Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2008, Vol. 28 No. 5

Functional Safety in the Life Science Industries

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This article presents an overview of functional safety within the life science industry based on international standards.

Introduction

For life science companies, the chemical safety of the process (plant design and operation) is as critical as the pharmacological safety of the products (drug quality). The use of flammable solvents, corrosive fluids, toxic gases, and explosive dusts present significant threats to the safety of production personnel, the local community, surrounding environment, and often expensive manufacturing equipment.

Functional safety contributes toward overall process safety and relies on the correct reaction (both action and speed) of automatic devices in response to actual or potential dangerous conditions, thus preventing hazardous events or mitigating harmful consequences.

Instrumented protective functions using electrical or electronic technologies achieve this via sensors to detect process deviations, logic solvers to evaluate the sensor data, and final elements to execute the required action to achieve or maintain a safe state. These Safety Instrumented Systems (SIS) have been widely used in the general process and pharmaceutical industries for many years, providing protection against deviations in pressure, temperature, level and flow, and other critical process parameters.

Correct management of the functional safety aspects of process plants is now globally recognized as the best way to reduce the inherent risks in hazardous industrial processes. International standards are driving major end users in the process industry to adopt the IEC61511[1] (ANSI/ISA–84.00.01[2] equivalent) lifecycle approach to safety. The aim of these standards is to make safety a priority throughout the entire life of any potentially hazardous plant or process.

Risk Reduction

Risk is a measure of the likelihood and consequences of a hazardous scenario when a process goes out of control or is otherwise compromised, leading to a loss of containment with the subsequent release of material and/or energy.

Companies have moral, legal, and financial responsibilities to limit the risk their operations pose to employees and members of the public to a level that is considered tolerable.

Determining whether a process plant is "safe enough" may sound easy, but in practice it means a very well thought out calibration of the As Low As Reasonably Practicable (ALARP) risk tolerability principle. ALARP has been documented by the UK Health and Safety Executive in their R2P2 publication,[3] which aims to provide a methodology for defining target frequency and severity (i.e., risk) of hazards to a minimum "tolerable" level.

The ALARP principle states that there is a level of risk that is "intolerable." Above this level, risks cannot be justified on any grounds. Below this intolerable level is the ALARP region where risks can be undertaken only if a suitable benefit can be achieved. In the ALARP region, risks are only tolerable if risk reduction is impracticable or if the cost of risk reduction is greatly outweighed by the benefit of the risk reduction that is gained. Below the ALARP region is the "broadly acceptable" region where the risks are so low that no consideration of them is warranted and detailed work is not needed to demonstrate ALARP because the risk is negligible. In addition, in this broadly acceptable region, risk is so low that no risk reduction is likely to be cost-effective, so a cost-benefit analysis of risk reduction is typically not undertaken.

In some countries, the law mandates tolerable risk levels whereas in others, such as the

United States, tolerable risk is determined by each company or organization and must be adopted consistently. Tolerable risk cannot be applied on a personal preference basis since everyone has their own view on what is tolerable (consider your own driving style for example).

Once an estimate is made on the likelihood of an unwanted event occurring, and the potential consequence of that event is calculated with a commercial value, the decision on whether to implement further protection measures is often a straightforward economical one. If the risk reduction is significant and the cost not prohibitive, then clearly the measure should go ahead. Conversely, if a measure is deemed to offer little impact on the overall risk reduction and it is prohibitively expensive, it is perfectly valid to consider the associated risk as "tolerable," assuming no other risk reduction measures are practical.

Safety Standards

IEC 61511 has been developed as a Process Sector implementation of the international standard IEC 61508:[4] which was prepared as an 'umbrella' standard from which industry specific standards (such as IEC 61511 for the Process Industry and IEC 62061 for the Machinery Industry) could be derived.

For end-users in the Life Science process industries (primary and secondary manufacture), IEC 61511 is applicable with the broader IEC 61508 limited to those who manufacture or supply Safety Instrumented System equipment or components. Hereafter we shall refer to IEC 61511 as 'the standard,' which has two key concepts that are fundamental to its application: the safety lifecycle process, and safety integrity levels which define required and achieved functional safety performance.

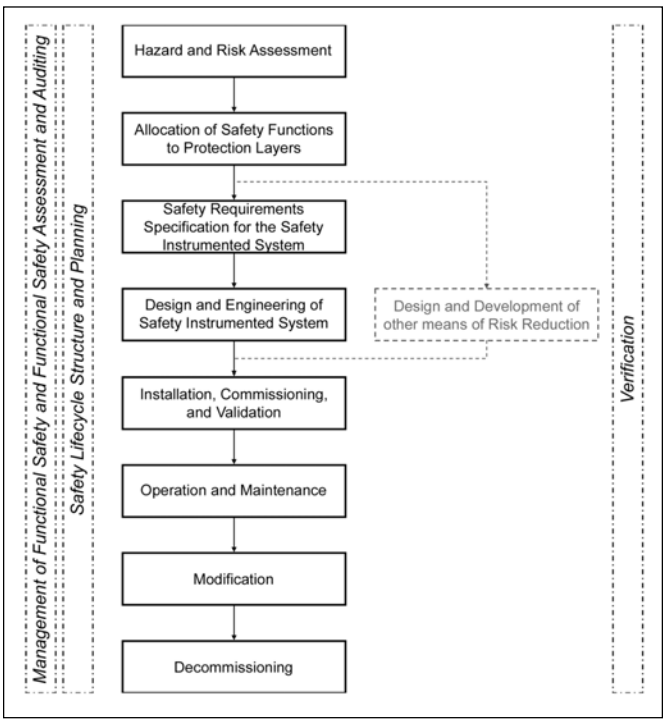

Figure 1. Functional safety lifecycle.

