ISSN : 2347 - 2243

Indo - American Journal of Life Sciences and Biotechnology

www.iajlb.com
Email : editor@iajlb.com or iajlb.editor@gamil.com

Indo-American Journal of Life Sciences and Biotechnology

Vol.17, Issue.4, Oct 2020

Continuous manufacturing is used in the pharmaceutical business. Mental Reorientation

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Abstract

The manufacture of pharmaceuticals is subject to strict guidelines known as good manufacturing practice. Though continuous processing might often result in the production of purer goods and thus have financial benefits, batch processing has traditionally dominated the industrial industry.

After the product and process have been licensed, the regulatory framework often stifles any efforts to make changes to the method. Because of this, many experts in the field now believe that batch operations are the only viable option. However, the regulatory authorities, especially the Food and Drug Administration in the United States, have realized that continuous processing has the potential to enhance product quality and are urging the sector to rethink its ideas. This study investigates how chemical engineers might take use of the newfound freedom afforded them by these revised regulations to reevaluate their own perspectives and inspire a paradigm shift in the field as a whole.

Keywords*: Continuous processing; GMPs; the pharmaceutical business; roadblocks to progress.*

INTRODUCTION

Many processes that would normally be continuous, such as in-line milling and spray drying, or semi-continuous, such as tablet compression, are converted to batch processes because of the pharmaceutical industry's preference for them. This has developed for historical causes, and it is reinforced by the regulatory atmosphere and the necessity to deliver new items to market as quickly as feasible. This is related to the belief that batch operations are necessary for any product development if the end result is to meet stringent quality standards imposed by government agencies.

Contrarily, there are a few issues plaguing batch operations, the most notable being the difficulty in scaling up and the challenge in producing uniform processing conditions. As a result, the quality of the produced goods is typically compromised. Unwanted effects may be caused by by-products, and it's possible that some products have been rejected during clinical testing in the past because they weren't pure enough.

There has been a shift in both the regulatory and commercial climates. Environmental, health, and safety law is pushing the pharmaceutical business toward more efficient procedures, and the licensing authorities recognize that continuous processing may play a role. It's becoming increasingly difficult and costly to test out brand-new items. time-consuming to find, develop, and bring to market, and generic producers have ramped up competition.

The time is ripe for technical experts in the field to further the efficient use of continuous processing. This paper looks at how this opportunity came to be and how to go forward with shifting the mindset of industry experts.

Pharmacology

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THE PHARMACEUTICAL MANUFACTURINGPROCESS

The Ingredients

A pharmaceutical product contains two groups of materials, active ingredients and excipients. The active ingredients are those materials that have a therapeutic effect, whilst the excipients have no therapeutic effect but are necessary to ensure the final dosage form acts as intended. Typical excipients include water, lactose, starch, sugar and colouring but in practice there are a very large number of excipients in common usage.

The Manufacturing Stages

The pharmaceutical manufacturing can be broken down into a number of stages, see Figure 1. Frequently it is broken down into two major stages usually known as Pri- mary and Secondary. These stages are commonly carried

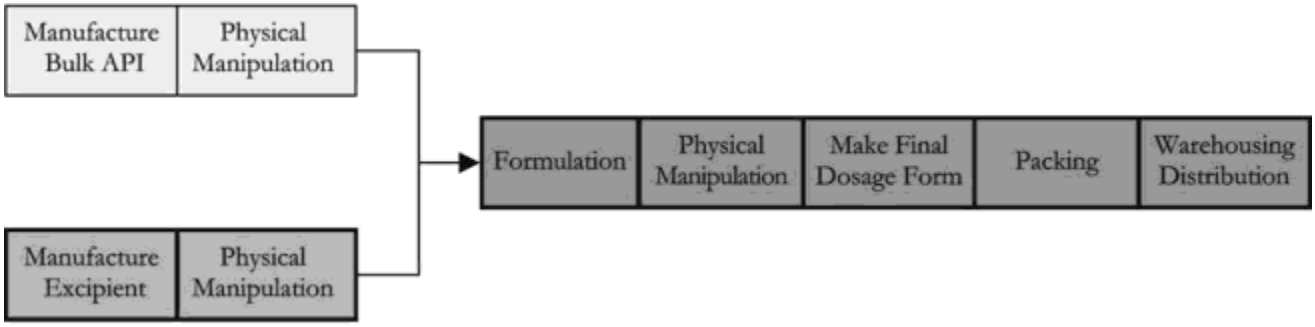


Figure 1. Overview of the pharmaceutical manufacturing process.

carried out at several locations, and by a variety of manufacturers. Production of APIs, which may include chemical synthesis or biological processing followed by physical manipulation steps including drying, purification, and size reduction, constitutes the Primary stage. Shipping the API in large quantities to a secondary production facility is standard practice.

