution of temperature/humidity sensitive materials. Discussions will include understanding the physical forces products are exposed to, transportation, manufacturing equipment qualifications, and monitoring, as well as strategic planning from the receiving dock to the shipping dock.

The Influence of Weather

Weather reports predict the results of physical forces in the atmosphere. The dynamics created as a result of rapid temperature differences may produce ancillary products such as moisture (rain) and negative or positive pressures (winds). Through technical means (discussed later in this article), a potential for stormy weather is produced inside an insulated container.

This example of weather may be illustrated in packaging as follows: temperature sensitive products are placed into insulated containers to protect them from ambient conditions. If the products must be kept at refrigerated or freezing temperatures, refrigerants, such as dry ice (CO_2) or Phase Change Materials (PCM), are used to drop the temperatures inside the protective box. The package is sealed. As the cold dry air is expunged from the refrigerant, it will collide with the warmer air trapped when the box was closed. As the temperature drops around the product, the moist air surrounding the product releases any moisture that it can't hold. The

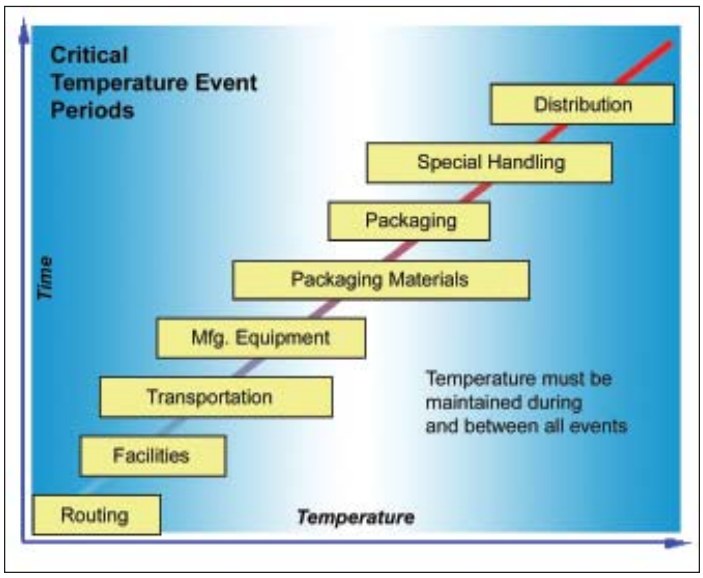


Figure 1. Critical temperature event periods.

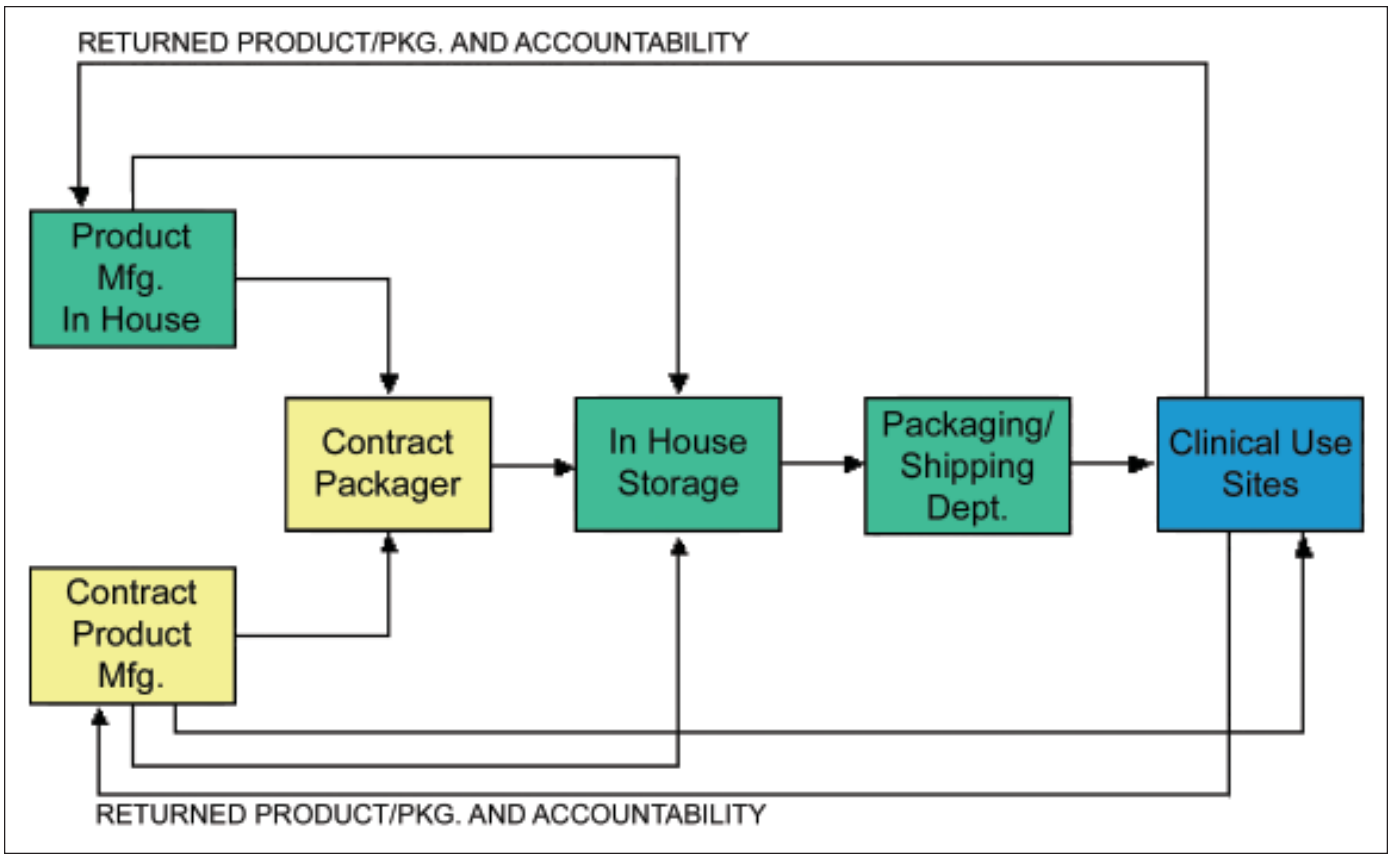


Figure 2. Clinical product distribution chain.

condensation may be controlled by proper design. All factors must be considered when designing a complete system to protect sensitive products. However, a system or "protective tunnel" should start long before the finished product is packed into insulated shipping containers and all aspects of the product's processes and journey should be considered.

Incoming Components

Each step should be analyzed as a detail to a complete system. The system must be continuous and not allow any part to fall between the cracks. For example, how do the basic ingredients arrive at the processing facility? If at least one component is temperature sensitive, there should be a process to check to see if that component has been exposed to dangerous temperatures or over excursion time durations during the shipping event. Single exposures may not be as important as the cumulative time the product has been exposed. Normally, there will be labeling depicting the temperature tolerances; however, a device should be included that will indicate any time/temperature variances. *Responsibility should be assigned to specific personnel to ensure the materials arrive as specified on the label or accompanying documents*.

Of course these steps should be detailed in Standard Operating Procedures (SOPs) as part of an overall protocol. The next step is not always accounted for when the material arrives. Specific procedures and responsibilities should be assigned to material handling in terms of exposure time documentation from the dock to the temperature-controlled environment.

Facilities

Most storage facilities today are adequately temperature controlled and monitored. However, when the products are taken from these areas on their way to an operation process, the exposure time from storage facility to the operations room is not always accounted for. Environmental *gaps* may exist that start the cumulative exposure time to degrading temperatures. Of course, the exceptions are when the entire operations facility is environmentally controlled to label temperatures, but that is pretty rare.

There should be a document and responsibility record that tracks the time/temperature during these material handling events added to the overall SOP.

Assuming that the operations room where the actual formulating or manufacturing process is being done is temperature controlled, the equipment that is used in the process should be validated to operate at the specific operational temperatures. Equipment that generates heat is often overlooked. Therefore, products may be exposed to machine generated temperatures during the process, even though the machines may be validated to be operational at given temperatures. The Installation, Operation, and Qualification (IOQ) of equipment should have provided certification of the validation. Included in the documentation should be data that depicts the time and the rise in temperature of the product during equipment normal running time as well as stoppages. Often, the characteristics may change and cumulatively affect the product.

In many cases, *primary* containers or the containers that

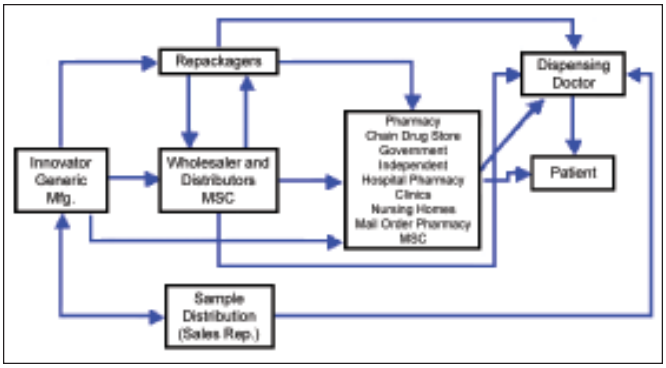


Figure 3. Pharmaceutical distribution chain.

the pharmaceutical product is actually touching such as a vial, blister pack, card packet, etc. and the *secondary containers* used to group and hold the primary containers in a "package" have been filled as part of the manufacturing process. After they are filled, these containers must now be transported to holding/storage facilities. Again, the transporting operation must be accounted for in terms of time/temperature as well as the validation certifications for the actual operations (manufacturing and filling), holding/storage facility, and the associated equipment as described above.

In the case of clinical supply groups, although the manufacturing process may not be relevant, the material handling procedures are very highly significant as to the products final efficacy - *Figure 2*.

Packaging and Packaging Material Considerations

Secondary containers (as described above) that are normally chipboard (cardboard) or thin corrugated boxes are then taken out of the storage facility and readied for tertiary, insulated, and protective packaging for shipping. There are many types of protective shipping systems that are available from specialty suppliers. However, any system used must be validated to ensure the protection of the product from environmental damage. Depicted in Figure 4 is a shipping system that contains insulated boxes, Phase Change Materials (PCMs) sometimes referred to as "gel packs and described below"), data loggers, heat sink materials, and in some cases, shock absorbing components. The configuration of the packaging components and total system is crucial to keep the products safe during shipping - *Figure 5*. If you do not have a qualified thermal packaging specialist in house, there are highly experienced independent consultants available that are not obligated to specific suppliers products and offer objective advice since they are actually working for you. (A source for independent consultants may be found at the Consultant's Council listed on the Institute of Packaging Professionals (IOPP) Web site. www.packagingconsultants.org.)

Figure 4. Shipping system.

An empirical validation test by an approved, independent laboratory, experienced in temperature controlled packaging and regulatory requirements, should be conducted - *Figure 6*. (Some suppliers provide these services. However, validation tests should be conducted at arms length by independent laboratories. The use of "pre-validated containers" is not recommended, but if used, be sure the supplier will certify that your specific shipping depiction for each packout meets their certification in a written and signed statement.

Insulation materials are a function of shipping duration

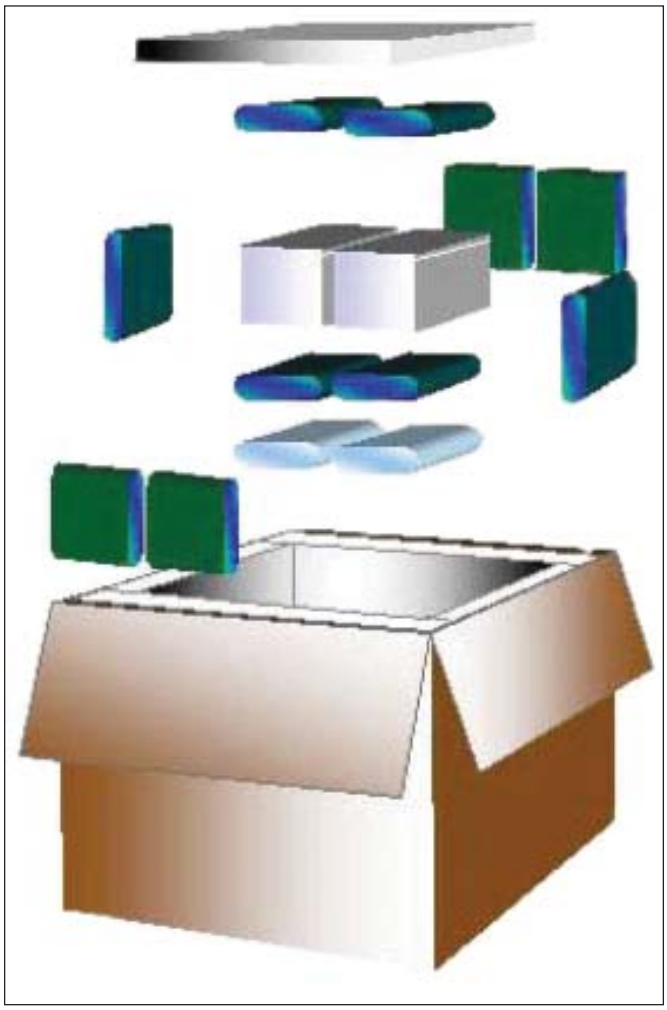


Figure 5. Configuration of packaging components.

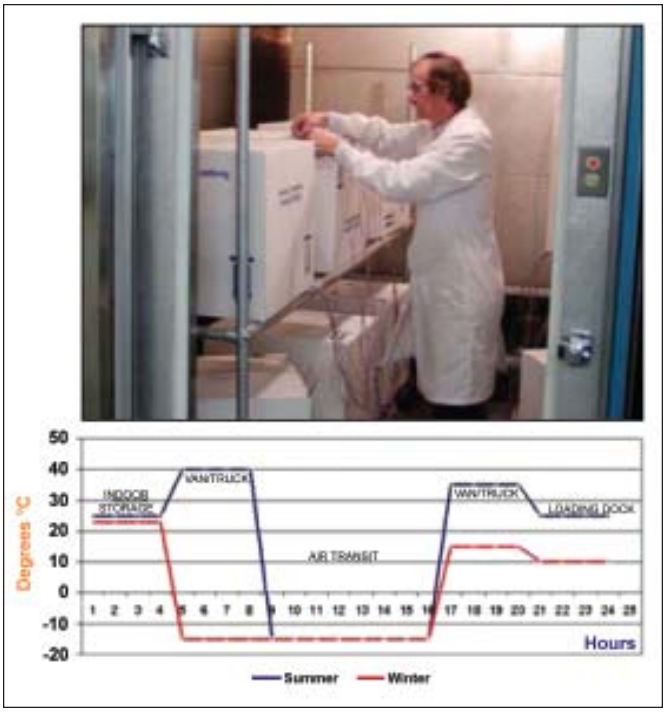


Figure 6. 24-Hour shipping profile.

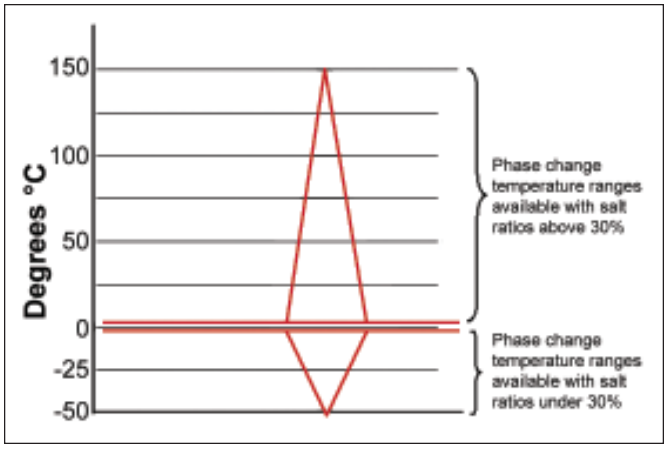


Figure 7. Phase chart - *salts added.*

time, anticipated ambient temperatures, label temperatures of the medical product, and PCM components used internal to the packaging system. The thickness of the insulation may vary depending on the volume of the stabilizing materials. (There are simple mathematical models available to determine the best materials to use.) - *Figures 11 and 12.* Until recently, most insulation materials used were foamed plastics, Expanded Polystyrene (EPS), or urethanes. We have actually tested and specified materials that have the same or better conductivity strength, are lighter (hence less expensive to ship), take up less space, have more puncture resistance, and are acceptable in all countries without financial penalties due to environmental concerns. The materials work out to be far less costly than traditional foamed plastics and in at least one case, the manufacturer is currently supplying several healthcare companies in the US and Europe.

PCMs are materials that change their physical state due to temperature. The type used in this discussion are basically water, therefore will turn to a liquid or "phase-change" when exposed to temperatures above 0°C. They solidify to ice at temperatures at or below 0°C. During the time the ice is still solid, the temperature will remain at a constant 0°C. The time the solidified, frozen water, ice type PCM is taken from below 0°C temperatures storage areas to above those temperatures is the "Heat of Fusion." (See definition and discussion at the end of this article.) Depending on the mass of the PCMs in relation to time, product, insulation and ambient temperatures, the internal temperatures will remain constant. The reverse is also true; these types of PCMs, like water, will solidify or "phase" to a solid state below 0°C - *Figure 7.*

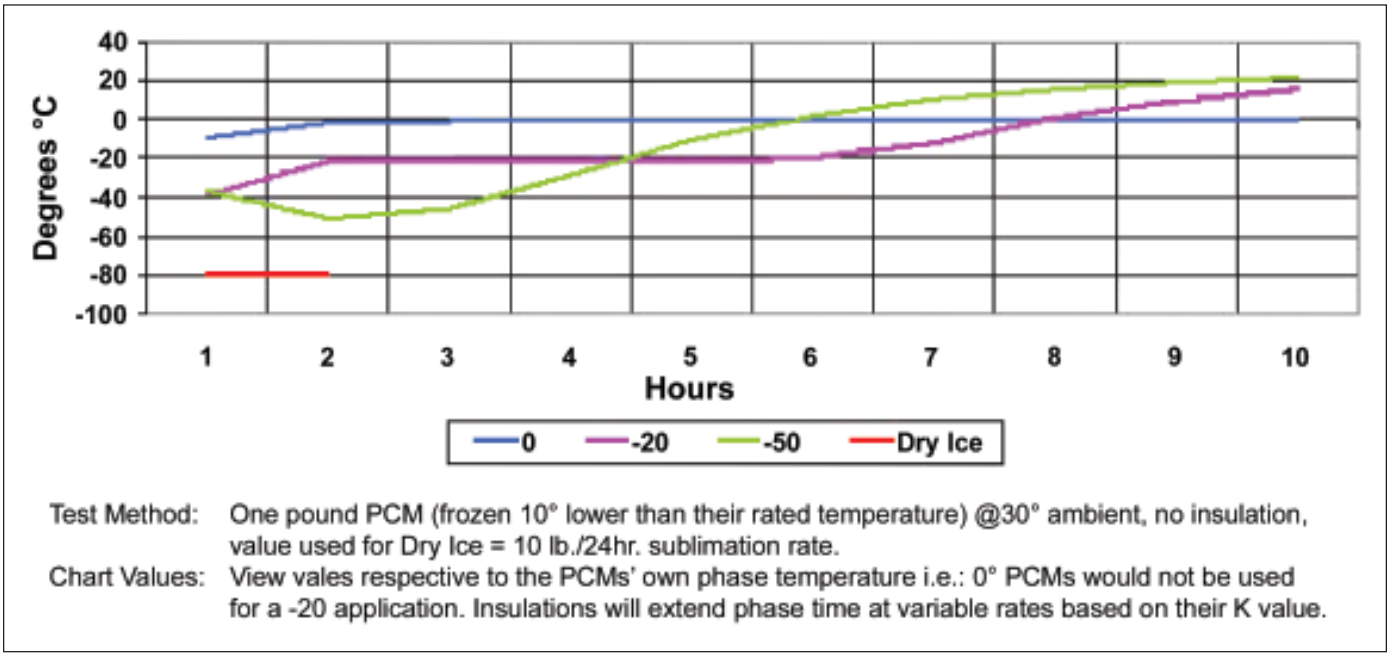


Figure 8. Phase change material comparison.

Type	Temperature Range	Note	Usage
Sponge/Water	0°C	Retains its shape when frozen, leaks easily	Used for <0°C, 2°C to 8°C, and above 8°C temperature ranged products
Phenol Foam/Water	0°C	Retains its shape when frozen	
Hydroscopic Polymers (Gel)	-10°C to 0°C	Widely used industry standard available in various outer wrap configurations	
Hydroscopic Polymers/added salts	-45°C to +26°C	COLD - Could replace some dry ice applications WARM - Help maintain room temperatures	
Paraffin	26°C to 60°C	Maintain room temperatures	

Table A. Phase change materials.

There are specialty PCM products available that will actually stay solid at various specifically controlled temperatures - *Table A*. For example: PCM formulae may remain at +4, +30°C or even above. Others remain constant at -10,-20, or lower. Products labeled temperatures from 2-8°C may utilize these PCMs. Products that are to be kept below -10 or -20°C can use the low temperature versions. (Dry ice is still required below -30°C.) There are pluses and minuses associated with using common type or specialty PCMs. In Figure 8, there is a comparison in the time it takes one pound (.45 kilograms) of various temperature PCMs and dry ice to phase from a solid to a liquid. Using mass multiplied by time, the chart should give a good indication of the expiration rate for each type. The phase time in this example assumes room temperatures approximately 65°F (18°C.) and does not take insulation values when placed in a closed container into consideration. A thermal packaging expert should be consulted for the most efficient solution as to which type to use.