Excipients are manufactured by mainstream companies that conform parts of their goods to the pharmaceutical requirements laid forth in the different pharmacopoeias, therefore technically speaking, excipient manufacturing is also part of the Primary stage. Except for sterile water used in injectable treatments, all other components in pharmaceuticals are typically manufactured off-site and subjected to the same rigorous quality controls as the drug's active ingredients.

Bulk formulation of the final product, including the combination of one or more APIs with a variety of excipients, often kicks off the Secondary stage. These might be subjected to further physical processing, including drying, sizing down, sizing up, filtering, and sterilizing. The final dosage form is created from the bulk substance. Although tablets account for well over 80% of all dosage forms, other options include capsules, liquids contained in ampoules, vials, or bottles, creams housed in tubes or jars, and aerosols housed in canisters or suppositories. Products are then placed into their final containers, such as bottles, blister packs, or foil wraps, which prominently display the product's information.

QUALITY REGULATION

Good Manufacturing Practice

The pharmaceutical industry is highly regulated with a number of regulatory systems. The technical requirements of Good Manufacturing Practice (GMP) are being harmo- nized but the regulations that oversee these are very different for the USA, the EU and Japan. However, all of these majormarkets require that products must be manufactured in linewith GMP if they are to be allowed into the market place. In the European Union the requirements for GMP are covered by Directive 2003/94/EC. Whereas in theUnited States the Federal Food, Drug and Cosmetic Act states that a pharmaceutical product may not be sold if it is adulterated. Section 501 (a)(2)(B) states that if a pharma- ceutical product is not made to GMP it is by definition

adulterated and cannot be sold.

GMP is defined by the EU Guide to Good Manufacturing Practice (European Regulations, Vol. 4, 2002) as follows:

Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required be the Marketing Authorisation or product specification.

GMP must be applied to the manufacturing process after the ‘critical step’, which usually occurs when the final active molecule is being produced or an intermediate is being produced that has a major impact on the quality of the final product. This critical step usually occurs near the end of the API manufacturing process. Quality assur- ance measures also need to be in place for those parts of the process prior to the critical step. Since excipients donot include APIs they are not subject to the same level of scrutiny but quality assurance systems must be in placeand the products must meet the specifications given

in the appropriate pharmacopoeia.
The major thrust of GMP is to prevent the product becoming contaminated by particulates and micro-organisms (particularly from the human plant opera- tives) in the room environment, particulates generated by equipment, chemicals leached from the product contact parts and from other products being manufactured. It isthe need to avoid contamination and cross contamination from other products that dominates the design of pharma- ceutical manufacturing facilities and leads to the need for regular and extensive cleaning. The guidelines to GMP, whilst not compulsory, form a detailed framework and working outside of them is only permissible if good scientific evidence for the alternative approach can be provided. The guidelines are fairly pre-

manufacture the product must have a manufacturing licence. Both of these licences are time consuming and expensive to obtain.
The product licence includes information about how the product is manufactured and therefore once the licence has been obtained it is to be expected that any change to process will require more time and money to be spent ona revised product licence.

Impact on Process Changes

It can be seen that the regulatory requirements to comply with GMP and the impact of including the method of man- ufacture in the product licence contribute to a mind set that is averse to moving outside the guidelines and/or changing the process after it has been licensed.

SAFETY, HEALTH AND ENVIRONMENTAL (SHE) LEGISLATION

There is a perception that the licensing and GMP regulations are more important within the pharmaceutical industry than SHE legislation. However, a recent incident (pers. comm., 2004) illustrates the fallacy of this view. A relatively minor incident relating to the cleaning equipment on some key manufacturing equipment in a tablet facility was report to the Health and Safety Executive as a result of the RIDDOR legislation within the UK. The resulting investigation nearly resulted in a Prohibition Order, if this had occurred the whole of the tablet facility would have shut down within a few days with the resultant loss of large amounts of money. This one safety issue could have stopped the production of a number of product ranges.