Whether or not a validation test is performed, a temperature monitor/data logger should be used as a safety factor. There are various types of indicators and monitors. Chemical indicators are one time, line of sight devices with no memory. *What you see is what you get*. The upside is that they are inexpensive. The downside is that they trip at a fairly wide tolerance of temperatures and may not be depended upon to indicate when the critical failure temperature was reached. These indicators should not be used for archival purposes, particularly for tight temperature tolerance, sensitive, and valuable medical products. Electronic devices vary as to cost quite broadly. The benefits are that they are very accurate, normally within +/- .5° C; provide a precise record of temperatures, humidity when required; may be archived and encrypted in accordance with 21 CFR Part11; and make available many types of alert signals-digitally and line of sight - *Figure 9*. Technology is changing rapidly in the electronic devices. There are products available that provide all of the information listed above in addition to a reduced size (approximately the size of half dollar coin), may be downloaded into a computer individually or added to other UPC logistic and anti-diversionary information, and monitored from a wireless remote location at any time during shipping or storage. In addition, the device has ranges down to and including -80°C and is less costly than most temperature data loggers presently offered. It is recommended that electronic data loggers be used even when the packaging has been validated for the assumed ambient weather exposures. Simply said, we believe all protective packaging should be empirically endurance tested for actual anticipated applications; however, on the rare occasion that the package is exposed to extraordinary conditions, the product may still be acceptable. The monitor will be the only evidence to save the shipment or have to reject it decisively at these latter unexpected events. Electronic devices may now monitor temperatures and locations even when diverted. Other inexpensive devices are available that provide end user verification.

Risk management should be employed when considering to either validate by laboratory testing a protective packaging system or to merely monitor each shipment. We believe that a properly tested system will give reasonable assurances that the product will remain within label temperatures throughout the shipping event and all subsequent shipments of similar materials and products. The endurance test is

Figure 9. 21 CFR Part 11 compliant.

Figure 10. Certified test report.

performed with the proposed packaging design in a temperature controlled test chamber at programmed predetermined temperatures to which the package will likely be exposed. Smaller or medium size packages are also tested in various physical attitudes, such as on their side and upside down, if appropriate, during the test to simulate material handling on trucks or aircraft. The certified test report that is published is an archived document that will serve as evidence that the protective packaging is appropriate for the applications investigated. The report should include a detailed description of the validated test equipment, packout depiction, and test results - *Figure 10.* Monitors by themselves, provide a "snapshot" of that particular shipment and do not provide assurances until after the event that the products will arrive safely at their destination. (Too late if out of tolerance.) Therefore, the laboratory validation test to predict a successful shipping event for valuable and high occurrence shipments in terms of weather environments and handling in addition to repeatability of such success is recommended. Shipments that are of low occurrence and low value may be considered for monitors exclusively.

Packaging Test Protocol and SOP

Documents must be generated to precisely depict the purpose and scope in addition to all of the shipping, handling, and ambient environment events that are expected to occur to measure the endurance to protect products during shipping and storage. Precise identification and traceability of packaging materials and medical products must be included. *The text should include all supporting documents that are needed such as temperature profiles, packaging configurations, quality standards (company and appropriate regulatory), relevant policies, and specific assignment of responsibilities by step, segment, and in total.*

Distribution

Commercial products and clinical studies vary in actual operations and distribution - *Figures 2 and 3.* However, in terms of temperature control, the two delivery systems have identical requirements. The protective packaging design will be the same. Whether packaged internally or at a contract packager, the responsibility and protocol/SOP documentation must be controlled by the owner of the project. For example, even *if the packaging and distribution is actually done at a contract packaging company, the responsibility for clear and precise protocols, SOPs, material lists, and any other required documents is still the project manager's.* The Project Manager may designate others such as the logistics manager to generate protocol/SOPs and manage their segments.

Quality and Regulatory Guidance

Whether products are manufactured in the US or the European Union (EU), all processes, personnel training, and equipment qualification must be followed in accordance with current Good Manufacturing Practice (cGMP). The guide for US regulations is found in the Code for Federal Regulations (CFR). Chapters 21 CFR Parts 210 and 211 include regulations for processing, packing, or holding of drugs and finished pharmaceuticals. Medical devices are covered in 21 CFR Part 820. Qualify testing methodology is covered in 21 CFR 211.60. The US Food and Drug Administration (FDA) is responsible for ensuring that products consumed in the US are produced and marketed to approved standards, regardless of the origin of manufacture. The federal government Agency audits the phases of biopharmaceutical development through all stages of manufacturing, testing, and initial distribution. There must be sufficient evidence that drugs and other related pharmaceutical products have been adequately tested to perform as purported and have a relative degree of safety during human usage. www.fda.gov.

The United States Pharmacopoeia (USP) is a quasi-government organization that is composed of regulatory agency personnel, academia, and industry groups interested in pharmaceutical standards. USP journals and periodic discussion groups generate proposals and guidelines. USP Resolution 10 is a guide for storage and shipment. When marketing in Europe, standards are produced by EU, European Economic Commission (EEC) Council Directives for products consumed within the European Community. As an example, 75/319/EEC is a standard that relates to analytical, pharmacological/clinical standards, personnel, premises, equipment, documentation, production, quality control, complaints, product recall, self-inspection, and testing. There are several amendments to the basic document and all are listed on the EC Web site. An interesting Web site to visit is at: http://ts.nist.gov/ts/htdocs/210/gsig/eu-guides/sp951/sp951.htm, *"NIST Special Publication 951 - A Guide to EU Standards and Conformity Assessment."* In the table of contents, there is a link to *"Standardization in the EU and the United States: A Comparison."* Most notably is a general statement that in Europe standards are developed centrally and in the US by sector.

The Plan

1. Gather product stability data
   - 1.1 Ensure documentation exists
   - 1.2 Ensure documentation is defendable
2. Define manufacturing, storage, and distribution environment
3. Map current or proposed product stream
   - 3.1 Collect all relevant protocols and SOPs applicable to processes, personnel, facilities, and equipment.
   - 3.2 Ensure there are complete SOPs for each step in the product stream
4. Define vulnerabilities of current documentation and systems, including gaps in material handling, movement, and processes.
   - 4.1 Evaluate effectiveness of current procedures SOPs.
   - 4.2 Develop new and/revise appropriate SOPs to adequately describe all procedures and methods required to achieve successful cGMPs.
5. Collect/develop all validation reports and documentation required for materials and equipment.

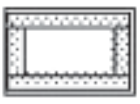
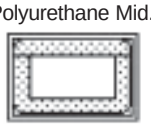
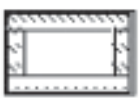
Heat Test (30°C) with 500 ml water (5°C) and 1 x 32 oz. Frozen Gel Bottle (-18°C)										
Container	**Insulation**	**k**	**wall thickness**	**R Value**	**Hours <10°C**	**Hours <20°C**	**Weight ACT/Dm**	**Est. Mat. Costs (500 qty) $**		
								Cost	**Gel**	**Total**
Corregated Only 	none	---	C Flute	---	2.5	17	4/4 lbs.	$0.75	$1.00	$1.75
Fabric Tote 	Thinsulate Style	0.25	3/4"	3	8	23	4/4 lbs.	$9.40	$1.00	$10.40
Molded Cooler 	Rigid Poly-urethane	0.14	1/2"	3.5	3	24	6/6 lbs.	$15.40	$1.00	$16.40
Corrugated w/Bubble 	Astrofoil double bubble foil	0.19	5/6"	3.3	6	27	4/4 lbs.	$6.00	$1.00	$7.00
EPS KD 	EPS 1.5 lb. Cu. ft.	0.25	2"	8	13	32	5/11 lbs.	$5.00	$1.00	$6.00
EPS Molded 	EPS 1.5 lb. Cu. ft.	0.25	2"	8	12	30	5/11 lbs.	$5.50	$1.00	$6.50
Polyurethane KD 	Rigid Poly-urethane	0.14	2"	14.3	26	48	7/11 lbs.	$12.00	$1.00	$13.00
Polyurethane Mid. 	Rigid Poly-urethane	0.14	2"	14.3	26	48	7/11 lbs.	$16.00	$1.00	$17.00
Vacuum KD 	Vacuum Panels	0.04	2"	50	54	80	10/11 lbs.	$44.00	$1.00	$45.00

Figure 11. Thermal comparison profile-insulation materials.

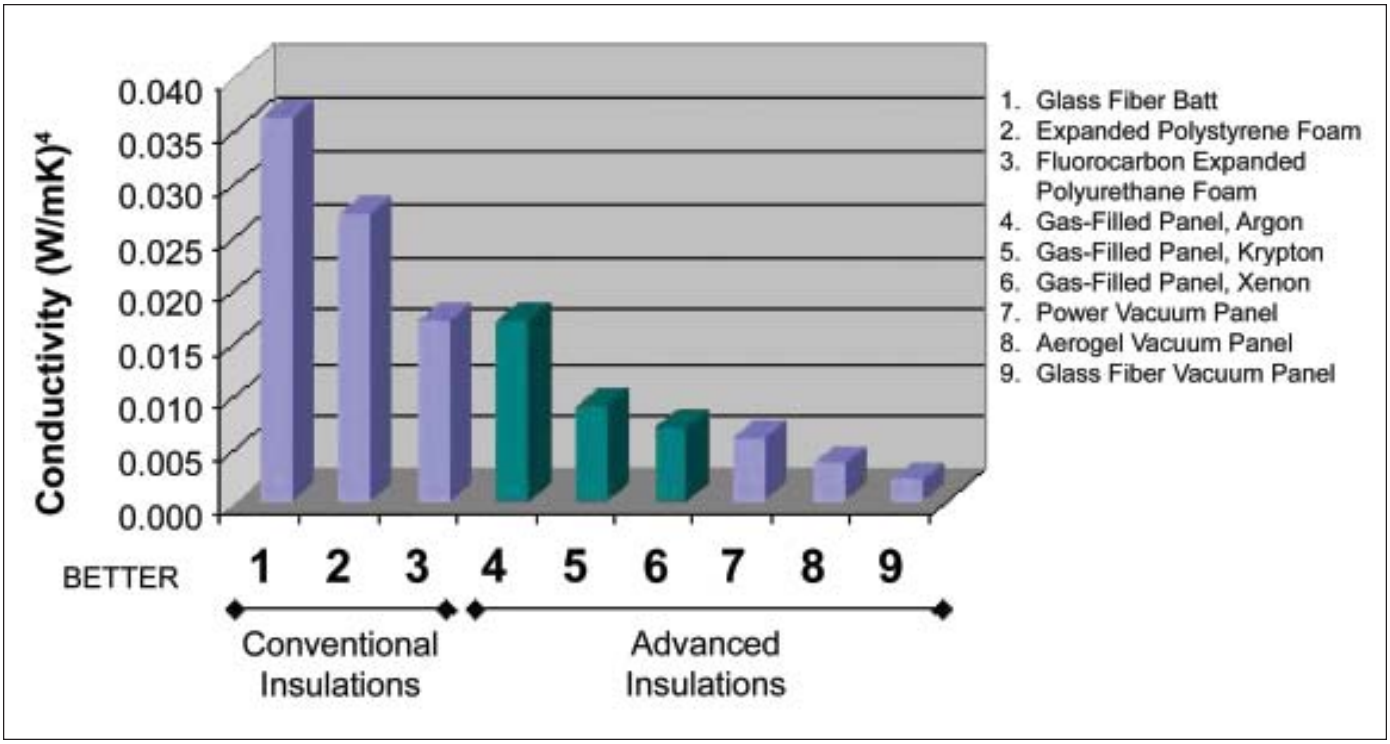


Figure 12. Performance data for conventional and advanced insulations.

Conclusion

Relevant to the history of the biopharmaceutical industry in the US and Europe in terms of time, the recognition that medical products may change their efficacy of their products for the worse due to temperature has been very short. Storage and packaging studies have evolved recently to generate highly effective procedures and materials. Each segment of the manufacturing and clinical test distribution process has recently been highly visible. Appropriate training, material familiarization, and validation studies have moved higher in priority by industry and regulatory agencies. However, there may be unprotected gaps in the procedures that commence at the actual receipt of ingredients and between each phase of the product cycle.

Material handling and movement between processes should be accounted for to guarantee that temperature excursions do not exceed acceptable accumulated exposure levels before and in addition to storage and packaging.

We need to ensure that product evaluations and effectiveness are not compromised at any point from receipt of components, manufacturing operations, clinical studies, and through all segments of distribution.

Heat of Fusion: Definition and Discussion

The **standard enthalpy change of fusion,** also known as the **heat of fusion,** is the amount of heat energy which must be absorbed or lost for 1 gram of a substance to change states from a solid to a liquid or vice versa. It is also called the latent heat of fusion or the enthalpy of fusion, and the temperature at which it occurs is called the melting point.

When you withdraw thermal energy from a liquid or solid, the temperature falls. When you add heat energy, the temperature rises. However, at the transition point between solid and liquid (the melting point), extra energy is required (the heat of fusion). To go from liquid to solid, the molecules of a substance must become more ordered. For them to maintain the order of a solid, extra heat must be withdrawn. In the other direction, to create the disorder from the solid crystal to liquid, extra heat must be added.

The heat of fusion can be observed if you measure the temperature of water as it freezes. If you plunge a closed container of room temperature water into a very cold environment (say -20°C), you will see the temperature fall steadily until it drops just below the freezing point (0°C). The temperature then rebounds and holds steady while the water crystallizes. Once completely frozen, the temperature will fall steadily again.

The temperature stops falling at (or just below) the freezing point due to the heat of fusion. The energy of the heat of fusion must be withdrawn (the liquid must turn to solid) before the temperature can continue to fall.

The units of heat of fusion are usually expressed as joules per mole (the SI units).

About the Author

Sanford Cook is a consulting and product development resource to the biopharmaceutical packaging industries and is President of Thermal Packaging Solutions, LLC. He has been the chief executive officer, chief engineer and chief marketing executive for global, public, and private companies engaged in the design, documentation, validation, testing, and manufacturing of economical, packaging,

devices, refrigerants, monitors, and operations processes that protect sensitive products against weather and handling vulnerabilities, as well as anti-diversion systems during shipping and storage for more than 25 years. An engineer and a graduate of Business Management, Rutgers University, he holds many patents in the fields of thermal dynamics and devices mentioned above. He has written and published many articles and papers, given numerous speeches, been featured in various national and local media events including the Discovery Channel's Medical Series, Bloomberg Television, ABC News, News Channel 12, the cover page of the Health Section of the Newark Sunday Star Ledger, the Wall Street Journal, and led many seminars to industry and government groups interested in these subjects, primarily in the biopharmaceutical, appliance, and medical device segments. Cook is serving as an officer in the IOPP, Consultants Council.

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This article presents a risk assessment technique used to quantify the impact of uncertainty and variability in the manufacturing of bulk pharmaceuticals.

Quantifying the Impact of Uncertain Parameters in the Batch Manufacturing of Active Pharmaceutical Ingredients

by Evdokia C. Achilleos, John C. Calandranis, and Demetri P. Petrides

Introduction

Active Pharmaceutical Ingredients (APIs) are usually produced in batch multi-product facilities. A typical process involves several stages, including intermediate filtration, centrifugation, and drying. Processes for new products are developed in the lab and later transferred to pilot plant for scale-up. The role of pharmaceutical pilot plants is to optimize new processes and supply materials for safety and clinical studies for drug development.[1] The pharmaceutical industry is under pressure to make new compounds available to patients as soon as it is safely possible. As a result, there may be remaining uncertainty in the operational and market parameters of the scaled-up process.[2-6] This uncertainty may lead to uncertainty in plant throughput, manufacturing cost, environmental impact, etc. Risk assessment techniques that quantify the impact of uncertain parameters on the final decision variables can

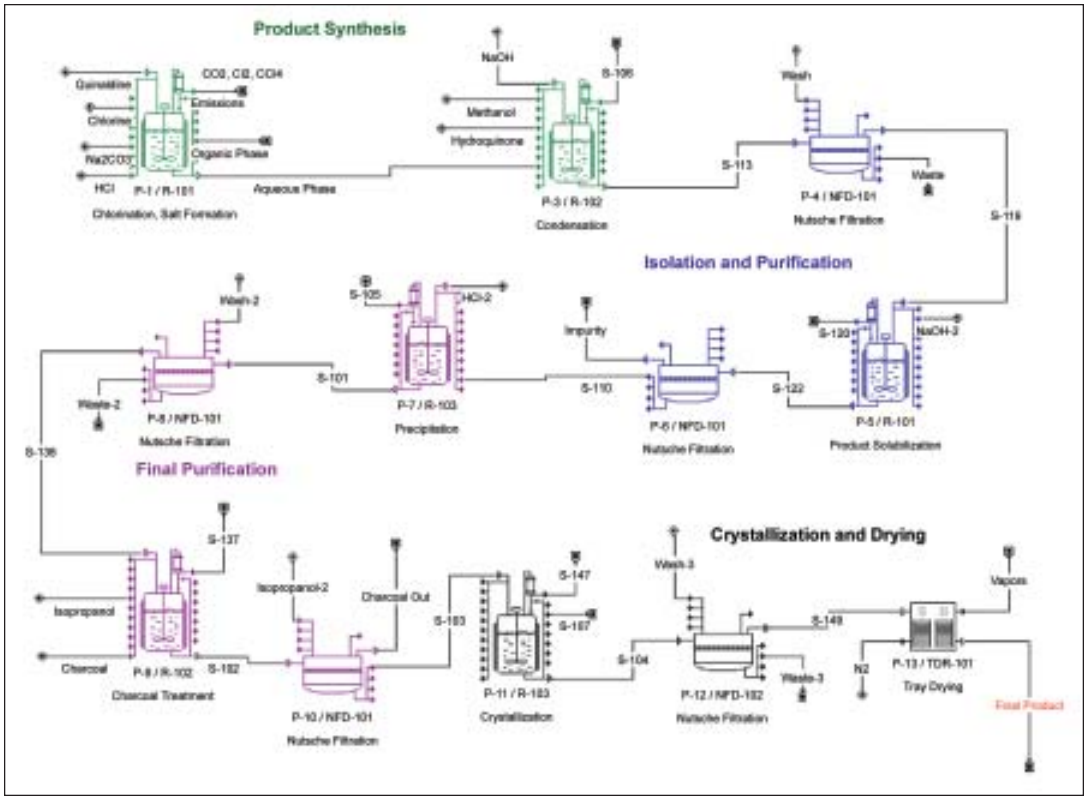

Figure 1. Process flowsheet for the production of an active pharmaceutical ingredient.

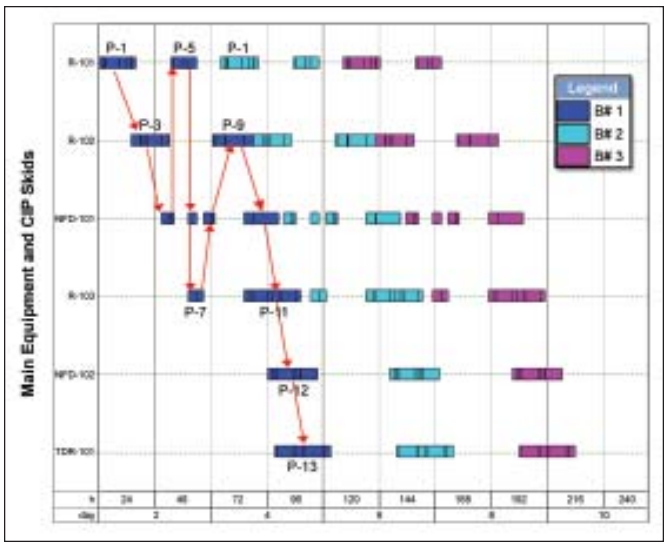

Figure 2. Equipment occupancy chart (three consecutive batches are represented by different colors).

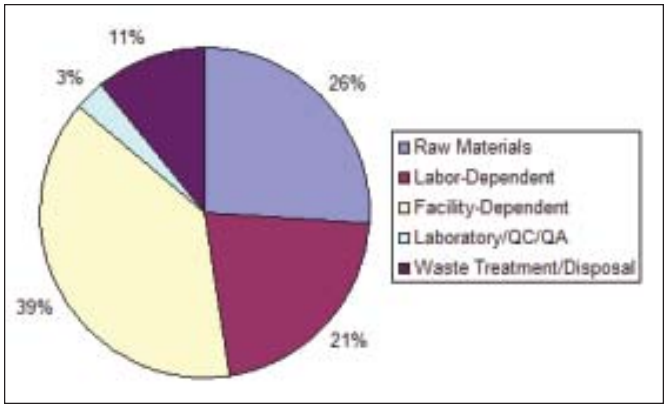

Figure 3. Manufacturing cost breakdown.

prove to be a valuable tool to management.

Typical process simulation tools used for batch process design, debottlenecking, and cost estimation employ deterministic models. These models do not account for random variation in the input variables and provide fixed and reproducible results for the outputs. In other words, they predict how the process will act in a given situation. If there is variability in the process inputs, the scenario modeled with a deterministic tool is taken to be the "average" or "expected" situation commonly referred to as the base case or most likely scenario. Modeling cases where key input parameters assume extreme values can help determine the range of performance with respect to key process parameters. However, such an approach does not account for the relative likelihood of the various scenarios. Monte Carlo simulation is a collection of a large number of simulated results (runs) and constitutes a practical means of quantifying the risk associated with uncertainty in process parameters. Uncertain input variables are assigned probability distributions. For each run, a set of values of the statistically varied input parameters is selected (with frequency based on their assigned distribution) and the outcome is recorded. The statistical distributions of the results are used to quantify risk. If the model of a process has been developed using a deterministic simulator, Monte Carlo simulation can be performed by combining the deterministic simulator with a tool that supports probabilistic and stochastic modeling.

Methodology and Tools

Processes for new products may be analyzed by developing computer models using spreadsheets or specialized process simulators. Such models serve a variety of purposes throughout the life-cycle of product development and commercialization in the pharmaceutical industries. During process development, computer models are used to evaluate alternative technologies (e.g., synthesis routes, purification technologies, etc.) that have the potential of reducing cost, shortening cycle times, and minimizing environmental impact. As a process moves from development to manufacturing, such tools are used to design new manufacturing plants and facilitate technology transfer (from R&D to manufacturing). Finally, in large-scale manufacturing, process modeling is used for capacity analysis, debottlenecking, and production planning and scheduling.

SuperPro Designer®, a comprehensive process simulator that focuses on pharmaceutical, specialty chemical, and biochemical processes, was employed in this study first as a standalone tool for modeling the process using the base case values for all input variables. The process simulator was subsequently integrated with a stochastic risk analysis tool in order to conduct the uncertainty analysis.