ATEX Directive

The European Union ATEX directive has had significant impact on pharmaceutical manufacturing within the union. This is because it has codified the requirements for poten- tial explosive atmospheres created by dust clouds. That is not to say that the industry has been ignoring the potential hazard but since there is now a legal requirement for manufacturers to classify the hazardous areas, equipment is being more rigorously specified and risk assessments have become more detailed. Also there is now a statutory requirement to reduce the potential risk by reducing the inventory of material within the manufacturing environment.

scriptive, the EU guidelines include 18 annexes that includeguidelines on the manufacture of various groups of pro- ducts. The annex covering sterile products for example, indicates that sterile products shall be terminally sterilized using steam in an autoclave unless there a scientific reason why this is not possible.

Product and Manufacturing Licences

Before pharmaceutical products can be sold they must have a product licence from the relevant regulatory body, Medicines and Healthcare products Regulatory Agency in the UK, the Food and Drug Administration in America, and so on. Also, the facility that is used to

Control of Substances Hazardous to Health (COSHH/OSHA)

As products become ever more potent, the requirement to comply with COSHH/OSHA regulations becomes more complex and expensive. Product containment making use of special devices such as split butterfly valves or various forms of barrier isolators is becoming common. However, these add significantly to the capital cost of the equipment [up to 50% more (Cliff, 2004)] and make the facility more complex to operate. Continuous processes allow the manufacturing equipment to be contained without resorting to this sort expensive measure and are likely to lead to significant capital cost savings.

Integrated Pollution Prevention and Control (IPPC)and Other Environmental Legislation

The production processes for APIs tend to have low yields. This leads to the need to dispose of large quantities of waste. With multi-step complex processes there will be more waste product than saleable product even if the yield of each step is greater than 90%. The disposal of this material is becoming more expensive and more com- plex. There is an obvious advantage is increasing yields and reducing this problem.

NEW PRODUCT DEVELOPMENT AND THE PHARMACEUTICAL MARKET PLACE

The driving force behind the pharmaceutical industry has been and remains the discovery of new molecular entities that can be patented. Once patented, licensed and launched on to the market there is the potential to make large profits. However, in general the cost of the research efforts is increas- ing whilst its efficiency is falling. The major pharmaceutical companies are finding it difficult to find new products at the rate necessary to continue with the expected profit growth. This means the issue of the cost of manufacturing products is starting to become more important. Following on from the recent mergers and acquisitions activities there is a drive to reduce costs by reducing the number of research, development and manufacturing facilities.

Laboratory Scale versus Manufacturing Scale

New molecular entities are obviously developed at the laboratory scale. A large number of new molecules are pro- duced by chemical synthesis or by biological fermentation processes, these are screened for pharmacological activity to find new products of potential commercial value. New molecules that appear to have potential have to be sub- jected to three stages of

clinical trials. Each stage requires ever larger quantities of materials as the number of trials required increases at each stage. This means that in parallel with the clinical trials it is necessary to carry out scale-up trials to demonstrate that the molecule can be produced at a large enough scale to supply the third stage clinical trials. Much of this work is abortive because products frequently fail to move forward because they are not suffi- ciently efficacious or have too many side effects.
The scale required for Stage 3 clinical trials is usually large enough to produce sufficient quality for the initial launch of a product but if it successful it is not very long before further scale-up is required to allow the required tonnage of material to be made.
One way to increase the speed with which a product can be brought to the market is to reduce the development time. If the scale-up step could be avoided it may be possible to gain months/years of additional time covered by the patent. Continuous processing via micro-reactors offers the possi- bility to avoid this scale-up phase as discussed before.

Commercial Risk

The opportunity cost of failing to sell a successful pharmaceutical product can easily run into hundreds of millions of dollars. This means that pharmaceutical compa- nies take a cautious approach to business risk. Using novel processes and untried manufacturing techniques will increase the business risk and so high level management will always err toward the tried and tested.
One area of risk that particularly affects the batch proces- sing mind set is product recall. If a batch of material is found to out of specification or contaminated and needs to be recalled this is inevitably expensive and it reflects badly on the manufacturer. The commercial risk is reduced if the batch size is kept small so that any recalls require the minimum amount of material to be returned and destroyed. The use of continuous processes will have to address this issue, if company managers are to accept the associated commercial risks.