Crystal Ball®, an Excel® add-in application, was used to facilitate Monte Carlo simulation. It enabled the user to designate the uncertain input variables, specify their probability distributions, and select the output (decision) variables whose values are recorded during the simulation. For each simulation trial (scenario), the application generated

Bulk Raw Material	Unit Cost ($/kg)	Annual Amount (kg)	Annual Cost	
			($)	%
Chlorine	3.300	19,075	63,000	2.72
Na_2CO_3	6.500	22,387	146,000	6.30
Water	0.100	631,933	63,000	2.73
HCl (20% w/w)	0.150	76,168	11,000	0.49
NaOH (50% w/w)	0.150	43,581	7,000	0.28
Methanol	0.240	117,895	28,000	1.22
Hydroquinone	4.000	36,534	146,000	6.32
Carb. TetraCh	0.800	105,973	85,000	3.67
Quinaldine	32.000	31,673	1,014,000	43.85
Sodium Hydroxide	2.000	15,803	32,000	1.37
Isopropanol	1.100	423,008	465,000	20.13
Charcoal	2.200	3,378	7,000	0.32
HCl (37% w/w)	0.170	46,363	8,000	0.34
Nitrogen	1.000	236,635	237,000	10.24
TOTAL		**1,810,406**	**2,311,000**	**100.00**

Table A. Raw material requirements and costs.

random values for the uncertain input variables selected in frequency dictated by their probability distributions using the Monte Carlo method. All input variables are perturbed simultaneously and their interactions are captured through the model as fluctuations of the output. The application also calculated the uncertainty involved in the outputs in terms of their statistical properties, mean, median, mode, variance, standard deviation, and frequency distribution.

In this study, the process simulator was combined with the add-in application to perform a Monte Carlo simulation of a bulk pharmaceutical process. The integration of the two tools was made possible by taking advantage of the Component Object Module (COM) technology built in the process simulator and the add-in application's inherent integration with Excel. The probability distributions of the uncertain input variables were defined in the application. Macros were used to link the uncertain parameters with their corresponding input variables in the process simulator. For each set of values of input variables, the process simulator performed material and energy balances, scheduling, and cost analysis calculations. The calculated outputs of the process simulator were transferred back to the Excel add-in application using additional macros.

Bulk Pharmaceutical Illustrative Example

The methodology developed for integrating the two tools is illustrated here using an example involving a pharmaceutical process for the manufacture of an active compound for skin care. This example is based on a study made in a previous publication.[7] This example is not intended to be an exhaustive examination of risk-assessment accounting for all possible variations under "real-world" conditions. It is rather intended to demonstrate how one can use this methodology to assess the impact of variability in key-process parameters on the decision variables.

Base Case Analysis

The process has been developed at pilot plant level and it is ready to be moved to large-scale manufacturing. Based on input from the marketing department, the objective is to produce at least 36,000 kg of active ingredient per year at a cost of no more than $250/kg.

The entire process model, is shown in Figure 1. The icons in Figure 1 represent unit procedures (processing steps) and not unique equipment. Multiple unit procedures may utilize the same equipment at different times. Each unit procedure contains a set of operations that are performed sequentially in the equipment. The following equipment items are available for the large-scale manufacturing of this compound:

- three 1,000 gal reactors (R-101, R-102, R-103)
- two 4 m^2 Nutsche filters (NFD-101, NFD-102)
- a tray dryer with a capacity of 1 kg/h removed solvent (TDR-101)

The process is divided into four sections identified by different colors on the flowsheet. The first section is the "Product Synthesis" section. Procedure P-1 (in R-101) involves the chlorination of quinaldine. Procedure P-3 (in R-102) involves the formation of the product through the condensation of chloro-quinaldine and hydroquinone. A side reaction leads to the formation of an impurity. The product and the impurity formed in P-3 precipitate out of solution. The second section of the process deals with product "Isolation and Purification." The precipitate of the product and the impurity formed in procedure P-3 is removed in procedure P-4 using a filter. The product is subsequently converted into a soluble form in procedure P-5 while the impurity remains in solid form and is removed in procedure P-6. The third section is the "Final Purification" section. The product precipitates in procedure P-7 and the precipitate is recovered using a filter (procedure P-8, NFD-101). The product is then dissolved in isopropanol (in P-9) and charcoal is added to remove certain impurities. The charcoal used for the treatment is removed by Filtration in P-10. Finally, the last section is the "Crystallization and Drying" section. The product solution is concentrated in P-11 (isopropanol is vaporized) and the product is crystallized (in the same vessel, R-103). The crystallized product is recovered using a filter (P-12) and dried using a tray drier (P-13/TDR-101). A more detailed description of the process can be found in the literature.[7]

Variable	Base Case Value	Distribution	Variation and Range
Quinaldine Cost	32 ($/kg)	Normal	S.D. =6 [10 – 110]
Chlorination Reaction Time (in P-1)	6 hr	Triangular	[4-8]
Condensation Reaction Time (in P-3)	6 hr	Triangular	[4-8]
Cloth Filtration Flux (in P4, P6, P8, P10) (Equipment NFD-101)	200 (L/m^2-h)	Triangular	[150-250]

Table B. The input parameters used for the Monte Carlo simulation and their variation.

Figure 2 displays the equipment occupancy chart for three consecutive batches. Each color represents a different batch. Multiple rectangles for the same equipment (e.g. for R-101, R-102, NFD-101, and R-103) within a batch represent reuse of that equipment by multiple unit procedures. The flow of material through the equipment is shown with the red arrows for the first batch. Reactor R-102 has the longest cycle time (from the start of P3 to the end of P9) and is by definition, the current time bottleneck that determines the maximum number of batches per year.

Considering the size of the available equipment, the process simulator calculates that each batch generates 246 kg of active ingredient. The minimum cycle time of the process is calculated as 52.3 h and it is determined by R-102. If the plant operates at its minimum cycle time of 52.3 h, it can process 150 batches per year. To meet the target production of 36,000 kg/year, a minimum of 147 successful batches are required per year.

The process simulator also was used to perform the cost analysis calculations for this process. The estimated manu-

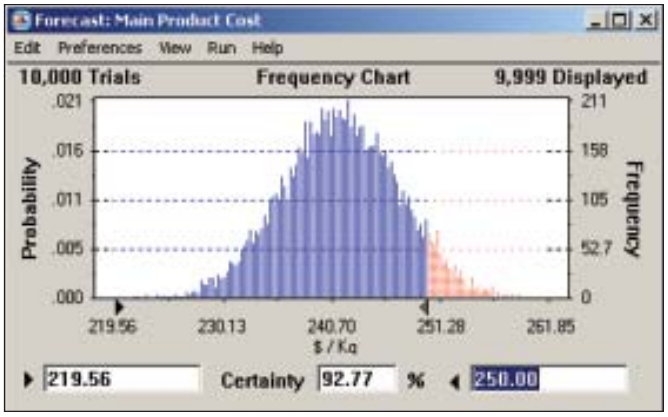

Figure 4. Probability distribution of the unit production cost (10,000 trials). Mean = 241.53, Median = 241.49, S.D. = 5.78, Range = 219.6 – 263.2.

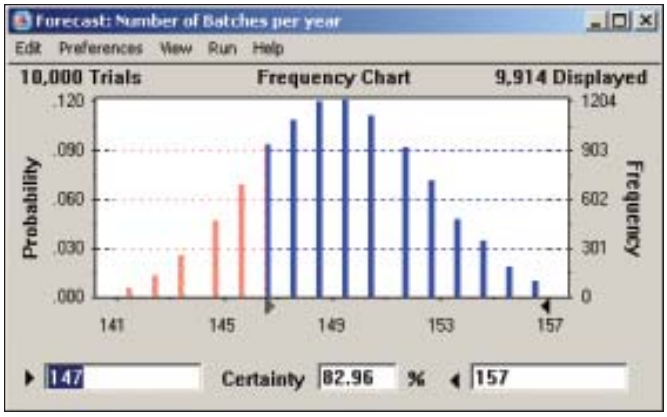

Figure 5. Probability distribution of the annual number of batches (10,000 trials) (mean = median = mode = 150, S.D. = 3, Range = 139-160.

facturing cost is $237/kg, which is below the upper limit of $250/kg. Detailed cost analysis for this process is available in the literature.[7] Figure 3 shows the distribution of the manufacturing cost. The facility-dependent cost (plant overhead) accounts for 39%, followed by raw material costs at 26%, and labor for 21%. The cost distribution of the raw materials can be seen in Table A. Quinaldine is the most expensive raw material accounting for around 44% of the raw materials cost which translates to about 11.4% of the overall cost.

Uncertainty Analysis

This exercise focuses on parameters that exhibit uncertainty or variability and can have a direct impact on the decision variables of this project: the manufacturing cost and the annual throughput. Table B shows the input parameters chosen for the Monte Carlo simulation and their assumed probability distributions. These are indicative parameters chosen for the purpose of the illustration and they do not represent all possible input process parameters that may exhibit variability. A normal distribution was assumed for the price of quinaldine, which is the most expensive raw material with a mean value equal to that of the base case ($32/kg).

The annual throughput (or number of batches per year) is determined by the process cycle time. Any process changes that increase the cycle time of R-102 (the time bottleneck) will result in fewer batches per year and lower annual throughput. Since procedure P-9 that utilizes vessel R-102 is the time bottleneck, any variability in the completion of P-9 leads to uncertainty in the annual throughput.

Please note that such changes are not limited to the operations of P-9. Variability in the completion of P-9 can be caused by variability in the operations of P-9 as well as by variability in the operations of the procedures upstream of P-9 (such as P-1, P-3, P-4, P-5, P-6, P-7, and P-8). Common sources of process time variability in chemical manufacturing include:

1. fouling of heat transfer areas that affect duration of heating and reaction operations
2. fouling of filters that affect duration of filtration operations
3. presence of impurities in raw materials that affect reaction rates
4. off-spec materials that require rework
5. random power outages and equipment failures
6. differences in skills of operators that affect setup and operation of equipment
7. availability of operators

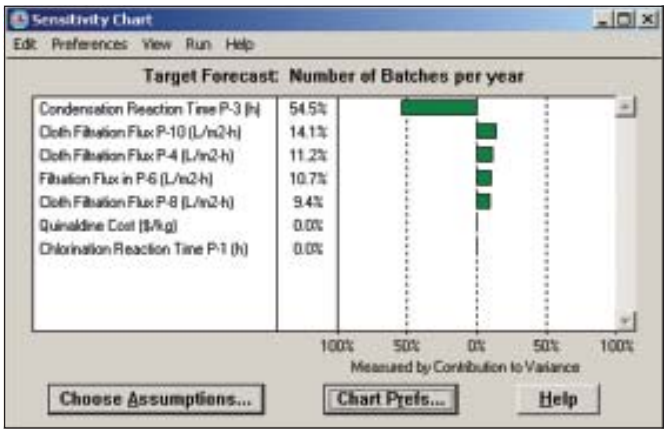

Figure 6. Contribution of uncertain parameters to the variance of the annual number of batches.

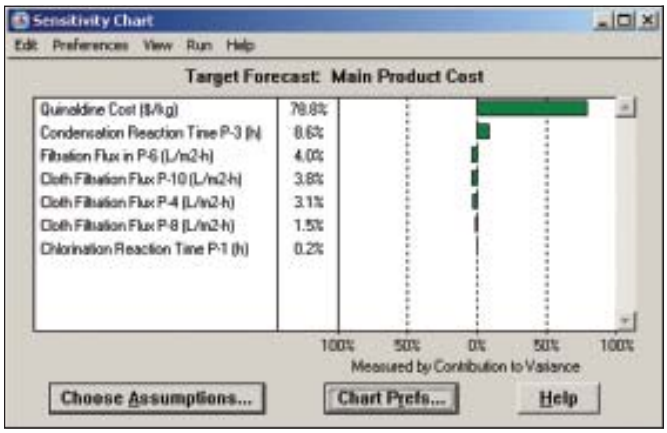

Figure 7. Contribution of uncertain parameters to the variance of the unit production cost.

Triangular distributions were assumed for the two main reaction operations and the filtration steps that precede P-9. Triangular distributions are typically used when limited data is available and when one has knowledge of the smallest, largest, and most likely value of the variable. Even though variability distributions were assigned to specific operations, it may be deemed more accurate to assume that they account for the composite variability of their procedures. If this type of analysis is done for an existing facility, historical data should be used to derive the probability distributions. The Excel add-in application has the capability to fit experimental data.

The two decision variables considered in this study are the number of batches that can be processed per year and the unit production cost. These are key performance indicators important for production planning and project economics. The output variables of the combined simulation are quantified in terms of their mean, median, mode, variance, and standard deviation. These results are shown in Figures 4 and 5 for the "Unit Production Cost" and the "Number of Batches" respectively. Based on our assumptions for the variation of the input variables, we note that average values (mean/median/mode) calculated for the decision variables satisfy the objective. The certainty analysis reveals that we can meet the unit production cost goal with a certainty of 93% (blue area of Figure 4). However, the certainty of meeting our production volume goal (of 36,000 kg or 147 batches) is only 83% (blue area of Figure 5). Such findings constitute a quantification of the risk associated with a process and can assist the management of a company in making decisions on whether to proceed or not with a project idea.

The dynamic sensitivity charts provide useful insight for understanding the variation of the process. They illustrate the impact of the input parameters on the variance (with respect to the base case) of the final process output, when these parameters are perturbed simultaneously. This allows us to identify which process parameters have the greatest contribution to the variance of the process; and thus, focus the effort for process improvement on them. The sensitivity analysis for the *Annual Number of Batches* and *Unit Production Cost* is demonstrated in Figures 6 and 7 respectively. The duration of the condensation reaction has the greatest impact on the number of batches and consequently the annual throughput. This is expected, as this operation is part of procedure P-3 that takes place in the time bottleneck equipment. Any increase in this operation time increases the cycle time of R-102; hence, increases the batch time and reduces the annual number of batches. If the management of the company is seriously committed to the annual production target, it would be wise to allocate R&D resources to the optimization of the condensation reaction. In addition, we can see that the purchasing price of quinaldine has the greatest impact on the manufacturing cost of the final product. Focusing the market research on lower cost suppliers for quinaldine would be advisable.

Conclusions

Deterministic process simulators facilitate modeling of complex systems in the chemical and pharmaceutical industries and provide reliable correlations between input and output process variables. Monte Carlo simulation tools estimate uncertainty of output variables from the uncertainty of input variables of a system. The combination of the two can be used to quantify risk and facilitate the decision-making process for complex systems. A simple process from the pharmaceutical industry was used to demonstrate the approach and illustrate how quantification of the risk involved in key decision variables can help management accept or reject a project idea. The same approach can be applied to considerably more complex systems.

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Containment Performance of a New Docking Station

by Hiroto Masuda, Yukio Fukushima, Satoru Hasegawa, Tadatoshi Iwabuchi, and Willy J. Lhoest

This article presents a research project conducted by Hitachi and Elveco on a docking station patented by Elveco and licensed to Hitachi Plant Technologies for East Asia. It describes how the ISPE Good Practice Guide: Assessing the Particulate Performance of Pharmaceutical Equipment was used throughout the project.

Introduction

As early as in the 19th century, Charles Darwin stated that : "The species that will survive are not the strongest, nor the most intelligent, but the ones most responsive to change." Already at that time, it was recognized that the ability to adapt to new situations is a vital condition to survive.

This is even more true today. This ability to adapt, that we now call "flexibility," remains a prime requirement in the pharmaceutical industry. Fully flexible and low-cost production systems are very much in demand.

At the same time, additional essential requirements need to be met. Modern pharmaceuticals are becoming increasingly more potent; therefore, a high level of protection must be guaranteed. Robust and perfectly tight production systems, fully reliable with respect to potential dust release and capable of preventing any cross-contamination, are needed.

Last but not least, production facilities must adhere to increasingly strict international regulations.

Purpose of the Study

In 2001, a Japanese engineering company entered into a technical agreement to implement the "Lhoest Concepts" in an Oral Solid Dosage Forms (OSD) manufacturing plant.

In closed, dust tight manufacturing lines, it is necessary to quantitatively measure the containment performance of the equipment. Docking stations are a vital element in plants built according to the "Lhoest Concepts," therefore, it appeared necessary to evaluate such docking stations and to report the results in terms of exposure risk and quality assurance in the design and engineering of a plant.

The description of the stations under investigation and the details of their functioning have been the subject of an earlier article.[1]

The present study was conducted using information developed by the Standardized Measurement for Equipment Particulate Airborne Concentration (SMEPAC).[2] This ISPE Good Practice Guide was established specifically for the evaluation of the containment performance of pharmaceutical manufacturing equipment.[3]

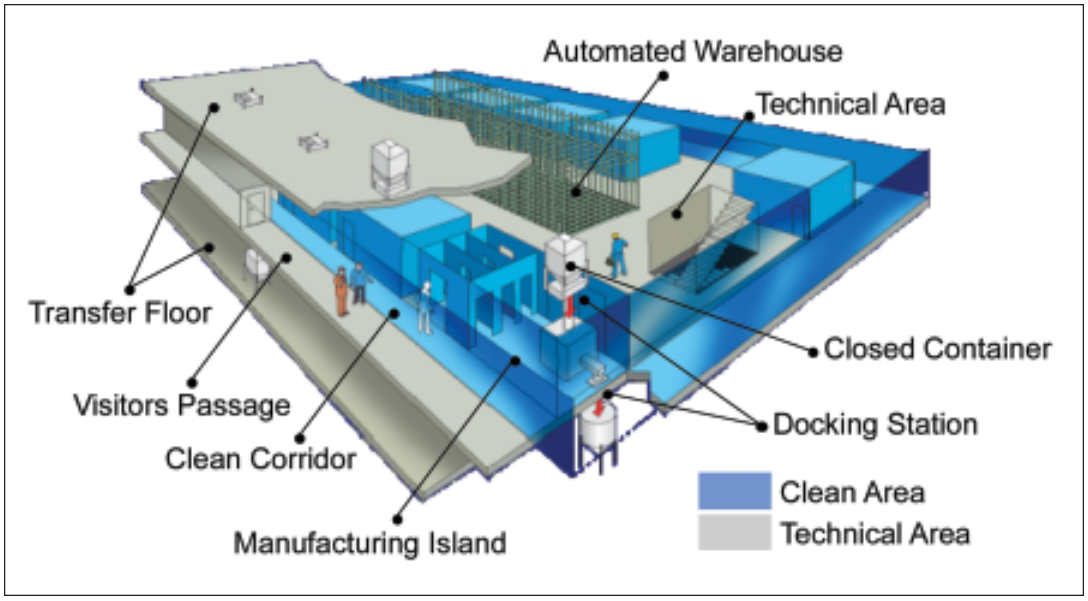

Figure 1. Schematics of a pharmaceutical manufacturing plant based on the Lhoest Concepts.

Figure 2. Outside view of docking station.

Since the reproducibility of the containment performance results of the docking station were confirmed by multiple data and repeated measurements, it was decided that the results should be reported, which is the purpose of this article.

The Docking Station

The schematics of a pharmaceutical plant based on the Lhoest Concepts appear in Figure 1. Machines, corresponding to every individual manufacturing process, are located in tight, independent production rooms called "Islands." The storage and transportation of ingredients, powders, granules, tablets, to and from basic manufacturing pieces of equipment, is achieved by means of closed containers and docking stations installed on separate floors, above and below the main manufacturing floor. Products are transferred strictly on basis of gravity flow.

Advantages are numerous and important:

- Since it is no longer required to bring the closed container(s) inside the production rooms, the surface area and the height of these production rooms can be reduced to the minimum. Their construction and maintenance costs, for example HVAC, drop significantly.

- The elimination of the back and forth movements of the containers, including their heavy transportation equipment, to and from each production room, simplifies the operations, reduces the size of clean corridors, and greatly enhances the overall cleanliness.

- Since production rooms are totally independent, including their ventilation systems, the risk of cross-contamination is mitigated.

The docking station is a vital component of the Lhoest Concepts. The outside view of the docking station is shown in Figure 2, and its outline configuration appears in Figure 3. Upon discharge of ingredients into the manufacturing equipment, maximum reduction in dust exposure risk is achieved due to its high containment performance and contamination is prevented by fully hermetic airlock mechanism.[1]

The upper docking stations, also called "Feeding Stations," operate as follows:

1. As the container, delivered by an Automatic Guided Vehicle (AGV), a fork-lift, or an equivalent engine, comes down to a level of two or three inches above the station, the upper stainless steel cover of its air box slides open.

2. The container is gently lowered and the sliding gate at the lower part of the container mates with a similar sliding gate at the top of the vertical chute connected to the manufacturing equipment.

3. Simultaneously, the inflatable gasket at the top of the air box is activated. It comes in close contact with a matching plate of the container and tightly seals the air box.

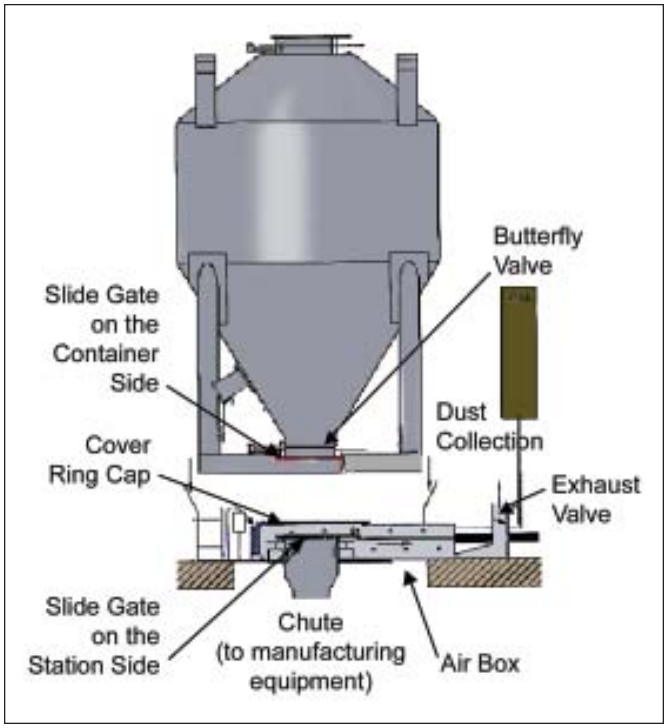

Figure 3. Outline configuration of docking station.

4. After the air box is thoroughly cleaned with jets of air, both sliding gates are pulled open, allowing the container and the chute to achieve a tight connection.

5. Upon command, the butterfly valve of the container is opened allowing the contained ingredients to drop into the manufacturing equipment. (Indeed, during the docking operation, the tail of the bin valve did engage into a rotating mechanism that can be commanded remotely by the operator in the clean production room.)

For the undocking, the same sequence is applied in the reverse order.

With this mechanism, ingredients can be discharged into the manufacturing equipment or from the manufacturing equipment into a receiving container without coming in contact with outside air, eliminating dust dispersion in corresponding rooms. During phases of cleaning and transfer of ingredients, the automatic opening of an exhaust valve allows the extraction of any potential dust particle and maintains a favorable negative pressure inside the air box.

Testing Method for Assessing the Containment Performance of the Docking Station

The methodology followed for the experimental part of this study is described in the ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment.[3]

Cleaning and Measurement of Dust Concentration in the Areas to be Tested

The experiments were conducted under realistic industrial conditions in a new solid dosage forms manufacturing plant built in Japan.[4,5] The rooms and concerned pieces of equipment have been carefully cleaned. Additionally, the dust concentration in the concerned rooms has been measured using a particle counter. This particle count has been checked before starting any other measurement, i.e., lactose, to ensure that the working conditions would be comparable at all times.

Cleaning

A thorough cleaning of the rooms and the equipment used for testing has been conducted and monitored by measurement of the dust dispersion rate (particle count). These areas included the tablet feed room where containment performance was measured, a production room used for storage of instruments, air filters, etc., a room used for cleaning the outer surface of the closed container after filling it with lactose, and the corridor as the AGV route from storage room to tablet feed room.

The cleaning was performed by wiping with a clean non fiber-releasing cloth, wetting with purified water, and in the following sequence: ceilings, walls, windows, and floors. The same methodology has been applied to the cleaning of equipment, the docking station, closed container, AGV, and lifter.

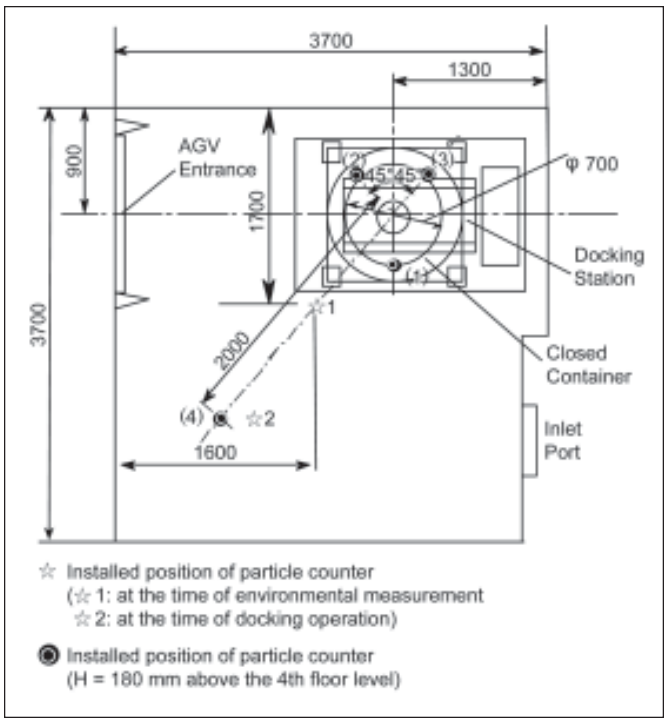

Figure 4. Installation layout of docking station and sampling points.

Particle Count Monitoring

An instrument (suction rate: 2.83 l/min.; simultaneous counting error: 5% or less) was used to monitor the dust concentration after cleaning as well as the variations in particle count caused by operators entering or exiting the premises. Likewise, it has been used to monitor the recovery time of the considered room prior to any other measurement, for example, lactose concentration in air.

In parallel with the measurement of the lactose dispersion rate of the docking station, the particle count has been determined in order to confirm its correlation with the dust containment performance.

Verification Method for Containment Performance

Measuring Points

The layout of the docking station installation and corresponding sampling points according to the ISPE Good Practice Guide are shown in Figures 4 and 5. The specifications for the

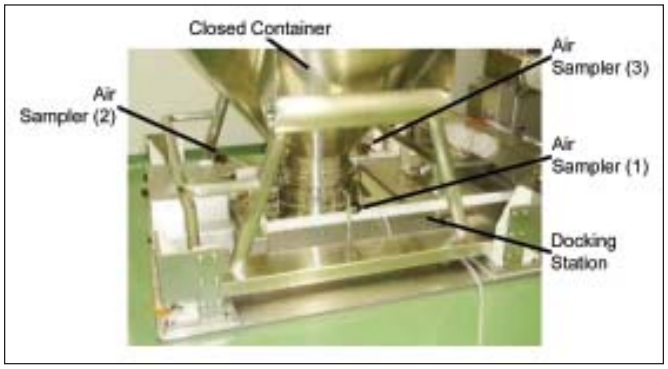

Figure 5. Installed condition of air sampler.

Item	Description
Type	IOM Sampler, 225-70A
Sampling Rate	2 l/min
Sample Media	25 mm filter, Whatman, GF/F

Table A. Specifications for air sampler.

air samplers are given in Table A. Air samplers were fixed at positions Nos. 1 to 4 as shown in the horizontal view of Figure 4, centering them on the butterfly valve used to drop ingredients through the docking station into the manufacturing equipment.

The confirmation by particle count of the environment situation has been obtained with the particle counter located near the center of the room while the particle count of the Docking station has been performed with the counter installed close to air sampler 4.

Test Sample

As recommended by the ISPE Good Practice Guide, a test sample of lactose, mass 25 kg, type 450M, has been used. Particles of diameter 63 micrometers or less accounted for 98%, and those of diameter 150 micrometers or less accounted for 100%.

Sequence of Operations During the Testing Procedure

The following sequence has been applied:

a. Clean the rooms and equipment.
b. Start the particle counter.
c. Confirm the increase in room recovery time.
d. Transfer the closed container into the tablet feed room using the AGV.
e. Start the pump of air samplers and at the same time, open the cover cap of the station (subsequently, the AGV leaves the room).
f. Feed the sample into the tabletting room by opening the valve of the container docked on the station.
g. After completion of the transfer, the AGV comes back in the tablet feed room to take away the closed container.
h. Stop the pump of the air samplers 15 minutes after closing the station's cover cap.
i. Collect the filters (test samples kept in cold storage and transported by refrigerated van)
j. analysis

Analytical Method

The quantification of the lactose dispersion rate has been obtained by HPLC using an electrochemical detector. The lowest Limit of Quantification (LOQ) was set at 4 ng/filter, and calibration was made from 0.004 to 20 mcg/filter.

Using a suction rate of 2 l/min. and a sampling time of 30 minutes, the detection limit of dispersion will be 67ng/ m^3. In the case of a LOQ of 4 ng/filter or less, the value of 4 ng/filter was used for calculation of the dispersion rate. The results obtained are shown in the graphs.

Testing Conditions

Tests were performed under three different conditions:

A. docking/undocking operations performed with a closed empty container (Blank 1)

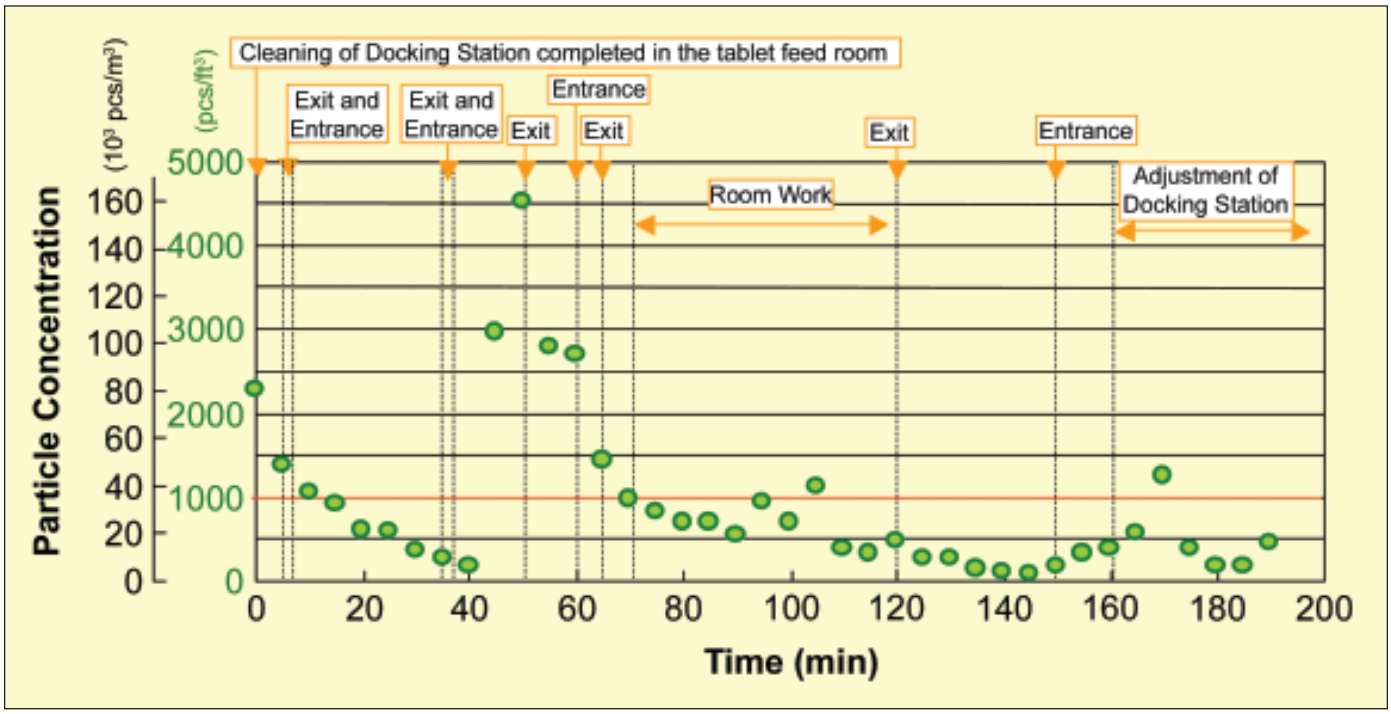

Figure 6. Particle count in the room after cleaning.

B. lactose loaded into the closed container, container regularly docked and undocked on the station, but lactose not transferred to manufacturing equipment (Blank 2)
C. normal operating conditions; lactose loaded into the container and transferred to the manufacturing equipment

Testing Environment

Temperature: 23.2 to 25.4°C; Relative Humidity: 19 to 54%. The dust dispersion rate of the docking station has been measured three times in total, all under identical working conditions.

Results

Dust Concentration After Cleaning

The results of dust concentration measurements made in the tablet feed room after cleaning are shown in Figure 6. The graph refers to particles of 0.5 microns or more counted after cleaning of the tablet feed room and equipment.

The particle concentration falls below the level of Class 6 (ISO Standard, equivalent to Class 1,000 USA Federal Standard) and stabilizes around 20,000 particles/m^3 within 30 minutes after cleaning operations, or after the entrance or exit of operators in the room, etc. For this reason, it was decided to start the measurement of dust dispersion rate of the docking station at least 30 minutes after the operators completed their preparatory work and after cleaning operations, the aim being to achieve particle concentrations of 20,000 particles/m^3 or less.

Measurement of Dust Concentrations at the Docking Station

The value of lactose concentration under Condition A (Blank 1), where the docking operation is made with a closed empty container, appeared at an undetectable level in all three measurements.

The results of the first series of measurements of lactose dust concentration during docking operations under Condition B and Condition C appear in Figure 7. The concentrations of lactose corresponding to the four sampling positions are within the range defined by the vertical red bars on the diagram.

The lactose concentration under Conditions B (Blank 2) where samples were not transferred to the manufacturing equipment runs between 70 and 180 ng/m^3, while the particulate concentration under these same conditions remains between to 10,000 and 20,000 particles/m^3. Since there is physically no possible release of lactose particles coming from the transfer operations, (since no transfer was performed and the container remained perfectly closed), this lactose concentration can only correspond to the background contamination of the premises. It is, in any case, below the category 4 Level of Merck's Chemical Hazard Standard.[6]

The lactose concentration under Normal Operating Conditions C, where samples were transferred into the manufacturing equipment, ranges between 50 and 130 ng/m^3, while the particle concentrations under these same conditions runs between 5,000 and 15,000 particles/m^3.

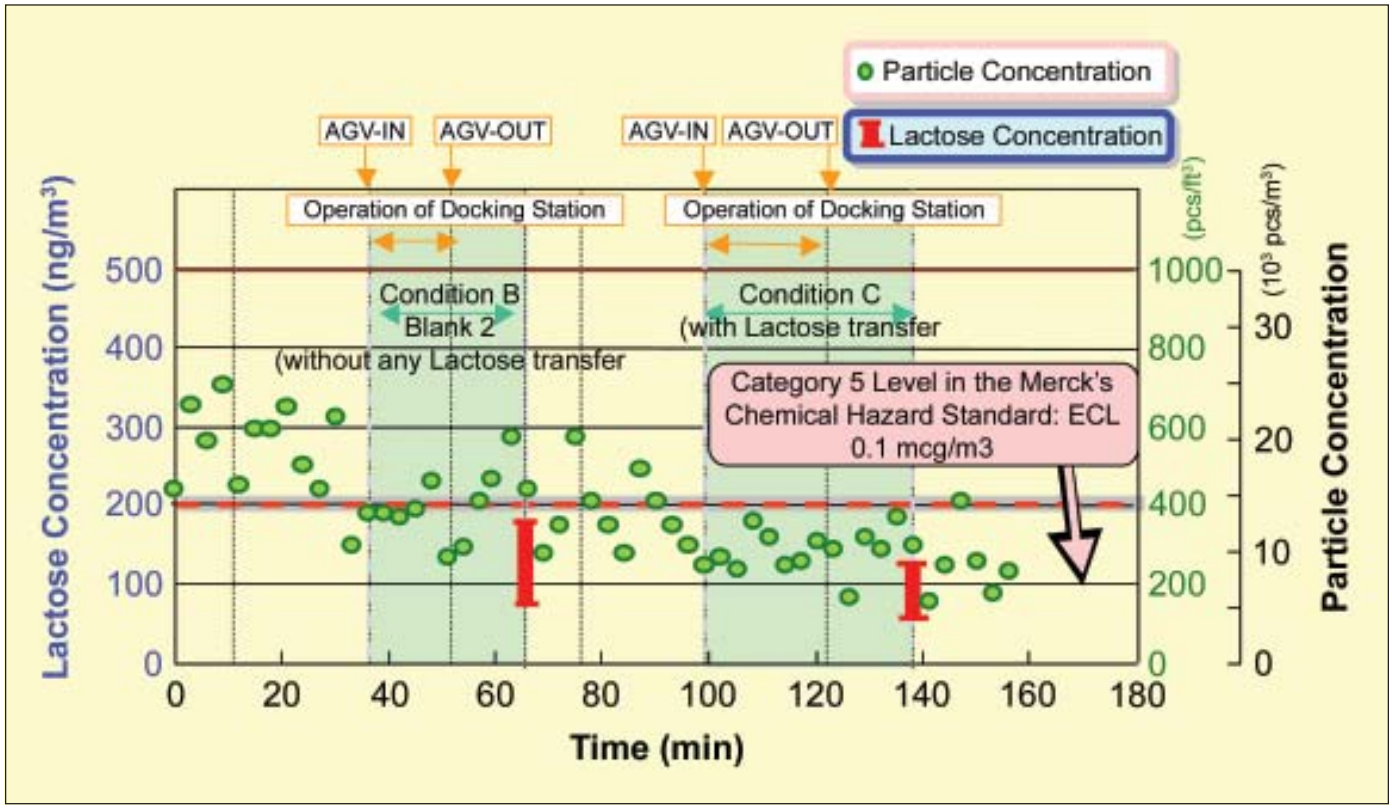

Figure 7. Dust concentration at the docking station.

	Range of concentrations measured during the three series of experiments	
	In absence of transfer through the station	With transfer through the station
First series of experiments	70 to 180 ng/m³	50 to 130 ng/m³
Second series of experiments	70 to 170 ng/m³	50 to 70 ng/m³
Third series of experiments	80 to 90 ng/m³	60 to 70 ng/m³

Table B. Lactose concentrations measured according to the ISPE Good Practice Guide indicate that the transfer of lactose is performed without any release of particles in the room environment.

The experiments described above have been repeated a second time and a third time under identical conditions and provided similar results, leading to identical conclusions. This is shown in Table B.

Comments and Discussion

In all cases, it appears that there was no measurable increase in lactose concentration during docking, undocking, or lactose transfer operations on the new docking station. This undoubtedly proves the tightness and good working conditions of the equipment.

Also, in all experiments, it appeared that the measured concentrations under Conditions C, when there is a transfer of lactose are lower than under Conditions B, when there is no transfer. In the authors opinion, this is only an appearance. Indeed, as can be seen in Figure 7, the sampling time is longer in the case of effective transfer and consequently the quantity of sampled air is also greater. The greater dilution may explain this lower concentration.

Under Conditions A (no lactose in the container), the concentration of lactose was below detectable limit. Under Conditions B and C; however, this concentration is 100 ng/m³. This is explained by the fact that a minute quantity of lactose has probably deposited on the closed container during filling and has been dispersed in the room by the HVAC system during transfer by the AGV. In other words, what was measured in these cases is a background concentration of lactose in the room.

The experience gained through these trials also has lead us to the following considerations. The selection of Lactose as a reference tracer for the trials performed by the working group in charge of developing the ISPE Good Practice Guide was based on the following: availability of this material worldwide, ease of standardization, relative ease of assay, etc. However, one may wonder since lactose is used extensively in industrial quantities, practically in all Oral Solid Dosage (OSD) Forms facilities, if it will not present inconveniences in some situations where there may exist traces or micro-traces of lactose in the room air. Making a blank on the room air is not always the best way, especially if the lactose contamination in air is relatively high and if the equipment is tested for micro-leaks. In such cases, the use of another tracer would resolve the issue and one might think of using a product like micro-pulverized sodium chloride, that is less in use in OSD facilities, easily available worldwide, and very easy to assay in trace amounts by flame photometry.

Summary and Conclusions

The application of the methodology presented in the ISPE Good Practice Guide for evaluation of the containment performance of industrial equipment, under strict experimental conditions, and in an industrial environment, resulted in the following:

1. No increase in lactose dust concentration between the blank where the lactose is not transferred and the real test with lactose transfer could ever be evidenced.
2. In all cases, the lactose dust concentration averaged 100 nanograms/m³, but this is also the background concentration measured with the lactose blank without transfer.
3. In the worst case, that is even if one would not take in account the lactose background concentration (blank) in the transfer room, the absolute maximum dispersion rate value obtained would be 130 ng/m³.
4. In no case has the dust dispersion rate ever reached 200 ng/m³; which demonstrates that the station is capable of fully meeting the Exposure Control Limit (ECL) level of 1 mcg/m³ or less, corresponding to Category 4 (high toxicity) of Merck's Chemical Hazard Standard.[6]
5. These results do position the station at the level or better than isolators in terms of containment of pharmaceutical equipment.

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PHARMACEUTICAL ENGINEERING Interviews Drs. Bernardus (Ben) N.M. Machielse, Senior Vice President, Operations, MedImmune, Inc.

This interview presents a candid look at MedImmune's Operational Excellence Program, including how they are implementing lean manufacturing (Six Sigma) in all aspects of their operations as a framework for continuous improvement.

It was conducted by Cathy Middelberg, Wyeth Biotech, and member of the ISPE Editorial Committee.

Drs. Ben Machielse was appointed Senior Vice President, Operations, in January 2005. Named senior vice president, quality, in September 2003, his most recent promotion expanded his area of responsibility to include all manufacturing and supply chain operations in addition to the company's quality operations. Since joining MedImmune in May 1999, Drs. Machielse has led the growth of the quality department from 80 to more than 300 people, including the incorporation of the quality-related activities from the U.S. Bioscience and Aviron acquisitions. Prior to joining MedImmune, Drs. Machielse was vice president of quality control and quality assurance for Xoma Corporation of Berkeley, CA. He also spent several years in various manufacturing and quality positions at Centocor BV of the Netherlands. Drs. Machielse holds a BS in medical biology and an MS in biochemistry from the University of Utrecht, The Netherlands.

Q MedImmune is implementing an Operational Excellence (OE) program. What is the purpose of the program?

A MedImmune has created a culture of continuous improvement among its employees. Our goal is to better address customer needs by meeting all production requirements and providing a faster response time for customers. An OE program also provides a framework for the organization's quality improvements. It is imperative to integrate the program into all aspects of operations, including manufacturing, quality, compliance, facilities, and the supply chain. Continuous Improvement (CI) is not the driving factor; it is the consequence of a flawless operation.

Q Has the FDA's Critical Path Initiative or the Pharmaceutical Quality Initiative influenced the structure or focus of your program?

A While the OE program is tied to the FDA's Critical Path Initiative, the implementation of the OE program is one of MedImmune's key business initiatives. A good OE program consists of active management of the process based on a strategic plan that defines long-term objectives. The program will actively measure improvements and gained efficiencies. Three elements are the essential basics of a successful OE program:

- a general understanding and acceptance of the program by all employees
- support by senior management
- ongoing employee training, such as Six Sigma, to provide employees with the skills and tools to support OE projects to the best of their abilities

Q What are the long-term goals and perceived benefits of this program?

A There are several goals and perceived benefits. We will benefit from a better process definition and less variability. The program will allow us to reduce production time and get our products into the clinic or to the commercial side of the business faster.