Product Pricing

The pharmaceutical market place falls into two major groups, the so called ethical products, prescription only patented products and generic products that have no patent protection. Generic products fall into two further categories, those that require a prescription and those that can be sold over the counter (OTC). The over the counter market differs in each country as the regulations covering the requirements for prescriptions are very different even across the EU. Antibiotics being OTC in Spain but pre- scription only in the UK, for example.
It would be expected that OTC products such as aspirin, paracetomol and ibuprofen would be under severe cost pressure, however this is not the case. A visit to any super- market will show that branded versions of these products still command a price premium of four or five times over the unbranded products. This is surprising when you consider that in a highly regulated market it unlikely that there will be any quality difference between the products. This seems to show the power of the 'reassuringly expensive' approach.
What is perhaps even more surprising that whilst these products are made in large volumes there are no

Speed to Market

The life of a patent is finite and varies around the world, in general more than half of the patent life of a new molecular entity is lost before the product can be launched. Once the patent protection has been lost it is possible forthe original product developer to lose up to 90% of their market share, to generic manufacturers, within 12 months. With large numbers of products coming off patent there are plenty of companies who can make good profits from entering the market as soon as a patent expires.This is a developing market place.

manufac- turers using a continuous process. However, this is one area where continuous processing could be a serious possibility, there are the production volumes to make use of the commercial available equipment and so scale down (see below) should not be a problem. Also, competition from supermarket own brands is likely to begin to have sufficient impact on the product cost to provide the driving force for a change.

THE NATURE OF BATCH PROCESS

Much of the resistance to change arises from the fear of the impact on product quality. However, batch processes are not actually very good for product quality. Although the product leaving a batch reactor, crystalliser, dryer or whatever may be homogeneous the heat, mass and momen- tum transfer environment that the molecules and crystals within the batch have experienced during the process will be significantly different. During the process, temperature, velocity and concentration profiles will vary with position within the equipment and with time leading to processing inefficiencies. Most of the practices within the industry have been developed to overcome these deficiencies but this is poorly recognized and many of the practices are seen as a prerequisite to good quality management.

Poor Understanding

Batch processes are poorly understood, time dependant and scale dependant operations. They are poorly under- stood at the micro-scale and have not until recently been studied in detail. In spite of this method of operation being used for thousands of years it still produces fluctua- ting and unpredictable results.
By comparison, most continuous processes are much simpler and far better understood. The mathematical tools to analyse these processes have been available for many years.

Poor Yield

The varying heat, mass and momentum transfer in a batch reaction generally mean that yields are sub-optimal. If a 10 stage process has a yield of 50% at each stage then the overall yield will be 0.510 ~ 100% i.e., 0.097% raising the stage yield to 80% raises the overall yield to over 10% thereby giving more than a hundred times greater throughput in the same equipment.
Continuous processes for making the relevant chemicals have been reported in the literature that give significant improvements in yield over the batch process mainly because of improvements in temperature control and mass transfer.

Intermediates

As a result of the low purity of materials made by batch processes and perhaps because of the approach taken by chemists at the laboratory scale, most APIs are isolated as a number of intermediates (usually solids). These arise as a result of the purification (often crystallization pro- cesses) that are required to isolate the desired chemical. Intermediates also allow the purity of the product to be checked at each stage and to identify problems before the final product is made. However, if reaction yields and con- versions were improved and classic stirred tank vessels. These processes are difficult to scale up and in general the regulatory authorities do not likeprocesses to be scaled up by more than 10 – 1 at each stageof development. The scale-up problem can be illustrated byconsideration of the blend time in a stirred vessel with baf- fles and a pitched blade turbine.

Nagata (1975) proposed that $u \cdot N$ (where u is the blend time and N is the impeller speed), for a geometry similarsystem, is constant for a Renold's number greater than 10^4. Also the power absorbed by an impeller is given by Oldshue (1985) $P = N_p r N^3 D^5$ (where N_P is the power number of the impeller, r is the liquid density, N is the impeller speed and D is the impeller diameter) for a pitched
blade turbine a typical value of N_p is 1.5.

Consider the scale-up of a process from 100 l to 10 000 l with a vessel L/T = 1 and D/T = 0.33. Table 1 shows that scaling up to give a constant blend time requires impractical increase in power consumption. Using constant power per unit volume gives a more practical solution but the blend time will increase. Similarly scale-up using constant tip speed, also gives a practical power consump- tion but the blend time will increase nearly five times with a commensurate
deterioration in yield and conversion resulting from a significant amount of time required toproduce a reaction mass approaching homogeneity.

As a further problem the velocity profile within the vessel varies, there will be a high velocity close to the tip of the impeller and lowering velocity as the distance from the impeller increases. Numerous studies have shown that they are frequently complete dead spots within a stirred tank. These variations in velocity lead to variations in reactions were more predic- table, less purification would be required. Also product quality could be monitored using on-line analysis.

A further major disadvantage of producing and analysing intermediates is cost of storing (working capital) and hand- ling the solid intermediates (labour costs).