MedImmune's state-of-the-art R&D facility and worldwide corporate headquarters is located in Gaithersburg, Maryland.

We [MedImmune] will utilize lean manufacturing (Six Sigma) techniques to optimize our processes and value streams, resulting in:

- reduced production time
- improved quality
- reduced cost
- faster response time
- reduced time to market

Q Will you apply this program to manufacturing, R&D and/or validation? Any other areas?

A Yes. We are looking forward to a broad implementation of the OE program. We expect the program to reduce production time, make processes more efficient, and improve process analysis. As MedImmune continues to grow, the company also has outgrown some of its manufacturing processes. The OE program will help us adjust our manufacturing process so that it remains efficient as the company grows.

Q What tools is MedImmune going to utilize in this program?

A There are tremendous opportunities to make our manufacturing operations more efficient. The plan is not to reinvent the wheel, but to apply the OE program to improve existing processes. Training our employees is the foundation of our program. Our manufacturing employees must receive technical and quality training. We must develop the skills of our middle management personnel. Since change occurs constantly, we are committed to reviewing and assessing the effectiveness of our training program on an annual basis.

Q How will MedImmune measure the success of the program? What metrics will they apply?

A We are developing the methodologies of the program, and will begin looking at measures for success as a next step. We will define simple metrics so that people understand the impact and benefit of the program.

It is important to have a firm grasp of the OE program to ensure a successful implementation. And, as a general rule of thumb, the OE program should be supported by senior management, but driven by all employees across the organization.

Q Can you provide an example of where you have, or will, apply this program?

A The program correlates with quality improvements and integrated excellence in all aspects of operations such as manufacturing, quality, compliance, facilities, and the supply chain. With the growth of MedImmune's business, our number of suppliers for raw materials and contract services have increased. Managing our supply chain has become increasingly complex and critical to our success.

Q What can professional organizations like ISPE do to support the development of OE programs?

A Professional organizations such as ISPE can help communicate the benefits of an OE program by hosting guest speakers, discussion groups, and workshops. The industry would benefit from the analyses of case studies and the development of best practices through collaboration of industry leaders. ISPE could facilitate the development of industry standards and benchmark databases.

Q What suggestions do you have for firms who are interested in starting their own OE program?

A Start slowly, identify the "low-hanging fruit" to prove the concept. Manage the flow of projects into the OE program so that the system isn't overloaded. As stated above, define simple metrics so that people can see and understand the impact the program has. From the beginning, design an OE program that provides real-time input so that operations can be assessed immediately.

About MedImmune Inc.

With approximately 2,300 employees worldwide, MedImmune is headquartered in Maryland with facilities in Pennsylvania, California, Kentucky, the United Kingdom, and the Netherlands. The company relocated its corporate headquarters to a new state-of-the-art facility in March 2004, designed to place research functions at the core and enhance the collaborative potential of researchers and developers.

The company is focused on the areas of infectious diseases, cancer, and inflammatory diseases. The company has four marketed products and an advancing pipeline of promising candidates, all designed to treat or prevent a number of debilitating or life-threatening diseases.

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Design, Qualification, and Performance of a Cost-Effective Water Purification System for a GMP Pilot Plant

by Joseph Tunner, George Katsoulis, Jeffrey Denoncourt, and Sean Murphy

This article describes a water purification system for a GMP pilot plant that uses modular, off-the-shelf purification components chosen to control cost, maximize validation efficiency, and meet USP requirements for purified water.

Introduction

One of the most critical utility systems in a plant operating in compliance with Good Manufacturing Practices (GMPs) is the purified water system. The United States Pharmacopeia (USP), which sets standards for different water qualities, states that "Water for Injection (WFI) is intended for use in the preparation of parenteral solutions".[1] However, for other pharmaceutical applications, the guidance is more general and intended to ensure that the user designs a water system fit for the intended purpose. In many applications, a suitable water system can be defined as providing water meeting the current USP monograph for purified water. This definition allows the system designer to consider alternatives to the typical stainless steel WFI system, while achieving the desired water quality in a more affordable and manageable manner.

A water purification system was constructed using modular, off-the-shelf purification components chosen not only to control cost and maximize validation efficiency, but also to meet the USP requirements for purified water. According to the ISPE Baseline® Guide on Water and Steam Systems, "Pharmaceutical equipment and

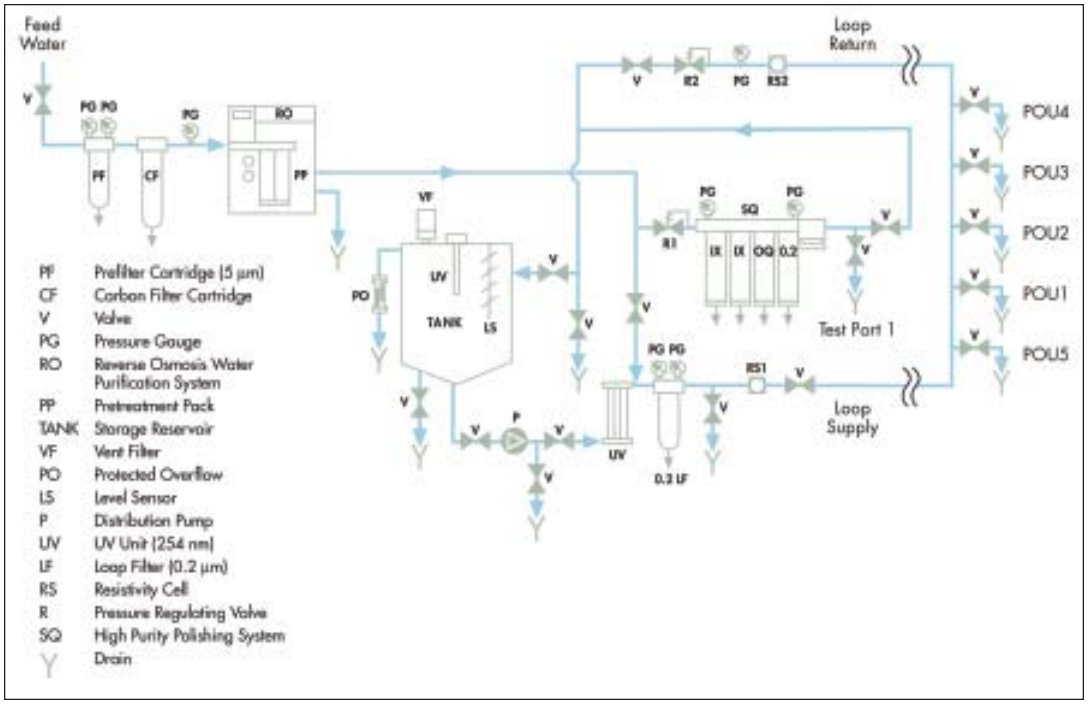

Figure 1. Water system schematic.

piping systems rely extensively on stainless steels to provide the non reactive, corrosion resistant construction needed in manufacturing and heat sterilization. However, thermoplastics are available that may offer improved qualities and/or lower cost."[3] The installed system utilized polypropylene piping rather than the traditional stainless steel distribution system to further control the system installation cost and ongoing maintenance.

This article describes a unique GMP pilot plant water system installed in a small solid dose pilot plant operating in compliance with GMPs for use in the manufacture of clinical supplies for human trials. Details of the design considerations and selection, system description, and system validation are presented. Water test results from the system performance qualification are detailed, followed by a complete data set for a year of operation. System excursions for TOC and microbial monitoring are noted and the actions taken to resolve them are presented.

Water Purification System Design Considerations and Selection

The project began with an assessment of an existing reverse osmosis/deionization (RO/DI) water system for expansion and validation. The existing system fed 10,000 square feet of laboratories with 20 Points Of Use (POU) and required expansion to feed a new 3,000 square foot GMP solid dose pilot facility (the main project) with five new POU. The user's requirement was for 150 gallons per day of purified water appropriate for equipment (product contact) and facility washing as well as for direct product addition.

Adopting a risk-based approach, the existing system was surveyed and found to be unacceptable for this purpose. Primarily a general laboratory system, it had evolved over time and incorporated many undesirable features, such as check valves on dead legs and some very long pipe runs. The most significant challenge, apart from the cost of remediation, was to gain control over a multi-user/department system where, for example, it was not uncommon to find flexible hose connections from laboratory faucets that dangled into the drains.

The option of creating a secondary loop from the storage tank of the existing system to the new facility was rejected quickly due to the distances and physical obstacles involved. In addition, the generation system was not controlled from a GMP perspective and required significant remediation effort.

Figure 2. Purified water system: major components.

Another option was to expand the existing RO/DI system and add a supplementary purification system at a single POU in the new facility, such as a water purification system. This option was rejected for four reasons. First, the required usage rate of 150 gallons per day was too high for such a system to be practical. Second, distributing water to the various suites would have involved transporting containers some distance and through multiple doorways. The nature of the potent drug substances in use would have necessitated decontamination of these containers before removal from the suites and the risk of contaminating the water was unacceptably high. Third, some applications would have required additional equipment to pressurize the water. Again, this was a cost and contamination risk. Finally, from a qualification perspective, the lack of control over the feed water quality to the terminal system would, by definition, translate to a lack of control over the supplied water from it.

A stand-alone system was justified and approved with issues related to the unanticipated incremental cost of the larger project. The water quality specification was set as described in USP 25 and a location for the system was identified, adding the constraint of a space 10 feet long, nine feet high, and three feet deep.

All except one of the vendors offered customized skid-based stainless steel systems centered on domestic RO membranes. These vendors would not guarantee the water quality output from their proposals and suggested a "build it and see" approach due to the unique nature of their systems. They were comparatively expensive due to the stainless steel design and incorporated unsophisticated controls. The skid designs were large and difficult to keep clean and accessible for maintenance.

The selected vendor offered a modular design with a number of 'off the shelf' components, each of which had an established history of use and performance as well as an attractive price. Each major component incorporated a high level of instrumentation including diagnostics, alarming, and I/O for

remote monitoring of pertinent status and performance data. Quotations indicated a 50% lower total cost, a faster delivery time, and the advantage of pre-written qualification protocols offered by the selected vendor for the major components.

A final design consideration was the selection of materials for the water distribution loop. A simple purified water loop does not require regular heat sanitization. Therefore, both stainless steel and all thermoplastic piping systems were possible options. The advantages of plastic systems are reviewed in detail elsewhere.[4] In short, a plastic system was selected based on cost, reduced maintenance, and ease of installation. Polypropylene (PP) was selected over Polyvinylidene Fluoride (PVDF) because it provided a more cost- effective system with high purity components.

The major components of the selected system are described below. The purification process is illustrated schematically in Figure 1. The actual system and a point of use are shown in Figures 2 and 3, respectively.

- A reverse osmosis water purification system (reverse osmosis system) with pretreatment as the starting point and initial purification of the total system.

- A 350 liter (90 gallon) storage reservoir system (storage reservoir) meets peak daily demands and includes an in-tank UV and vent filtration to prevent contamination at this point.

- A high purity polishing purification system (polishing system) utilizes ion exchange, organic removal, and membrane cartridges to polish water to higher purity levels. In this system, this device is used to both polish the reverse osmosis water and maintain quality of the stored and distribution loop water.

- Distribution equipment including pump, loop UV unit (254 nm), and 0.22 micron filtration deliver water to distribution piping and ensure water quality. A resistivity meter continuously monitors resistivity of the distributed water. Purified water is recirculated continuously through 343 linear feet of 32 mm /1.02 inch ID (DN-32) polypropylene piping with 33 elbows and five tees (the POU).

System control, monitoring, and alarm inputs and outputs were included with each major component (listed above). The key alarms from each major component were consolidated to a single alarm input of a validated electronic data recorder. An analog output from the resistivity meter also was fed to a channel of this unit, which was configured with high, low, and low-low alarms as well as data logging and historical trending.

Feed water from the city supply first passes through pretreatment including a five micron prefilter and carbon filter cartridges before entering the Reverse Osmosis (RO) system. The RO system includes an additional integrated pretreatment cartridge pack with activated carbon, a 0.5 micron prefilter, and a calcium hardness sequestering compound. This combination of pretreatment protects the reverse osmosis membrane from damage due to fouling from particulates, chlorine oxidation, and formation of mineral scale on the membrane surface. The sequestering agent is a solid, long chain polyphosphate that weakly binds calcium ions and minimizes calcium carbonate precipitation (scale). The use of the sequestering agent within the system pretreatment cartridge pack was particularly important in the system design as this eliminated the need to use softening for removing calcium hardness from the feed water supply; therefore, saving considerable space.

Pretreated water continues through a high pressure pump that boosts water pressure before entering the reverse osmosis membrane cartridge. The high pressure forces water through the reverse osmosis membrane with contaminants being rejected by the membrane between

Figure 3. Point of use.

95 and 99%. Water is rinsed continually along the upstream side to continually flush contaminants to drain. Approximately 35% of the feed water entering the system is processed through the membrane as product water at a rate of 30 liters per hour, providing the required 150 gallons per day. Reverse osmosis system performance is monitored including feed and product water conductivity and the calculated % ionic rejection.

The water leaving the reverse osmosis system requires additional purification to meet the USP purified water quality requirements. Therefore, the reverse osmosis system product water enters the polishing system, which includes mixed-bed ion-exchange, organic removal, and 0.22 micron membrane filter cartridges to remove ions, organics, and bacteria effectively. A resistivity meter monitors the water quality exiting the polishing system as the last step before delivery to the 350 liter storage reservoir.

The primary purpose of the 350 liter conical bottom storage reservoir is to buffer the fluctuating demands of up to 350 liters (~90 gallons). In addition, the storage reservoir includes a built-in UV light to prevent bacteria growth and vent filtration. Vent filtration in-

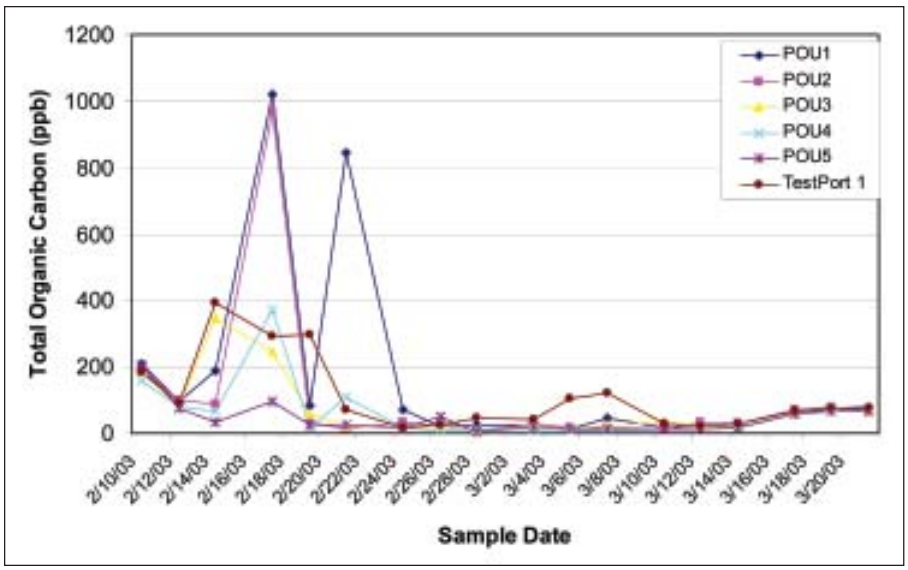

Figure 4. TOC readings during the PQ.

cluded a 0.5 µm nominal filtration and a solid granular soda lime integrated into a single cartridge to prevent ingress of airborne contamination. A tank level sensor interfaces with the reverse osmosis system to refill the storage reservoir automatically and provide a low storage reservoir water level signal that protects the distribution pump.

The distribution pump delivers water through the loop 254 nm UV unit that serves to disinfect the purified water followed by a 0.22 micron absolute membrane filter for additional bacteria control. The purified water is distributed at 15 gallons per minute to the five use points before returning to the 350 liter storage reservoir. A back pressure regulating valve at the return assures a minimum pressure is maintained at all POU.

Points of use in the manufacturing sites were recessed in the wall - *Figure 3*. This protected the ports from damage as the pilot plant utilized portable powder processing equipment, which was large and cumbersome to move. However, the recess was difficult to access and as a design feature could promote the practice of leaving flexible hoses in place. This did not occur because the area operators also were responsible for system sampling and fully understood the importance of avoiding this practice.

The distribution pump and distribution piping were selected together to meet target flow rates and pressure requirements and to assure that a minimum flow velocity of five feet per second was sustained. Maintaining minimum flow velocity, continuous recirculation, and reducing dead legs are considered industry "good design practices" to minimize risk of bacteria proliferation. A 15 Gallons Per Minute (GPM) flow rate though 32 mm (1.02 inch ID) polypropylene distribution piping results in a flow velocity of ~5.9 ft/s.

An important design feature of the system includes the use of the polishing system to both process the reverse osmosis system product water and process approximately three gallons per minute of distribution flow from the loop UV unit before recirculating directly back to the 350 liter storage reservoir. In summary, 18 gallons per minute from the distribution pump passes through the UV unit, 15 GPM continues through the 0.22 micron filter and facility distribution loop piping, while three GPM is processed through the polishing system back to the storage reservoir. Pressure selection at key points during the design allows both the reverse osmosis product water and three gallons per minute of the distribution flow to be processed through the polishing system. This dual use of the polishing system maintained the distribution loop resistivity above USP Purified Water requirements, consistently greater than 16 megohm•cm in the main loop.

During start up, the system initially was filled with RO water and sanitized utilizing bleach at approximately 200 ppm concentration and drained. The polishing loop cartridges and loop filter were installed and the system refilled and polished until the required water quality based on TOC and conductivity measurements was met. The periodic system maintenance procedure required the same sanitization and cartridge change out process annually.

Water System Qualification

The typical three-stage qualification approach was followed, starting with the Installation Qualification (IQ), transitioning to an Operational Qualification (OQ), and finishing with the Performance Qualification (PQ). For the IQ and OQ, full advantage was taken of the vendor-supplied validation protocols for each major system component, which were supplemented with an internally generated protocol tying the system together as a whole.

As USP 25 specifies, the IQ stage should consist of "instrument calibrations, inspections to verify that the drawings accurately depict the as-built configuration of the water system, and where necessary, special tests to verify that the installation meets the design requirements."[6] The vendor-provided IQ protocol package for each of the individual primary components (reverse osmosis, polishing system, and storage reservoir systems) was used to provide verification of the hydraulic and electrical connections as well as the system drawings. An internally generated IQ protocol collected the details of all reference documentation, instrument and utilities verifications, spare parts verification, and drawing verification for the entire system as a whole.

The vendor supplied OQ protocol and a vendor technician were used to test the primary components to prove that they were operating according to the vendor's specifications. According to USP general chapter 1231, "A validation master plan for a water system typically includes... an OQ stage consisting of tests and inspections to verify

that the equipment, system alerts, and controls are operating reliably..."[6] This included testing of the equipment's controls and operation with both liquid path hydraulic and electronic tests. Specific testing of the system operating alerts was performed by simulating values on the system and exceeding the system limits using a calibrated instrument from the manufacturer. The internally generated OQ protocol provided the overall system OQ, which verified system operation including the distribution loop (point of use pressures, temperatures, and flow rates), water system generation, storage system operation, and alarms.

The purpose of the Performance Qualification was to demonstrate that the system produced and maintained re-circulating water that meets the compendial requirements of USP purified water over a suitable time period. The qualification period was chosen to strike a balance between time and testing burden (cost), the need to demonstrate a robust system (reliability), as well as the knowledge that the system was intended for an oral dose facility and would continue to be monitored indefinitely following completion of the qualification testing (risk mitigation). After considering these requirements, a six-week qualification period was approved.

A test schedule was prepared with samples drawn from every room Point Of Use (POU1 through POU5) and Test Port 1 at the outlet of the polishing system on Mondays, Wednesdays, and Fridays. Test Port 1 was of particular note as it immediately follows the polishing system without the UV light or final loop filter that precedes all loop ports. Hence, Test Port 1 provides the microbial performance of the purification system independent of the loop bioburden control elements. All samples were tested for Total Organic Carbon (TOC), conductivity, and bioburden. The city feed water to the system also was tested for bioburden and coliform bacteria.

Acceptance criteria for the system were based on USP 25. All ports in the system required a TOC result ≤ 500 ppb. Conductivity specifications are

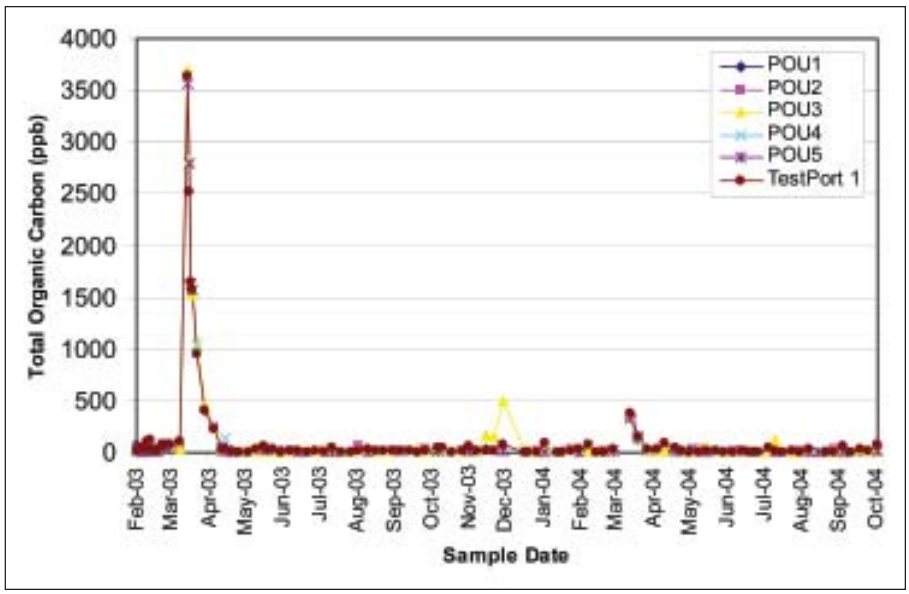

Figure 5. Regular weekly monitoring TOC results.

temperature dependent, with a range of ≤ 1.0 and ≤ 1.1 µS/cm corresponding to a "normal" room temperature range of 15 to 20°C.[5] The USP bioburden requirement of <100 CFU/mL was used.[6]

The city feed water was monitored for bioburden For Information Only (FIO). The feed water was required to have no detectable coliform bacteria.