Batch Processes Do Not Scale Up Well

Most pharmaceutical batch operations are carried out in agitated vessels, for liquids and slurries these will be the

heat, momentum and mass transfer causing variations in temp- erature and concentration within the stirred mass. These variations lead to sub-optimal reaction profiles and a reductions in product quality. In summary a stirred vessel is not good at producing a high quality consistent product.

The discussion above has been based on stirred tanks containing liquids or slurries but the above points also apply to more solid based processes such as crystallization,filtration and drying.

Table 1. Batch agitation scale up

Parameter		Units	Lab	Pilot	Production
Volume	V	l	100	1000	10 000
Vessel diameter	T	m	0.503	1.084	2.311
Height of liquid	L	m	0.503	1.084	2.311
Impeller diameter	D	m	0.168	0.361	0.771
Liquid density	r	kg/m^3	1000	1000	1000
Liquid viscosity	m	Pa·s	0.001	0.001	0.001
Scale-up on constant blend time i.e., constant speed					
Speed	N	s^{-1}	5.00	5.00	5.00
Renold's number	Re		137 807	639 643	2 968 962
Process power	P	kW	0.023	1.097	50.94
Scale-up on constant power per unit volume					
Speed	N	s^{-1}	5.00	2.99	1.80
Scale-up on constant tip speed ND					
Speed	N	s^{-1}	5.00	2.32	1.08
Renold's number	Re		137 807	296 896	639 645
Process power	P	kW	0.023	0.109	0.509

Flexibility

One major advantage of batch processing equipment is flexibility. A set of stirred tank reactors, batch filters, centrifuges and dryers can, with persuasion, make virtually any chemical providing the materials of construction are suitable. Since the annual requirements for the APIs can often be very low, production facilities need to be as flexible as possible. Continuous processing will need to match this level of flexibility.

CONTINUOUS PROCESSES

In contrast to batch processing, continuous processing is relatively well understood. At steady state, there are only three-dimensional problems instead of four dimensional problems because time is not relevant. Small scale conti- nuous processes are easy to control and a constant tempera-ture profile is easy to maintain.

Number Up Instead of Scale Up

The Institution of Chemical Engineers 2004 Conference 'Switching from Batch to Continuous' had a number of papers demonstrating that various forms of micro-reactors can be used for chemical synthesis with very promising improvements in conversion and product quality. Thesereactors have the advantage that a large number of themcan be used in parallel and so that basic scale is not altered. The production rate is increased by numbering up insteadof scaling up.

A major advantage of this approach is that there is no need to carry out the scale-up development work in parallel with the clinical trials and scale-up to full manufacturing is achieved by having sufficient micro-reactors in parallel to achieve the require throughput.

At present this approach has a major problem. The micro-reactors so far developed are suitable for liquid but not for solids due to their very narrow pathways. Since most pharmaceutical active ingredients are large

molecules they are also in general solids. This means that an alternative approach is required for crystallization, purifi- cation, drying, and other physical manipulation activities such as milling and granulation.

Solid Processing and the Scale Down Problem

By the very nature of the pharmaceutical industry the product quantities are usually small. Figure 2 shows the product portfolio of a major pharmaceutical company. The biggest output is only 1200 t.p.a and most products are in the 100 – 1000 t.p.a. range. However, as products become even more potent the trend is for lower production rates in the range 10 – 100 t.p.a. Suitable equipment isavailable to manufacture most stages of the secondary production by continuous means, however most of this equipment is too large to be of use. For example, the Hosokawa Bepex laboratory scale Extrud-o-mat2 that can be used for continuous granulation produces 10 – 25 kg h. If this were operated continuous for 6000 h per annum it would produce 60 to 150 t.p.a., i.e., greater than the full production scale for many of the new potent products.

Laboratory development trials either require even smal- ler machines than those currently available or alternatively short product runs have to be carried out with the associated start up and shut down problems. This scale down problem needs to be addressed if progress is to be made in this area.

Naturally Continuous Processes

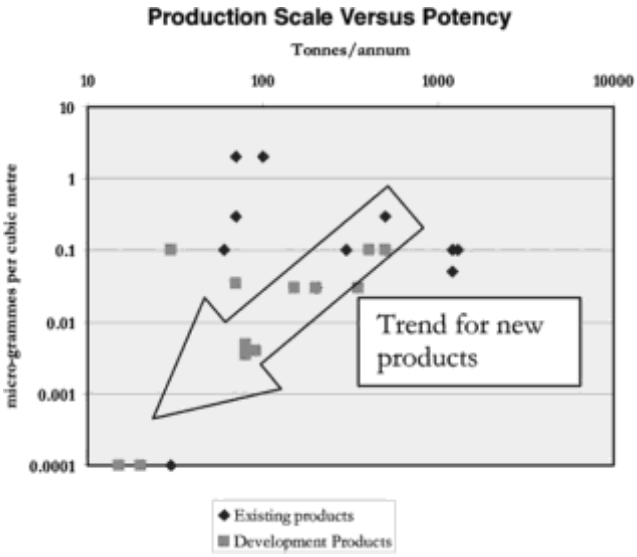
Pharmaceutical processes often contain naturally continuous processes such as in-line milling and spray drying and semi-continuous processes such as tablet compression. However, the desire to maintain the batch approach and to form intermediates for analytical testing is so great, that these processes are started and stopped to make them batch processes. This start up and shut down is likely to form out of specification material so the whole 'batch' is charged to a blender to ensure the resulting batch is homo- geneous. These naturally continuous processes are one of the obvious areas to start to change the mind set. Also, it will be easy to connect batch processes to these naturally continuous processes and run them semi-continuously and avoid the need to blend away the start up and shut down material.

Process Analytical Technology

The Food and Drug Administration (FDA) in the USA has launched an initiative under the umbrella of Process Analytical Technology (Guidance for Industry, 2004). The initiative is promoting the use of in-line analytical technology as a way of improving the development, manu- facture and quality assurance of pharmaceutical manufac- turing. Interestingly the guidance document says that the initiative is: 'Facilitating continuous processing to improve efficiency and manage variability

- using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities;
- improving energy and material use and increasing capacity'.

Figure 2. Typical product portfolio (Cliff, 2004).



Process analytical technology has been successfully applied in a number of areas, laser diffraction for on-lineparticle size analysis during in-line milling, near infra-red (NIR) technology for determining blend homogeneity and NIR technology for the on-line determination of moisture content. These successes have demonstrated the potential for these methods to be used to control continuous pharma- ceutical processes in real time.

Reduced Waste

One of the major advantages of continuous processing should be the reduction in the amount waste produced asa result of higher yield under better control. With environ- mental legislation become ever more restrictive and the cost of waste disposal rising rapidly, this is likely to a major driver for the improvements to pharmaceutical processes.

Reduced Energy

Batch processes are inefficient users of energy. They require large fixed utility generation equipment that is subject to large variations in load. A recent study by Thomas (2004) showed that by converting a batch process to a continuous process many of the utility and energy requirements could be cut to as much as 95%. One of the major area of saving arises from the heating, ventilatingand air conditioning savings arising from a much smaller facility. Similarly, an actual conversion (Thomas and Ramsay, 2004) from batch to continuous realized signifi- cant savings by eliminating the need for 16 000 tonnes of solvent and improving equipment efficiency from 30% to greater than 81%.

Reduced Cost

With reduced waste and reduced energy, cost savings should accrue. Savings are also likely to occur in labour costs. The handling of batches of solids is nearly always labour intensive and close coupled continuous processes could overcome this problem.

Cost savings should also arise from smaller equipment (because of smaller utility needs as well as improved effi- ciency) but also form the space saved.

Since secondary pharmaceutical manufacturing space costs in the order of
$3000 per m^2 there is a lot of potential for capital cost saving in this area.

THE MIND SET

The Current Mind Set

The current mind set is perhaps typified by following words from Guidance for Industry (2004):

> Unfortunately the pharmaceutical industry has been hesitant to introduce innovative systems into the manufacturing sector for a number of reasons. One reason often cited is regulatory uncertainty, which may result from the perception that our existing regulatory system is rigid and unfavourable to the introduction of innovative systems. For example, many manu- facturing procedures are treated as being frozen and many process changes are managed through regulatory submissions.

This is also true in the European Union, Lennart Ernerot (2004) suggests that the EU directives and GMP guidelines emphasize the need to consider batches and homogeneity.

The ideas and approaches of the regulatory bodies have permeated through the minds of all of the professionals within the pharmaceutical industry so that they are reluctant to move away from the tried and tested approach. It is not possible to blame any one group since they have all become used to this environment.

Changing the Mind Set

There is now a window of opportunity to change the mind set of the professionals within the industry. The FDA have launched the Process Analytical Technology initiative that recognises that new approaches are required if product quality is to be improved. They have also recog- nized that continuous processing has a role to play.