Samples were collected using a hose attached to the port via a tri-clamp fitting with an initial 3 L purge prior to collection. If the area had been used for powder processing, the port was cleaned prior to either sampling or use with water and alcohol and the purge volume was doubled to ensure removal of the alcohol. Samples for chemical analysis were collected in a 50 mL glass vial with an untreated Teflon-faced stopper, which had been prepared by triple rinsing, 3% hydrogen peroxide rinsing, and then final rinsing again prior to sample collection. Microbial samples were collected in sterile 125 mL polypropylene bottles.

Chemical analysis was performed in-house using an Anatel Corporation TOC Analyzer, Model Access 643P, which reported both TOC and conductivity. All microbial testing was performed by Quandrants Scientific. Bioburden was determined by the Heterotrophic Plate Count procedure[2] where 1 mL of water was mixed with molten R2A agar (agar below 46°C), plated, and incubated at 30-35ºC for three to five days. Samples were tested in duplicate, and the average of the two plates was reported. Total coliform was tested using the Standard Total Coliform Membrane Filtration procedure[7] where 100 mL of water was filtered through a sterile 0.45 micron filter, the filter was placed on LES m-Endo Agar, and incubated at 34.5-35.5°C for 24 hours.

Performance Qualification testing was performed during February and March of 2003. Conductivity at all points in the system behaved similarly with values ranging from 0.10 µS/cm to 0.70 µS/cm with most values well below 0.50 µS/cm (data not shown). All results met the process qualification conductivity requirements.

TOC testing during this period demonstrated two days during the second week with unacceptably high TOC readings above the 500 ppb acceptance criteria in three samples - *Figure 4*. Analytical Laboratory Investigations did not identify a testing error, and an investigation was performed. Review of the sampling indicated that a new technician had collected the high samples. Considering that other ports in the system demonstrated acceptable results on the test days in question and that the primary technician had likewise consistently collected passing samples, the deviation was attributed to operator technique. As is

typical, the technician in question underwent technique review with retraining to correct issues observed. Following this, all samples for the remaining four weeks of the qualification were acceptable.

System bioburden during the test period was consistently very low. More than 100 samples were taken over the course of the qualification with bioburden results of zero for all but six samples, which yielded one CFU in five cases and two CFU in the last case. These isolates were identified to the genus level FIO. Of the seven isolates, three proved non-viable and could not be further propagated, one was *Staphylococcus hominis*, one was *Bacillus cereus*, and two isolates were *Pseudomonas aeruginosa*. Of these isolates, *P. aeruginosa* is of special concern as it does have the capacity to cause disease and can thrive in nutrient poor environments. It is an aerobic gram-negative bacteria found in water, soil, and on the surfaces of plants and animals. Both isolates were from the same sample, and were the only sample from that port collected that yielded an isolate. As this isolate was not obtained in any other sample, and was never isolated from this or any other location during the remaining weeks of the qualification, it was treated as an isolated event and the system was accepted with continuing monitoring. Over the course of the next year, no further isolates of any nature were obtained from this location, which underscored this event as isolated.

Feed water monitoring results were as expected for potable city water. Bioburden typically ranged from 1,000 To Too Numerous To Count (TNTC). However, at no time were coliform bacteria isolated in the feed water. The bioburden results for the incoming water when compared to results for the re-circulating system demonstrated the robustness of the incoming water treatment system.

Final evaluation of the system demonstrated consistently low TOC, conductivity, and bioburden in the system. Following approval of the validation report in June of 2003, the system was considered acceptable for the manufacturing of solid dose (i.e., tablets) clinical supplies.

Water System Performance

Following the process validation, ongoing system monitoring and release of tested water is a standard requirement for GMP water systems. Water was sampled and released on a weekly basis. The two points considered to be most critical, Test Port 1 at the generator and POU3 in the primary GMP manufacturing room, were always tested. The remaining four ports in rooms used for development and for equipment cleaning were sampled on a rotating basis every month. The city water also was tested on the monthly schedule to verify the absence of coliform bacteria.

Test results for each week were compiled by the analytical chemistry team and submitted to the quality assurance group for weekly release. The release certificate for each week was attached to the lot files for any GMP drug product batches manufactured. As part of batch release, acceptable release results were required from the sampling date prior to and after the used date of the water in the drug product batch. This system testing was performed from the close of the validation in March 2003 through October of 2004 with the resulting data set covering more than one year of system operation.

TOC results over the course of this period are generally acceptable with most values consistently below 50 ppb - *Figure 5*, which is consistent with a recent survey indicating more than 90% of pharmaceutical water systems are operating with TOC levels below 70 ppb.[8] However, two excursions above the 500 ppb system limit and one spike are noteworthy.

In April 2003, the TOC spiked above the action limit of 500 ppb with values on the order of 3500 ppb. These results were consistent across all ports in the system. It was determined that the root cause of the incident was an error in the equipment operating procedure, EOP-000-075, which specified use of an inappropriate refilling procedure of the storage tank acid overflow device. This resulted in system contamination, as was evidenced by the high TOC results. The system was drained, sanitized, deionization beds replaced, flushed, and restarted with testing in late April. Following sanitization, the initial TOC values were on the order of 250 ppm, and within a week, the continuous re-circulation of the water through the deionization loop had restored the system back to 20 to 40 ppb by the following test date.

The timing of this sanitization was advantageous because it provided the opportunity to solve a system design problem. As the system was utilized over the first months of operation, the Teflon-faced diaphragms in the valve ports had proven difficult to close and several locations had developed minor leaks and drips, which were difficult to control and required a system shut down to repair. While correcting the system contamination, the valve diaphragms at the point of use drops throughout the system were changed from Teflon-faced to EPDM to prevent further leakage. This replacement was documented as part of the normal facility change control process. No subsequent issues were noted with the new diaphragm material, which permanently solved the drip issue.

The second excursion was a TOC reading of 501 ppm. As this was greater than the 500 ppm limit, an investigation was initiated and performed. In this case, however, the sample was specific to one location and not reproduced at other drops in the system. The investigation identified that when the sample was taken, significant powder processing was ongoing the same day. Subsequent follow-up samples were at the normal level below 50 ppb. This excursion was then closed as an isolated incident with an assignable cause. The corrective action was to restrict sampling to occur prior to any powder processing on the sampling day and proved effective at preventing recurrence.

The final spike in TOC is noteworthy as it demonstrates the effect of annual maintenance performed in late March 2004. Per procedure, the system was taken down for annual cali-

bration and maintenance. This included complete system sanitization using bleach followed by replacement of the deionization beds and system flushing. As noted during the April 2003 excursion, the system again started with an initial higher than normal TOC reading which returned to below 50 ppb once the re-circulation through the deionization beds had returned the system to normal.

Conductivity results were acceptable with results continuously well below 1.0 µS/cm (data not shown). It is noted that the conductivity monitoring did not identify the two excursions and one planned system sanitization that were identified by the TOC results. This underscores the utility of TOC monitoring as a highly sensitive technique for water system monitoring.

Bioburden results were, with two exceptions, always acceptable - *Figure 6*. The system limit was set at < 100 CFU/mL based on USP criteria. Most weekly results were negative for bioburden, with occasional single isolates and rare samples up to 10 CFU/mL. The significant exceptions occurred in late June 2004 when on one test date the generator, Test Port 1, was sampled at 8 CFU/mL (acceptable), POU3 at 233 CFU/mL (out of specification), and POU2 at zero CFU/mL. The following week in July, the wash room port, POU5, result was TNTC, while the other two ports sampled that day were at zero CFU/mL. In both cases, an investigation by the test laboratory did not identify an assignable root cause; therefore, the results could not be invalidated due to assignable laboratory error.

The colonies isolated in late June were speciated and identified as *Pseudomonas mendocina* at both POU3 and Test Port 1. This is not an organism of special concern, hence the issue was with the magnitude of the POU3 result. Each test sample is plated in duplicate and the resulting counts from both plates averaged. Review of the data indicated that for both the POU3 and generator ports, the colonies were only located on one of the two plates, while the second plate had zero colonies. This made the test data unusual and in question, despite the lack of an assignable laboratory error. The following test data for POU3 for the following three weeks were acceptable with zero or one CFU isolated. According to the approved site investigation procedure, three successive acceptable follow-up test points allows conclusion that the system is under control and the excursion was an isolated event; therefore, the investigation was closed.

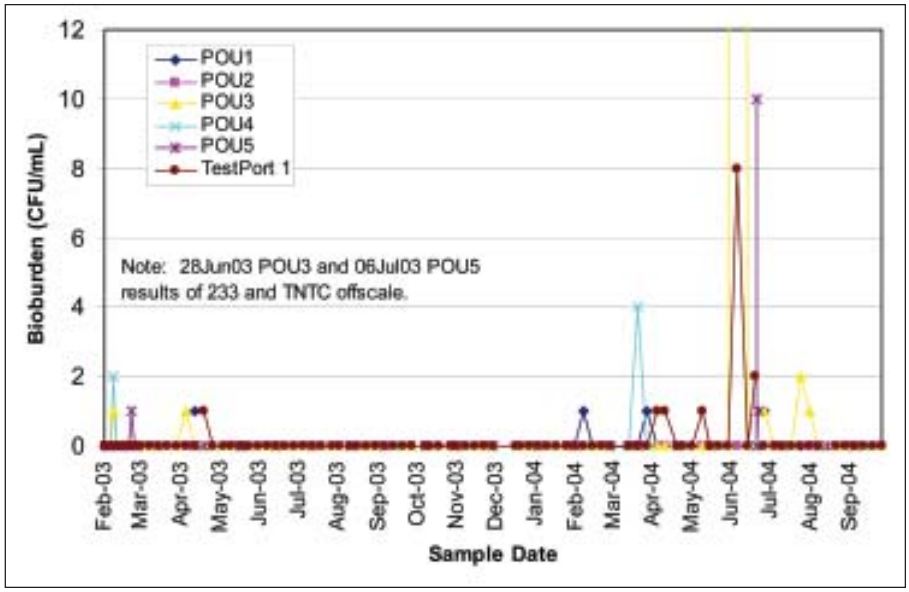

Figure 6. Regular weekly monitoring bioburden results.

The excursion in early July 2004 at POU5 was suspicious in its timing, but independent of the previous week's excursion. In this case, it was not possible to speciate the isolate. It only could be characterized as an unidentified gram-negative rod of genus *Pseudomonas*. Immediate follow-up testing over a three day period, yielded values of 10, zero, and one CFU/mL. This allowed conclusion that the high result was an isolated event and allowed closure of the investigation. As a precautionary measure subsequent to these excursions, the monitoring personnel reviewed their technique and procedures to ensure consistency and adherence to proper sampling technique.

During the course of these investigations, no manufacturing operations were in progress. If GMP water use had been required during this period, the contingency plan of utilizing released bottled water would have been implemented. Following these excursions, there were no further significant counts isolated through October 2004. Then monitoring was discontinued as the area was re-designated for development use only with changing business practices at the site.

Conclusions

A pharmaceutical water system utilizing available off-the-shelf components and a plastic distribution system was assembled and validated. Since the water system was intended to generate water meeting the USP purified water specification rather than WFI water, which is produced traditionally by distillation with a stainless steel distribution system, standard laboratory water system components and a plastic rather than stainless steel system were acceptable. This allowed rapid construction of the system at a lower cost than is typical for many pharmaceutical systems. Use of standard components also expedited the validation process as the vendor-supplied protocols covered the component details and allowed simplification of the internally generated IQ/OQ protocols to focus primarily on the system details. The PQ was completed successfully and established all ports met the required water purity requirements.

Post-validation system monitoring was performed for more than a year. TOC analysis of the system proved to be a very useful tool as non-microbial system events, such as chemical contamination or post-sanitization recov-

ery, could be identified immediately and followed. However, conductivity testing was not sensitive enough to identify the events captured by the TOC monitoring. Ongoing bioburden monitoring of the system yielded occasional counts and two investigations. At no time was there verified evidence of microbial contamination in the system, which typically exhibited zero bioburden in the test samples pulled each week. The results all support the robustness of the purified water generation and plastic distribution system presented.

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Debottlenecking of a Batch Pharmaceutical Cream Production

by Jully Tan, Dominic Chwan Yee Foo, Sivakumar Kumaresan, and Ramlan Abdul Aziz

This article describes the use of a batch process simulator in the modelling and debottlenecking of an anti-allergic cream production line at an existing pharmaceutical facility.

Introduction

Computer Aided Process Design (CAPD) and simulation tools have been widely used in the bulk and petrochemical industries since the early 1960s. It involves the use of computers to perform steady-state heat and mass balancing as well as sizing and costing calculations for a process.[1] However, the use of these CAPD and simulation tools has only emerged in pharmaceutical manufacturing in the past decade.[2-8] Compared to the readily available process simulators in the bulk and petrochemical industries, there are only a limited number of simulators available for pharmaceutical process modelling. This situation is mainly due to the uncommon unit operations and the batch operation nature of pharmaceutical processing. Due to its relatively new emergence, more work needs to be done in this sector.

Due to the increasing customer demand of the anti-allergic cream product, the pharmaceutical facility management team was looking for alternative expansion schemes to increase the current production rate as the production capacity was limited by the current operating condition and equipment setup. Hence, a debottlenecking study is needed for an increase in production. In addition, the debottlenecking study will assist the management team in future expansion plans.

Background Theory

In order to increase production throughput, process bottlenecks that limit the current production need to be identified. Bottlenecks are process limitations that are related to either equipment or resources (e.g., demand for various utilities, labor, and raw material). Hence, *process debottlenecking* can be defined as the identification and removal of obstacles in the attempt to increase the plant throughput.[5] In batch manufacturing, two types of process bottlenecks can be categorized. These are the equipment capacity-related *size* bottleneck (an equipment that is limited in size) as well as the *scheduling* bottleneck (due to the long occupancy of a piece of equipment during a process).

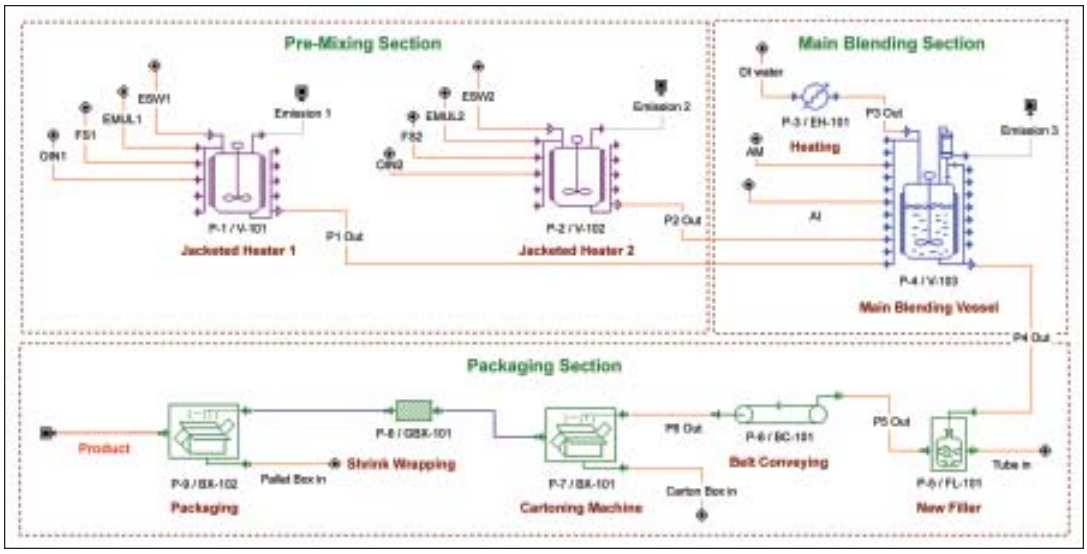

Figure 1. Base case simulation flowsheet for the production of anti-allergic cream.

The ability to identify and remove process bottlenecks that create obstacles in a manufacturing process will increase plant throughput and fulfill customer needs.

A good tool to identify batch process bottleneck is via a throughput analysis study. Throughput analysis measures the equipment utilization in a batch process with two variables, i.e., the *capacity utilization* and *equipment uptime*.[5-6] Capacity utilization is defined as the percentage of the current operating load of a piece of equipment (e.g., vessel volume for a reactor or filtering area of a filter) relative to its maximum load. For instance, a vessel with 100% capacity utilization means that its current content has reached its maximum level.

Equipment uptime measures the effectiveness of a piece of equipment that is utilized in time. It is given as the percentage of the equipment utilization time over the plant cycle time. For example, a reactor that operates for five hours within a plant with a cycle time of 10 hours has an uptime of 50%. The product of equipment capacity utilization and its uptime defines the *combined utilization* of the respective equipment.[5-6]

In an ideal situation, a plant should have all equipment running at 100% combined utilization to achieve maximum production. However, this is often not the case. All process equipment will normally feature different utilization. The ability to raise utilization of the equipment will help in raising process throughput. The processing step with the highest combined utilization is normally identified as the first candidate for process debottlenecking. Simulation tools that are capable of tracking capacity utilization and equipment uptime can facilitate the identification of process bottlenecks and the development of the scenarios for process debottlenecking. By using the "what if" scenario, process alternatives can be simulated via the use of simulation tools to reveal potential candidates for the debottlenecking study.

The Cost Benefit Ratio (CBR) is among the criteria that can be used to evaluate the economic performance of debottlenecking alternatives. As the name suggests, CBR is a measure based on the ratio of benefits obtained for a given expansion cost.[9] The first step in CBR analysis is to determine the beneficial elements, disbenefits, and expansion cost for a project. For the case of pharmaceutical process debottlenecking, CBR formulation can be defined as shown in the following equation:

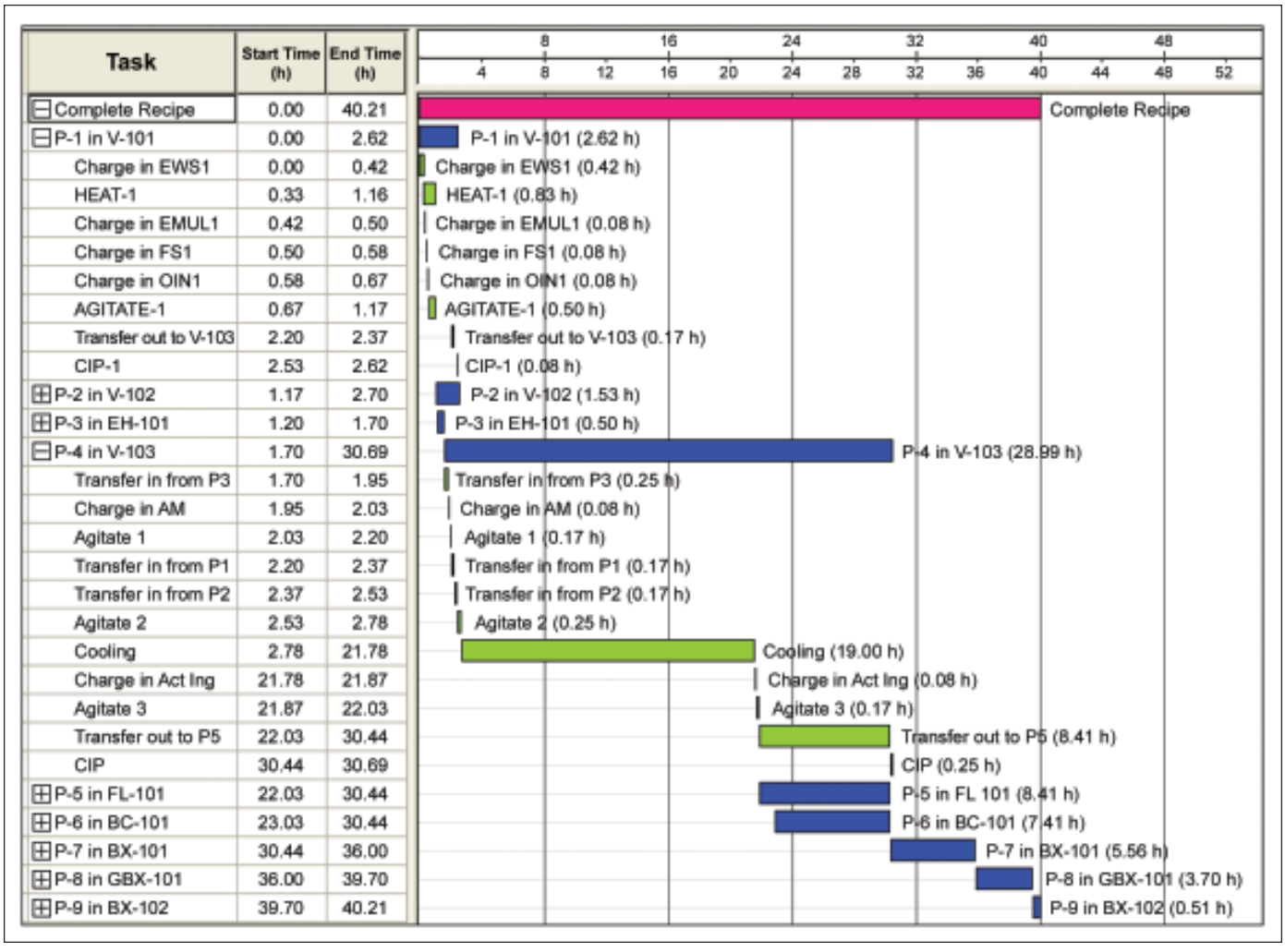

Figure 2. Operation Gantt Chart for the base case simulation.

$$CBR = \frac{\text{Revenue of alternative} - \text{Revenue of current operation}}{\text{Investment cost of alternative} + \text{Operating cost of alternative} - \text{Operating cost of current operations}} \quad (1)$$

Model Development – Antiallergic Cream Production

Figure 1 shows the base case simulation flowsheet for the production of anti-allergic cream modelled in a process simulator.[10] The base case simulation model was developed to reflect the actual operating condition in the existing pharmaceutical manufacturing facility that is operated in batch processing mode. This modelling environment, involves the modelling of a few *operations* that take place sequentially in a single *unit procedure*.[10] For instance, the Jacketed Heater procedure P-1 in the Pre-Mixing section - *Figure 1* was used to model the sequential operations of raw material charges, material heating (for melting purpose), agitation processes, as well as product discharge. All these individual operations took place in the single vessel of V-101. The modelling of these single operations is described next.