The regulatory authorities have recognised that a time basis can be used instead of a batch basis for the release of finished products. They have also recognized the value of parametric release whereby a product is released by the Qualified Person on the basis that it has been manu- factured in compliance with a number of parameters. Actual final analytical testing does not take place untilafter the material has been released.

Importantly the quality assurance professionals are starting to change their views, Michael Warmuth (2004), Corporation Divisional VP, Corporate Quality Operation, Abbott Laboratories, said:

> Today the pharmaceutical industry focuses on R&D, with less emphasis on operations and maintenance and continuous improvement. Speed to market, no matter what production efficiency, was considered the key to success. But now the development of blockbuster drugs has slowed down the indus- try now needs to refocus its energies. The paradigm shift that the industry must make, to move forward, will be to gradually change from batch processes to continuous ones.

To make use of the window it will be necessary to have a strong group of people who will act as project champions and have the will to progress the necessary changes. In the author's opinion, Chemical Engineers are uniquely positioned to act as project champions because their education and experience provides them with the necessarytools and skills. Also, their drive will be enhanced by knowing that the reputation of the profession is likely tobe greatly enhanced by helping to make the changes. However, success will depend on much more than justtechnical skills.

To ensure that all the relevant professionals are engaged in this exercise it will be necessary to focus on the follo- wing aspects.

- The potential to increase product quality thus helping to diffuse the concerns of quality assurance professionals and regulatory bodies. Also the potential to increase the benefit to the users of medicines in term of increased efficaciousness and reduced side effects.
- The technical solutions required to allow pharmaceutical products to be produced continuously.
- The benefits to pharmaceutical producers in terms of the speed to market for new products and/or in reducedproduction costs.
- The benefits to everyone resulting from improved occu- pational health, safety and environmental performance.

As well on focusing on these aspects it will be beneficial to keep the focus as tight as possible and initially attack the batch processing mindset in two distinct areas. Firstly, there is one area where continuous processing should be acceptedmore readily than other areas, this is the primary productionof APIs by chemical synthesis. The second area is the sec- ondary production of tablets, change will be more difficult in this area but since more than 80% of pharmaceutical products are sold as tablets, it is very important to change the mind set in this area.

Example 1—API chemical synthesis

APIs manufactured by chemical synthesis will benefit significantly from continuous production and implemen- tation should be relatively straight forward particularly for those steps upstream of the critical step where GMP require- ments are less onerous. This is because simpler to understand and control continuous processes should improve product quality, reduce SHE issues and reduce waste. Perhaps most importantly of all, allow the time to market to be reduced due the elimination of the need to scale-up the process.

The papers presented at the 2004 Conference 'Switching from Batch to Continuous' demonstrated that there is significant interest in this area. Research within universities has demonstrated that the required chemical reactions can be carried out in continuous reactors that can be numbered up to the required production scale. There are however, a number of stumbling blocks. Firstly, in order to move into secondary processing the products will need to be separated as solids and this area does not appear to have had much attention. Secondly, it is difficult to change existing pro- cesses to continuous processes because of the embodiment of the process in manufacturing licences.

The author is in no doubt that the focus will move to the solid separation problem once continuous processes are developed for new products. It is the speed to market factor that is most likely to drive this change and once a continuous route is chosen it will be locked in by the man- ufacturing licence. Also, if it can be demonstrated that an API produced continuously is purer than one

produced by a batch process then the regulatory authorities will be push- ing for as many new APIs to be manufactured continuously as is possible.

Moving from batch to continuous processing in this area is currently being championed by a number of organization including the Institution of Chemical Engineers and the Crystal Faraday Partnership. Their annual conferences are providing a show case for the new technology and creating significant interest.

In summary, the change of mind set needs to take place in the development departs of the pharmaceutical manufac- turers where there is the opportunity to introduce conti- nuous process for new products, thereby author has already taken a lead in this area by setting a working group under the auspices of the Institution of Chemical Engineers Pharma Subject Group (PSG). This working group includes a wide cross section of engineers and the scientists from the pharmaceutical industry. The objectives of this group are:

To make use of the naturally continuous processes to overcome the conservatism of the industry by adapting the stages of the manufacturing process so that conti- nuous concepts can be developed with well known and trusted processes, thereby minimizing commercial risk.

To examine the product quality benefits that can arise from using continuous process and how the use of 'Process Analytical Technology' will be simpler with continuous processes. Also to quantify the impact of the poor control resulting batch processing on product quality.

To set up a precompetitive demonstrator project with the intention of demonstrating the practicality and flexibility of producing pharmaceutical products in tablet form using a continuous process.