In the base case process, there are nine major processing steps in three different sub-sections. This includes raw material melting in the Pre-Mixing Section, deionized (DI) water heating, and material blending in the Main Blending Section, as well as filling, conveying, cartoning, shrink wrapping, and shipment packaging in the Packaging sections. Due to the capacity limitation of the pre-mixing vessel, the raw material is divided into two sub-mix batches in the Pre-Mixing Section. Two batches of Emulsifying Wax (ESW) and Foam Stabilizer (FS) are independently heated in the heating procedures P-1 (carried out in Jacketed Heater V-101) and P-2 (in Jacketed Heater V-102) to approximately 100ºC before the emulsifier (EMUL) and ointment (OIN) are added. The emulsifier and ointment are originally in wax form and need to be melted for uniform mixing. All raw materials are charged at room temperature.

DI water is heated in the electric heater EH-101 (procedure P-3) before being transferred into the Main Blending Tank, V-103 (P-4) in the Main Blending Section. An Antimicrobial Agent (AM) is next added into the hot DI water, followed by agitation for 10 minutes. The mixture in the jacketed heater V-101 and V-102 is then transferred into V-103. The mixture of all ingredients in V-103 is blended once more for 15 minutes in order to produce a uniform composition. The mixture is then left in an air-conditioned dispensing room to be naturally cooled to room temperature. This cooling operation took approximately 19 hours to accomplish due to the slow rate of natural cooling. Upon the completion of the cooling operation, the Active Ingredient (AI) of the anti-allergic cream is finally added. The products are once again blended for 15 minutes to obtain uniform composition before the product mixture is sent to the Packaging Section.

Upon the completion of the Main Blending Procedure, the blended product is next transferred to Filler P-5/FL-101 in the Packaging Section where it is filled into the tubes of 15 g each. The existing filling machine is operated at a speed of 30 tubes/min. The tubes are then sent to the cartoning packaging procedure P-7 (using a belt conveyer P-6/BC-101) where the anti-allergic cream in tubes are packed manually by two operators into the tube cartons, each at a speed of 20 cartons/min. Next, 12 cartons of anti-allergic cream are packed into one wrapper in the Shrink Wrapper (P-8/GBX-101) with a speed of five wrappers/min. Finally, six wrappers are packed into each of the pallet boxes in Packing Machine P-9/BX-102 (equivalent to 72 tubes/pallet box) before they are sent to the warehouse. Approximately six sealed pallet boxes are packed per minute by the operator manually.

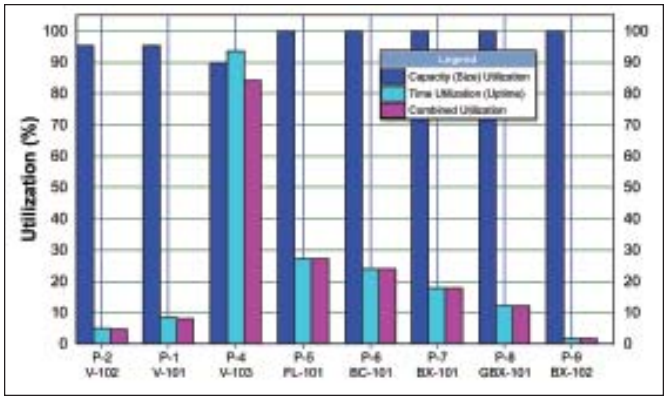

Figure 3. Capacity, time and combined utilization for unit procedures in base case simulation.

As the manufacturing process is carried out in a batch operation mode, efforts have been made to document the scheduling details of each processing step. The Operation Gantt Chart for the complete recipe of a single batch operation is shown in Figure 2. It also should be noted that the process time for certain operations are dependant upon other operations of other procedure (e.g., transfer-out operation in P-4 is set equal to the filling duration of P-5). Hence, the duration of this *slave* operation is set to follow to the duration of the *master* operation using the Master-Slave Relationship function.[10] The customer demand for this anti-allergic cream product is expected to rise another 150% of the current production capacity in upcoming years. However, the process is currently running at its maximum capacity and any attempt to increase production is not possible due to the process bottleneck. This calls for a systematic procedure to analyze the current production facilities and next to debottleneck the process. Apart from debottlenecking the current production, the debottlenecking study also will develop solutions for future expansion.

Bottleneck Identification Strategies

In the current operation, the annual operating time for the anti-allergic cream manufacturing is taken as 2080 hours, which is based on 52 operation weeks, five days a week and eight hours operation per day. From the base case simulation, a complete batch of pharmaceutical cream production is found to have a process batch time of 40.2 hrs and a *minimum*

Economic Parameters	Base Case	Scheme 1	Scheme 2	Scheme 3	Scheme 4	Scheme 5
Batch Production (tubes/batch)	13,333	13,333	13,333	13,333	13,333	13,333
Plant Batch Time (hour)	40.2	41.7	26.2	23.3	27.7	24.8
Minimum Cycle Time (hour)	29.0	21.6	15.0	12.0	9.9	7.6
Number of Batches/year	66	87	121	147	173	215
Annual Production (tube/yr)	880,000	1,160,000	1,613,300	1,960,000	2,306,600	2,866,600
Cost of Investment ($)	-	10,000	255,000	555,000	265,000	565,000
Annual Operating Cost ($)	947,200	1,310,000	1,432,700	1,536,000	2,167,200	2,393,500
Unit Production Cost ($/tube)	2.30	1.13	0.89	0.78	0.94	0.83
Annual Revenue ($)	2,200,000	2,900,000	4,033,000	4,900,000	5,766,700	7,166,700
Gross Margin	57.0	54.9	64.5	68.7	62.7	66.6
Cost Benefit Ratio (CBR)	-	1.88	2.47	2.36	2.40	2.47

Table A. Throughput and economic evaluation of base case study and various debottlenecking schemes.

cycle time of 29 hrs - *Figure 2*. The minimum cycle time of the process is defined as the minimum time possible between the start of two consecutive batches. It is equal to the longest occupation time among all pieces of equipment involved in this process.[10] In the case of anti-allergic cream manufacturing; the minimum cycle time corresponds to the prolonged cooling operation in the Main Blending procedure P-4. With an interval of two hours for tank cleaning between batches, this sets the plant annual production at 66 batches. The throughput of the base case is summarized in Table A (column 2). The simplest option to increase the process throughput by increasing daily operating duration is determined to be uneconomical due to the high operating cost in hiring additional staff. This leads us to explore the use of combined utilization concept as has been discussed earlier.

Figure 3 displays the capacity, time, and combined utilization of all the procedure/equipment pairs in the base case simulation. As shown, the Main Blending Procedure P-4 (V-103) with an equipment capacity utilization of 89.9% and the equipment uptime of 93.6% has a much higher combined utilization percentage of 84.1% as compared to other procedures. The high equipment uptime of this procedure is mainly due to the long cooling operation (19 hours) and Transfer-Out operation (8.4 hours). This also makes P-4/V-103 the scheduling bottleneck of the process, i.e., process with longest operating duration (see Operation Gantt Chart in Figure 2). Note that certain procedures (e.g. Filler P5/FL-101, Belt Conveyer P-6/BC-101, etc.) are not considered as size bottlenecks even though they have 100% size utilization, as the operation speed of this equipment can be adjusted according to the operational needs.[5]

After identifying the Main Blending Procedure P-4 (V-103) as the first process bottlenecking candidate, debottlenecking strategies will next be focused on reducing either the size or time utilization of this procedure/equipment. However, since there are two pre-mixing tanks that serve as the mixture preparation proceeding to P-4/V-103, any attempt of changing a larger Main Blending vessel will lead to the replacement of the two pre-mixing tanks V-101 and V-102. This has been determined by the management team to be an infeasible option at the present moment. Hence, debottlenecking options will only focus on the reduction of equipment uptime of P-4/V-103. This is described in the next section.

Debottlenecking Schemes

After identifying the candidate for process debottlenecking, the feasibility of various debottlenecking schemes were evaluated. Five debottlenecking schemes were analyzed in which all schemes were applied focusing on reducing the equipment uptime of P-4/V-103 as the process time bottleneck.

Alternative Debottlenecking Schemes

Figure 4 shows the simulation flowsheet for debottlenecking Scheme 1. As shown, a new intermediate tank V-104 is installed after the Main Blending vessel. The main rationale underlying this scheme is to reduce the equipment uptime of Main Blending vessel (P-4/V-103), by spending a minimal investment cost of US $10,000 (purchase cost for V-104). By adding the intermediate tank V-104, the two subsequent procedures P-4/V-103 and P-5/FL-101 are disconnected. The Transfer-Out operation in P-4/V-103 is no longer constrained by the slow filling operation in Filler P-5/FL-101. Upon the completion on the blending operations in P-4/V-103, the product mixture is transferred into the newly added V-104 for temporary storage while waiting for the filling operation to complete. The main blending procedure can then be carried out for a subsequent operation. Simulation results showed that the annual production for this scheme has increased to 87 batches due to the reduction of minimum cycle time that limits the number of annual production from 29 hrs (in the base case simulation) to 21.6 hrs (shown in the third column in Table A). This corresponds to an increase of annual production rate of 32%, but is insufficient to fulfill the projected customer demand.

Scheme 2 for process debottlenecking is shown in Figure 5. It focuses on the reduction of cooling operation of P-4/V-103 instead. A multifunctional blending tank with a cooling system (purchase cost of US $255,000) is installed to replace the main blending tank. This reduces the cooling time of the product mixture from the current 19 hours to five hours.

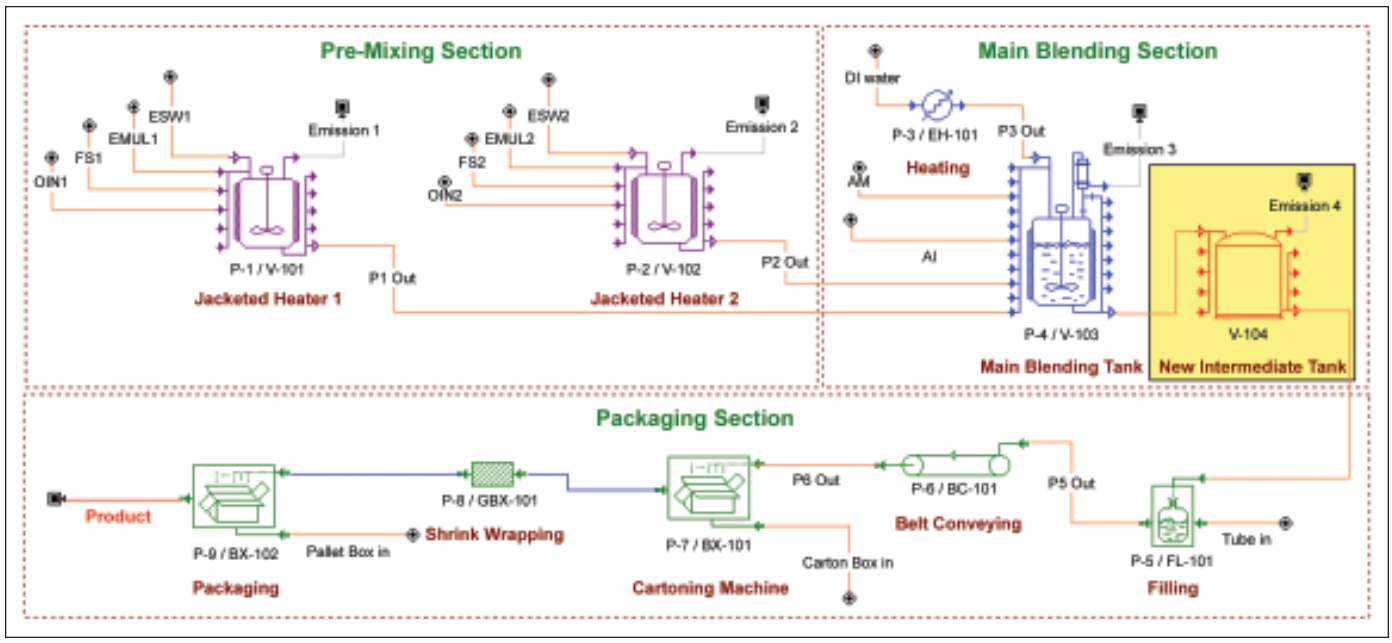

Figure 4. Debottlenecking Scheme 1 with the installation of an intermediate tank.

Chilled water is used as cooling agent to cool the mixture from 85ºC to room temperature. This leads to the reduction of minimum cycle time to 15 hrs. Hence, an increase of 83.3% is achieved for annual production as compared to the base case, i.e., from 66 to 121 batches (fourth column in Table C). From Table B, it is shown that even although P-4/V-103 remains as the overall process bottleneck, its combined utilization value has actually been reduced from 84.2% in the base case simulation to 79.3%, due to the reduction of its uptime. On the other hand, combined utilization of other unit procedures have increased significantly. This leads to an overall increase of process throughput. Further debottlenecking can only be achieved if the long duration of the Transfer-out operation in P-4/V-103 (to filler P-5/FL-101) can be reduced.

Figure 6 shows the simulation flowsheet of Scheme 3 that explores the reduction of P-4/V-103 uptime from a different perspective. As the Transfer-Out duration of P-4/V-103 is dependent upon the filling rate in P-5/FL-10, one alternative to reduce the duration of Transfer-Out operation in P-4/V-103 is to install a high speed filler to shorten the filling duration in P-5/FL-10, and hence the Transfer-out duration in P-4/V-103. As shown in Figure 6, a new filler (50 tubes/min; purchase cost of $300,000) is installed in addition to the new multifunctional blending tank in Scheme 2 to accelerate the filling rate. Simulation results showed that with the reduction of Transfer-out duration in P-4/V-103, combined utilization values of P-4/V-103, P-5/FL-101 and P-6/BC-101 have been reduced slightly, while other unit procedures increase in their combined utilization values - *Table B*. The net result is the reduction of minimum cycle time to 12 hrs and an increase annual production rate of 147 batches, i.e., 122.7% compared to the base case (fifth column in Table A).

Another debottlenecking alternative focusing on reducing the overall uptime of P-4/V-103 is presented in Scheme 4 - *Figure 7*. Instead of installing a new filling machine as in Scheme 3, an intermediate storage tank (V-104; purchase cost of US $10,000) is added in addition to the installation of a new Blending Tank (P-4/V-103). This scheme exhibits the same characteristics as the combination of Scheme 1 and Scheme 2. Simulation results showed that the annual production for this scheme is 173 batches with a minimum cycle time reduced to 9.9 hrs (sixth column in Table A). This corresponds to an increase of annual production rate of 162%, fulfilling the future market demand. It also should be noted

Equipment Tag		Procedure Name	Base Case	Scheme 1	Scheme 2	Scheme 3	Scheme 4	Scheme 5
V-102	P-2	Jacketed Heater 2	4.71	6.19	8.59	10.41	12.26	16.00
V-101	P-1	Jacketed Heater 1	8.04	10.56	14.66	17.76	20.92	27.30
V-103	P-4	Main Blending Tank	84.12	82.30	79.34	77.11	57.27	79.13
FL-101	P-5	Filler	27.13	35.65	49.48	38.81	70.61	56.81
BC-101	P-6	Belt Conveyor	23.90	31.41	43.60	31.68	62.21	46.38
BX-101	P-7	Manual Cartoning	17.93	23.56	32.70	39.60	46.66	57.97
GBX-101	P-8	Shrink Wrapping	11.95	15.70	21.80	26.40	31.10	38.65
BX-102	P-9	Manual Pallet Packaging	1.66	2.18	3.03	3.67	4.32	5.37

Table B. Combined utilization for different debottlenecking schemes.

Raw Material	Symbol	Price ($/kg)	Unit/Batch	Cost/Batch ($)	Annual Cost ($)	% Contribution
Emulsifier	EMUL	15.50	30.00 kg	465.00	30,690.00	11.15
Emulsifying Wax	ESW	5.05	3.60 kg	18.18	1,200.00	0.44
Foam Stable	FS	3.00	14.40 kg	43.20	2,851.00	1.04
Antimicrobial Agent	AM	4.00	0.24 kg	0.96	63.00	0.02
Active Ingredient	AI	650.00	2.00 kg	1,300.00	85,800.00	31.17
Emulsifying Ointment	OIN	15.00	12.00 kg	180.00	11,880.00	4.32
Deionized Water	DI water	0.50	137.76 kg	68.88	4,546.00	1.65
Water	Water	0.03	69.63 kg	2.09	138.00	0.05
Tube	Tube	0.10	13,333.00	1,333.30	88,000.00	31.97
Carton Box	Small box	0.05	13,333.00	666.65	44,000.00	15.98
Pallet Box	Big box	0.50	185.00	92.50	6,110.00	2.22
TOTAL COST				**3,635.44**	**239,939.06**	**100.00**

Table C. Cost of raw material for base case simulation.

that after the installation of intermediate storage tank V-101, filler P-5/FL-101 has became the unit procedure with the highest combined utilization value. As shown in Table B, all unit procedures experienced an increase in their combined utilization values except that of P-4/V103. This is consistent with the finding of Koulouris *et al,*[5] where new bottleneck equipment will emerge after the current bottleneck is overcome. Debottlenecking efforts are stopped at this scheme as the debottlenecking objective is reached, i.e., achieving the 150% increase in production as compared to current production. However, to cater for future expansion plan as requested by the management team, the replacement of a new P-5/FL-101 is studied in the next debottlenecking scheme.

Figure 8 shows the simulation flowsheet for Scheme 5, which includes filler P-5/FL-101 for debottlenecking. With the presence of the additional intermediate tank and the high speed filling machine, the production increases to 215 batches per annum, i.e., an increase of 225% with minimum cycle time reduced to 7.6 hr (seventh column in Table C). The capital investment needed in this scheme is calculated as the summary of individual equipment in the previous schemes, i.e. $565,000.

All the proposed debottlenecking schemes have demonstrated significant improvement on the annual production throughput. This is mainly due to the reduction of minimum cycle time associated with main blending tank procedures. As previously mentioned, Scheme 4 serves as the debottlenecking scheme for current increase of production; while Scheme 5 with the highest process throughput is reserved for future expansion plans.

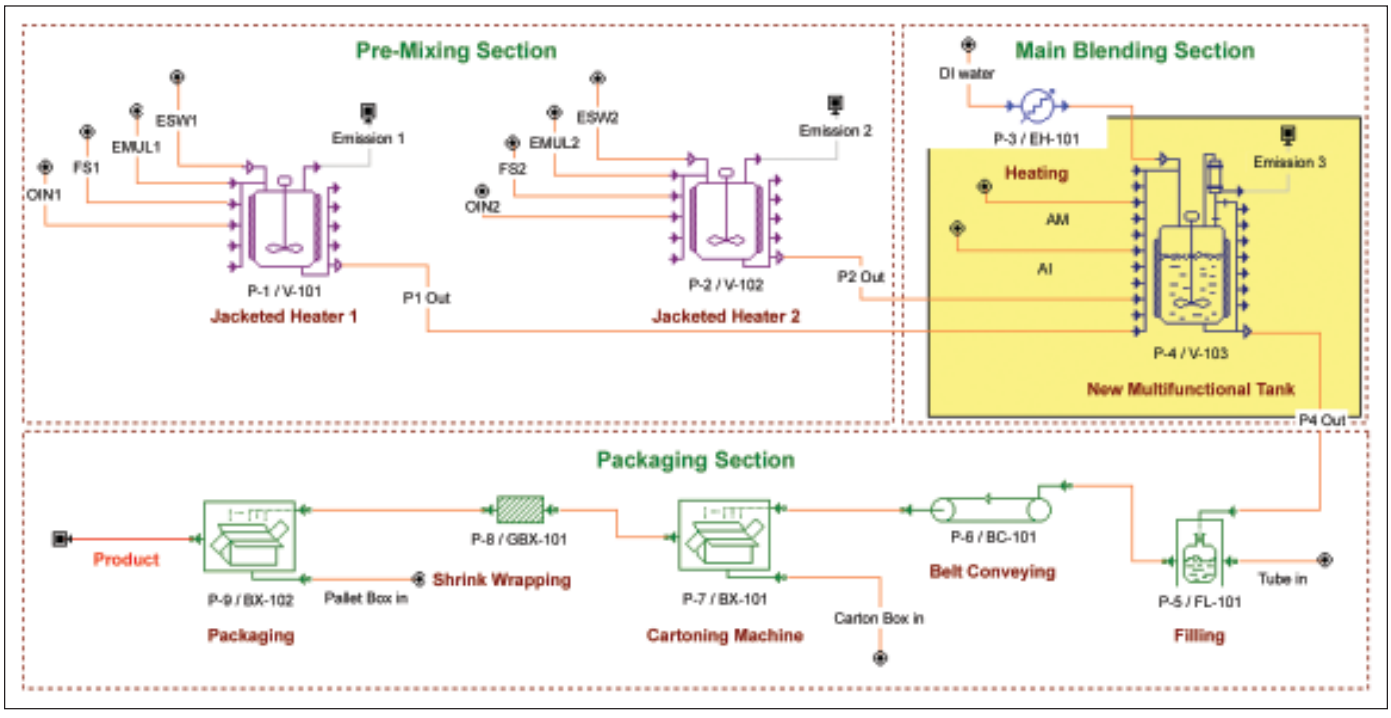

Figure 5. Debottlenecking Scheme 2 with the installation of new multifunctional blending tank.