To investigate the scale down problem with particular emphasis on allowing production lines to be dedicated and thereby reduce the need for extensive down time for between-product cleaning.

To fully quantify the benefits of continuous processing in terms of safety, occupational health, environmental, issues in particular, COSHH, ATEX and IPPC; including the impact of reduced inventories resulting for compact continuous processes.

To fully quantify the achievable reduction in product cost.

To investigate the impact of continuous processing on the whole supply chain where there is opportunities for significant simplification and cost saving.

To develop sources of funding that will allow the tech- nology to be moved forward independent of immediate commercial requirements.

It is the general view of those involved that the technical issues will be easier to overcome than the softer issues of the natural conservatism of a highly regulated industry. However, in spite of the attraction of making the full jump to a continuous process, taking small steps forward is likely to be more effective in overcoming conservatism and reducing commercial risk.

An example of this kind of step forward would be the use of the naturally continuous processes of milling wet granulate before drying and milling the dry granulate and replacing the batch drying with continuous drying. These three stages are at the heart of the traditional granulation process and the batch drying is very energy and space intensive and significant benefits could be achieved by just changing the drying process. If the rest of the process remains unaltered confidence can be built allowing this technology to permeate into the API manufacturing indus- try and overcoming the difficulty of the manufacturing process being embodied in the manufacturing licence.

Example 2—Tablet manufacture

Although the manufacturer of tablets is heavily focused on solids and materials handling, Chemical Engineers have built up a significant amount of expertise in this tech- nology and can also act as champions in this area. The

up in continuous processing and further continuous steps added over time.

What are the Chances of Success?

A number of companies and groups of professionals have tried to make this move in the past. In view of the poor per-formance of batch process illustrated above, it would have been expected that this move would have been easy to make. However, the conservatism of the regulators and

the industry has fixed batch processing into the mind set and attempts to move to continuous processes have notbeen a success.

However, recent changes have increase the likelihood of success.

The regulatory authorities, particularly the FDA have begun to realise that batch processes are not as easy to bring under control as continuous process.

Research projects are demonstrating that many of the required chemicals can be made to a higher purity with continuous processes than batch processes.

The pressure to bring new products to market is signifi- cantly greater than it used to be.

The cost of manufacture is becoming more important as established products reach the end of their patent life.

The pharmaceutical industry is coming under increasing pressure to improve their safety, occupational health and environmental performance.

Chemical engineers have become more and more involved in the pharmaceutical industry over time and they have now realised that they are in a lead position to drive forward the technologies to make this change.

In the discussions that the author has had with other tech- nical professionals there has been a strong recognitions the softer people orientate issues will be more difficult to over- come that the technical issues. This acceptance is causing the group set up by the PSG to look at ways of meetingthe challenge of the people issues.

With technical professions spending time thinking about how to get their ideas generally accepted and bearing in mind these significant changes listed above, along with amount interest that has been shown and the progress that has been to made to date; the chance of success appear tobe high.

We should also remember that there are significant benefits to moving to continuous processes. The benefits will affect all parts of the industry and have an impact on the speed to market, product quality, facility capital cost and product cost as well as leading to a marked improve- ment in safety, occupational health and environmental factors. These benefits will be more marked now than they would in the past because the climate of the pharma- ceutical industry has made all of them

significantly more important. Such as the strengths of these benefits that they should far outweigh the negative effects of conserva- tism and concerns about the commercial risk. As Michael Warmuth (2004) said, without the blockbusters to carry the industry forward a paradigm shift is required to embrace the benefits of continuous processing.

THE CHEMICAL ENGINEER'S CHALLENGE

As a profession, Chemical Engineers must now ensure that they are involved with pharmaceutical product of their efforts to improve efficiency, I believe that the Chemical Engineers working within the pharmaceutical industry are duty bound to set about changing their own mind set and helping to change that of others.

If this opportunity is missed, it is unlikely that the profession will have another opportunity to have such an impact on the industry and the initiative will pass to a different group of professionals. It is unlikely than any other group will have the required skill to reap all of the benefits to mankind that Chemical Engineers can and we will all be the poorer for their failure.

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develop- ment in the laboratory, so that they can use their skills to ensure that the most efficient process is used to manufacture pharmaceutical products. If they work together with the other professionals in the industry they have the opportunity to bring about the level of change that came about within the oil and gas industry during the 1950s and 1960s. Since the health mankind and the industry's impact on the natural environment of the world will be to a great extent dependent