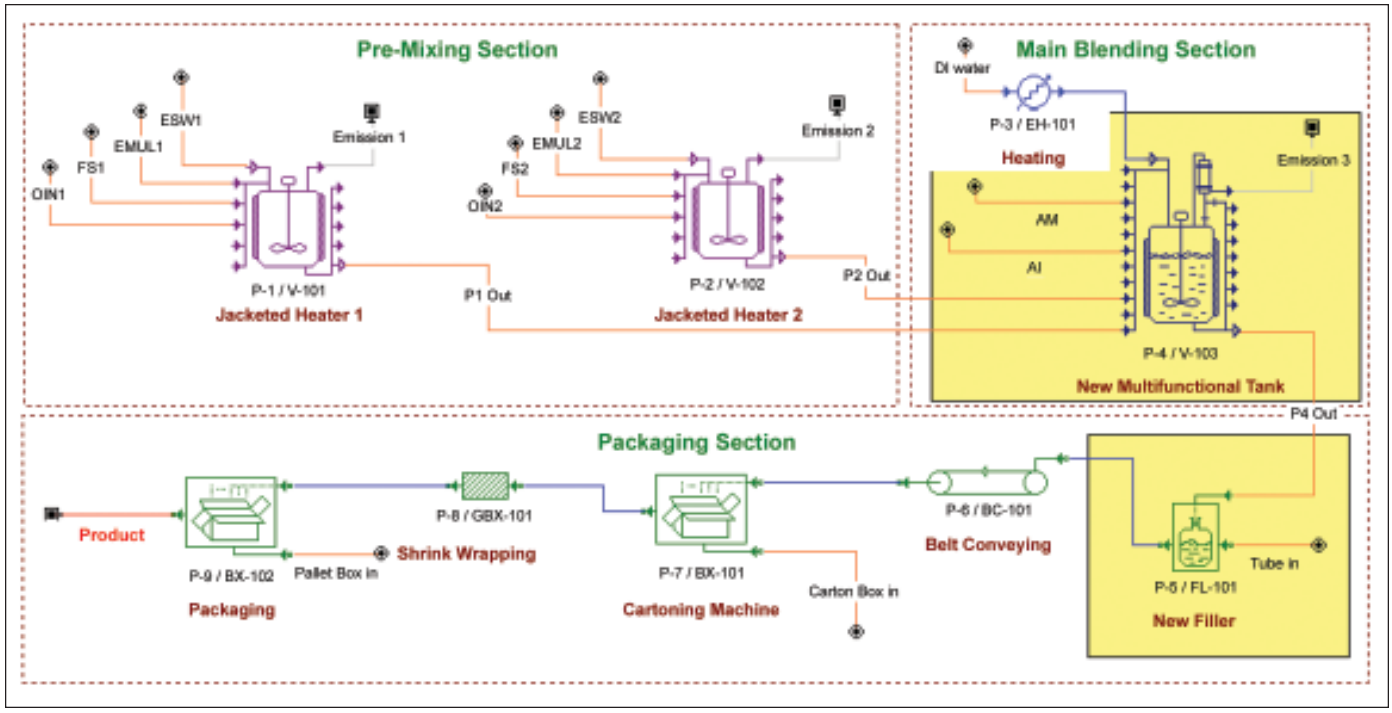

Figure 6. Debottlenecking Scheme 3 with the installation of new multifunctional blending tank and new filler.

Economic Evaluation

Preliminary economic evaluations are next carried out for the base case simulation and each of the debottlenecking schemes. This is done via the economic evaluation function of the simulation software.[10] In order to regenerate a realistic cost estimate, raw material costs and equipment purchase costs are obtained from local industrial suppliers. Table C shows the cost of the raw material for the production of anti-allergic cream and their contribution to the overall production cost in the base case simulation. The active ingredient for the anti-allergic cream and the tube (where 15 g of cream is filled) dominate the raw material cost, each contributing 31% of the overall production cost. Note that the distribution of raw material costs remains the same for all schemes as shown in Table C, only differing by total annual cost for each scheme due to the different annual throughput.

The economic evaluation comparing the various debottlenecking schemes with respect to the base case study is shown in Table A. The Cost Benefit Ratio (CBR) is used as a tool in comparing the alternative schemes. As shown, except for Scheme 1, all other debottlenecking schemes are having similar CBR values with Scheme 2 and Scheme 5

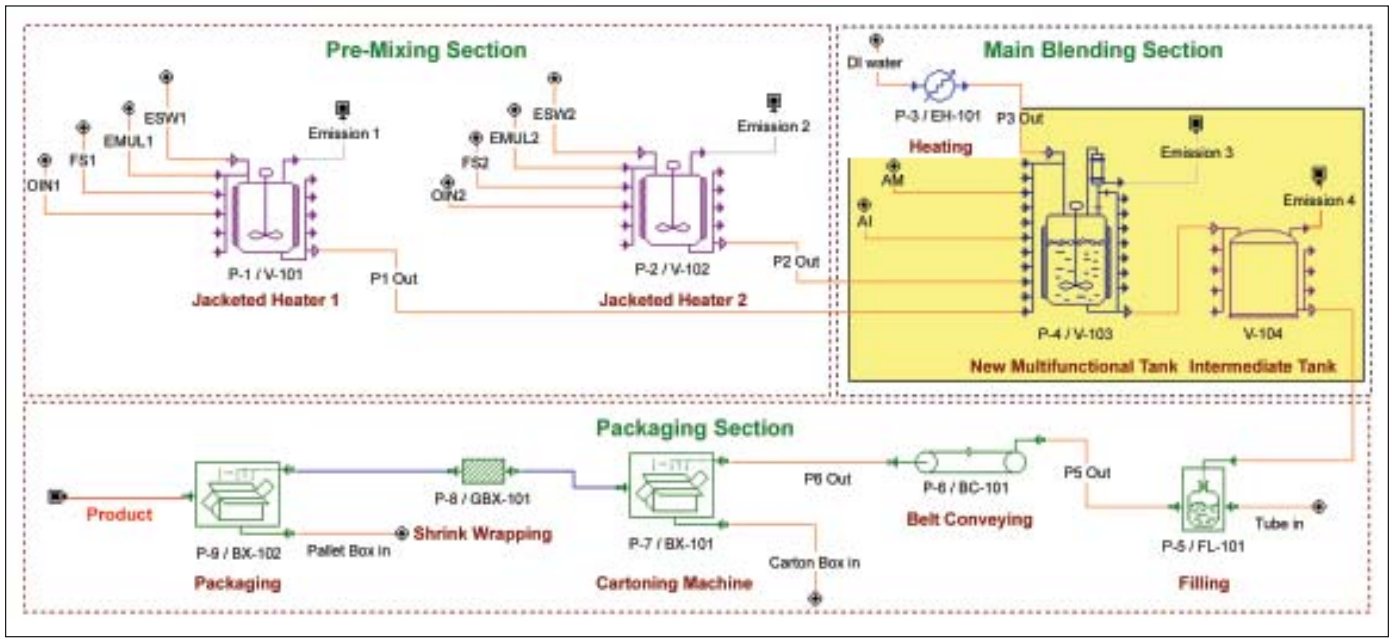

Figure 7. Debottlenecking Scheme 4 with the installation of intermediate tank and new multifunctional blending tank.

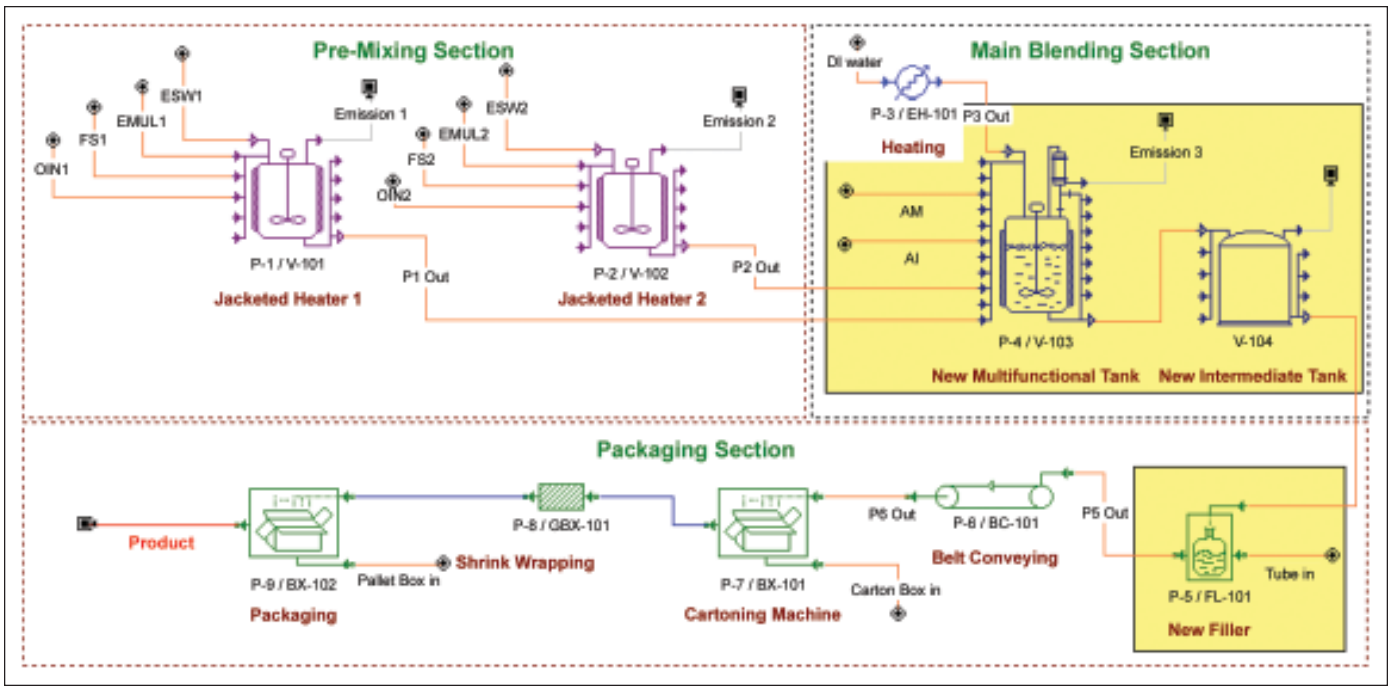

Figure 8. Debottlenecking Scheme 5 for future plant expansion.

having the highest value of 2.47. This indicates that except for Scheme 1 all debottlenecking schemes have equal value for investment.

In the previous debottlenecking section, it is shown that Scheme 4 was selected to be the debottlenecking scheme due to its fulfillment to future customer demand, i.e., by producing more than 150% of the current production. On the other hand, Scheme 5 that has been identified to be the future debottlenecking scheme also shows a promising CBR value of 2.47.

Conclusion

In this work, Computer-Aided Process Design (CAPD) and simulation tools are used in the systematic identification of the process bottleneck and a debottlenecking study. An operational pharmaceutical case study of anti-allergic cream production is used to demonstrate the effectiveness of the tools. The base case and four debottlenecking schemes are simulated using SuperPro Designer. The annual process throughput is increased significantly with the reduction of equipment uptime of the process time bottleneck. The study produced a debottlenecking scheme that achieves the current production needs, with a scheme that will cater for a future expansion plan.

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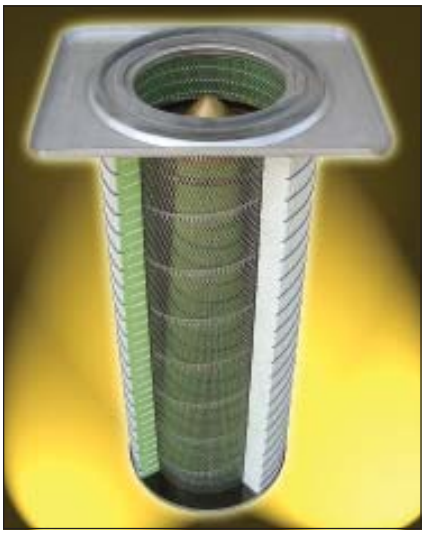

The "HemiPleat™ High Efficiency (HE)" Filter Media from Farr APC offers an unsurpassed MERV 15* efficiency rating and double the service life. With a filtration efficiency of 99.999 percent on 0.5 micron particles and larger, it is ideal for the capture of toxic and other ultra-fine dusts, and for applications where process air is recirculated downstream of the collector for energy savings.

Farr Air Pollution Control, 3505 S. Airport Rd., Jonesboro, AR 72401, www.farrapc.com.

Hose Tracking and Analysis System

The AdvantaPure division of NewAge Industries, Inc., has announced that its Hose Track Process Equipment Identification and Lifecycle Analysis System has been validated for 21 CFR Part 11. The third party validation, conducted by VALSPEC of Royersford, PA, affirms the product's compliance with Title 21 of the Code of Federal Regulations, Part 11, which relates to electronic records and signatures.

Advantapure, 145 James Way, Southampton, PA 18966, www.advantapure.com.

Software

Emerson Process Management has enhanced the functionality of its DeltaV SIS products with the release of version 8.4 software. The 8.4 release extends bulk edit capability to SIS modules and remote I/O, version control is extended to SIS modules and Logic solver configuration, a new report was added to verify that periodic software upgrades do not impact the DeltaV SIS logic solver configuration. This upgrade will significantly reduce engineering time and effort on large projects as well as improve IEC 61511 compliance.

Emerson Process Management, 12301 Research Blvd., Bldg. 3, Austin, TX 78759, www.emersonprocess.com.

Water Purification System

Millipore has announced the new purification strategy behind Millipore's Q-POD unit, the remote dispenser of the Milli-Q® Advantage system. The last water purification step is performed at the outlet of the Q-POD unit by a specific POD Pack, which removes contaminants critical for specific experimentations just before the water leaves the system.

Millipore Corp., 290 Concord Rd., Billerica MA 01821, www.millipore.com.

Cleaning Validation Support Package

GE Analytical Instruments, a division of GE Water & Process Technologies, has announced its new Sievers Cleaning Validation Support Package (Sievers CVSP), a comprehensive set of documentation providing guidance for the use of Total Organic Carbon (TOC) methodology in laboratory and on-line cleaning validation applications. The Sievers CVSP includes guidance, examples, worksheets, templates, and sample protocols that will significantly reduce the time and effort required to define and execute cleaning validation requirements.

GE Water & Process Technologies, 6060 Spine Rd., Boulder, CO 80301, www.geinstruments.com.

Manufacturing Execution Systems (MES) Software

Werum Software & Systems America, Inc., a leading supplier of MES for the pharmaceutical and biotech industries, has launched new versions of its PAS-X PHARMA and PAS-X BIOTECH product lines. Designated PAS-X PHARMA V2.3 and PAS-X BIOTECH V2.2, the updated software suites in-

clude a number of improvements and attractive new features. The user prompts for both PAS-X PHARMA V2.3 and PAS-X BIOTECH V2.2 have been further optimized, now providing new dialogs and an up-to-date user interface that promotes the use of work centers.

Werum Software & Systems, 9 Campus Dr., Parsippany, NJ 07054, www.werum-america.com.

Conductivity Sensors

Mettler-Toledo Thornton has announced the availability of certified sanitary conductivity sensors which meet USP <88> Class VI requirements for polymeric wetted materials. This includes both 2-electrode and 4-electrode sensors suitable for pharmaceutical water, CIP (clean-in-place) and other pharmaceutical water monitoring requirements.

Mettler-Toledo Thornton, 36 Middlesex Turnpike, Bedford, MA 01730, www.thorntoninc.com.

Intelligent Reactor Systems

Powder Systems Ltd. has announced the availability of its PSL ChemFlux Reactors, a series of intelligent reactor systems which allow any chemical or biological process to be monitored, controlled and optimized to help get products to market faster. The systems provide effective process analytics in the form of enthalpy, power and heat transfer coefficient enabling a clear and accurate measure of the status and progress of any reaction.

Powder Systems Ltd., Estuary Business Park, Liverpool L24 8RG, United Kingdom, www.powdersystems.com.

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FDA Counterfeit Drugs Task Force Report

The FDA has announced new steps to strengthen existing protections against the growing problem of counterfeit drugs. The measures, which were recommended in a report released by the agency's Counterfeit Drug Task Force, emphasize certain regulatory actions and using new technologies for safeguarding the integrity of the US drug supply. The latest Task Force report is the third in a series of documents exploring the means of ensuring the safety of the US drug supply. The first report, issued in 2004, outlined the framework for protecting the public from counterfeit medicines, and the second report, released last year, assessed the progress toward implementing the 2004 recommendations. All Task Force Reports can be found at http://www.fda.gov/counterfeit/.

Pfizer Facility Receives Awards from Environmental Organizations

The Pfizer Clinical Research Unit (CRU), of New Haven, Connecticut, has been recognized by two national environmental organizations for the successful utilization of "high performance" and "eco-friendly" principles, procedures and materials during design and construction. Completed in April 2005, the 62,000 sq. ft., three-story Pfizer CRU which features state-of-the-art, flexible lab and research space for the clinical trials of drug products has been awarded Silver Leadership in Energy and Environmental Design LEED™ Certification by the United States Green Building Council (USGBC), the first such designation for a building in Connecticut. The Green Building Initiative, a non-profit network of building industry leaders committed to bringing sustainability to mainstream residential and commercial construction, also awarded the Pfizer CRU a "Three Globes" designation under its Green Globes environmental assessment and ratings system, for the incorporation of energy and environmental considerations in planning and construction.

Pfizer Inc., 235 East 42nd Street, New York, NY 10017, www.pfizer.com.

O'Neal Awarded Contract

O'Neal, Inc., a Southeastern US leader in planning, design and construction has announced that United Therapeutics Corporation, a biotechnology company based in Silver Spring, MD, will contract with O'Neal for consulting services related to its solid dose facility that will be built in Research Triangle Park, NC. O'Neal, which was recently ranked 15th nationally for building pharmaceutical facilities by ENR Construction, will assist United Therapeutics in the architectural, engineering and pre-construction services of the approximate 125,000-square-foot facility, which will ultimately employ up to 300 people.

O'Neal, Inc., 10 Falcon Crest Dr., Greenville, SC 29607, www.onealinc.com.

FDA Takes Action Against Unapproved Drug Products

The FDA has acted to improve drug safety and quality by strengthening efforts against unapproved drug products. FDA efforts will begin against prescription products containing the antihistamine carbinoxamine, because of safety concerns regarding their use in children less than two years of age. The agency is also issuing a final guidance document outlining its approach to addressing other medicines that are marketed without FDA approval. The FDA estimates that there are several hundred different unapproved active ingredients in prescription drugs on the market, with less than 2% of prescribed drugs being unapproved. FDA's unapproved drugs Web page is http://www.fda.gov/cder/drug/unapproved_drugs/default.htm. PE

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August 2006

10 San Francisco/Bay Area Chapter, Golf Tournament and Winery Tour, Chardonnay Golf Club, Napa, California, USA
17 Boston Area Chapter, Annual Golf Tournament, Granite Links Golf Club, Quincy, Massachusetts, USA
17 San Diego Chapter, Vendor Night, Hilton La Jolla Torrey Pines, La Jolla, California, USA
18 San Diego Chapter, Golf Tournament, Twin Oaks Golf Course, San Marcos, California, USA
22 Greater Los Angeles Area Chapter, Commuter Conference, California, USA
22 San Francisco/Bay Area Chapter, Commuter Conference at Novartis, Emeryville, California, USA
24 Pacific Northwest Chapter, Educational Event, Vancouver, British Columbia, Canada
30 Nordic Affiliate, Conference, "New Concepts for Commissioning and Qualification," Copenhagen, Denmark
31 Puerto Rico Chapter, Members Night, Puerto Rico

September 2006

11 - 13 Great Lakes Chapter, Educational Tracks + Social Event + Golf Outing, Educational Tracks at the Crowne Plaza, Evening Social Event at the NCAA Hall of Fame, Golf Outing at Heartland Crossing, Indianapolis, Indiana, USA
11 - 15 ISPE Boston Classroom Training and GAMP Americas Forum, Hyatt Regency Cambridge, Cambridge, Massachusetts, USA
12 Delaware Valley Chapter, Program Meeting, USA
12 Nordic Affiliate, Conference, "Operating Efficiency joint with Mentor Communications," Malmo, Sweden
14 Ireland Affiliate, Seminar, "R&D Pilot Plant Commercialization," Ireland
14 UK Affiliate-North West Region, Joint Seminar with IChemE, United Kingdom
18 - 22 ISPE Vienna Congress, InterContinental Wien, Wien, Austria
19 Chesapeake Bay Area Chapter, Annual Golf Tournament, Whiskey Creek Golf Course, Ijamsville, Maryland, USA
20 - 21 DACH Affiliate, Fachdiskussion, Water and Steam, Basel, Switzerland
21 Greater Los Angeles Area Chapter, Golf Tournament, California, USA
21 Pacific Northwest Chapter, Educational Sessions and Vendor Night, Bell Harbor Int'l Conference Center, Seattle, Washington, USA
22 Rocky Mountain Chapter, Golf Tournament, Vista Ridge Golf Course, Denver, Colorado, USA
26 Boston Area Chapter, Pilot Plants Seminar, USA
28 Puerto Rico Chapter, GAMP Puerto Rico Forum, Puerto Rico

October

5 Nordic Affiliate, GAMP Conference, Copenhagen, Denmark
5 San Francisco/Bay Area Chapter, Commuter Conference at Pipe Trades Training Center, San Jose, California, USA
9 - 12 ISPE Prague Training, Crowne Plaza, Prague, Czech Republic
10 Delaware Valley Chapter, Program Meeting, USA
12 Ireland Affiliate, "Pharmaceutical Documentation" Seminar, Ireland
12 Italy Affiliate, "Cost Efficiency New Technologies Effectiveness and Quality in Pharmaceutical Supply Chain" Seminar, Italy
12 UK Affiliate-North West Regio, "Management of Pharmaceutical Waste" Seminar, United Kingdom
18 Boston Area Chapter, 2006 Vendor Night, Gillette Stadium Clubhouse, Foxboro, Massachusetts, USA
19 DACH Affiliate, Workshop, Biberach, Germany
19 France Affiliate, MES/EBR Conference, France
24 Greater Los Angeles Area Chapter, Commuter Conference, California, USA
26 Nordic Affiliate, Freeze Drying Seminar, Sodertalje, Sweden

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