Safety Lifecycle

Similar to GAMP,[5] a lifecycle approach forms the central framework that links together the key concepts of the standard and is acknowledged good engineering practice for Safety Instrumented System implementation.

In order to achieve and sustain functional safety throughout the life of a facility (i.e., from initial conceptual design to final decommissioning), a number of technical and management activities must be performed, reviewed, and documented. Similar in many ways to the ISO 9000 quality process, the execution of the functional safety lifecycle is presented in Figure 1.

This lifecycle can be classified into three distinct groups of phases:

Analysis – How Much Safety is Required

Analysis focuses on identifying hazards and hazardous events, the likelihood that these hazardous events will occur and their potential consequences, the availability of layers of protection, as well as the need for any Safety Instrumented Functions (SIF) and their allocated Safety Integrity Level. The phase concludes with the development of the Safety Requirement Specification (SRS) to properly define the requirements for all Safety Instrumented Functions.

Implementation – How Much Safety can be Achieved

The implementation phases begin with a conceptual design of each Safety Instrumented Function based on equipment selection, architectural voting configuration, and periodic test interval to achieve the risk reduction defined in the Safety Requirement Specification.

These phases include detailed hardware design and build, software configuration, system integration, and testing prior to delivery to site. Implementation also includes advanced planning for installation, commissioning and validation, as well as long-term operation and maintenance.

Operation – How to Sustain Safety

The operation phases are the longest phases of the safety lifecycle and involve the validation of the Safety Instrumented System and all its Safety Instrumented Functions to confirm that it functions as per the requirements in the Safety Requirement Specification.

Following successful validation, the system is put into service and must be properly operated, maintained, and tested until permanently taken out of service. During this phase, all modifications must be fully evaluated and documented to ensure they do not compromise safety.

Management of Functional Safety

Like any execution process, functional safety management requires careful forward planning which defines the required activities along with the persons, departments, or organizations responsible to carry out these activities. The main purpose is to reduce the risk associated with systematic failures of specification, design, and procedure execution that

Executive Summary

Compliance with local, national, and international process safety regulations can be achieved efficiently and effectively by following established and well proven functional safety standards and principles. Best practice for achieving and sustaining functional safety has close parallels with pharmaceutical compliance.

can lead to harmful accidents.

Plans should be updated and related activities adjusted as necessary throughout the safety lifecycle to reflect any nonconformance, changes in scope, technology, or other influences. Regular independent monitoring and objective auditing is key to ensure that proper management is provided to support the technical execution of the project.

A key element of resource planning is to ensure that, according to the standard, "***Persons, departments, or organizations involved in safety lifecycle activities shall be competent to carry out the activities for which they are accountable.***"

This competence can be demonstrated with qualifications, experience, and qualities appropriate to their duties and should include:

- training to ensure acquisition of the necessary knowledge of the field for the tasks that they are required to perform
- adequate knowledge of the hazards and failures of the equipment for which they are responsible
- knowledge and understanding of the working practices used in the organization for which they work
- an appreciation of their own limitations and constraints, whether of knowledge, experience, facilities, resources, etc., and a willingness to point these out

Internationally recognized accredited schemes are available which formally establish the competency of those engaged in the practice of safety system application in the process and manufacturing industries.

Verification and Validation

Pharmaceutical validation is defined as "***Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.***" Safety validation is synonymous with this principle and we could simply replace the word '*quality*' with '*safety*' to provide a mission statement for functional safety.

In common with pharmaceutical compliance, safety compliance adopts the proven principles of verification and validation. Very often these terms are misused as they define similar, but fundamentally different concepts.

Verification is defined as "***demonstrating for each phase of the safety lifecycle by analysis and/or tests that, for the specific inputs, the deliverables meet the objectives and requirements set for the specific phase***" and ensures that the final product meets the original design (low-level checking), i.e., you built the product right. This is done through procedural cross checks such as inspections, reviews, and audits.

Validation is defined as "***demonstrating that the safety instrumented function(s) and safety instrumented system(s) under consideration after installation meets in all respects the safety requirements specification***" and checks that the product design satisfies or fits the intended usage (high-level checking), i.e., you built the right product. This is done through dynamic testing and other forms of challenge or trial.

In other words, verification is an ongoing quality assurance activity throughout the lifecycle ensuring that the procedures have been followed and the Safety Instrumented System has been built according to the requirements and design specifications, while validation is a quality control activity at a specific point in the lifecycle, which ensures that the Safety Instrumented System actually meets the user's needs.

Information and Documentation Requirements

In common with process validation principles, accurate information and documentation underpin the implementation of a successful project and provide ongoing reference material for the support of operating processes.

An important aspect of functional safety management is to ensure that the necessary information is available, documented, and maintained in order that all phases of the safety lifecycle can be efficiently executed and that the necessary verification and validation activities can be effectively performed.

Process Hazard and Risk Analysis

Each process has its own inherent risk (i.e., potential to cause harm) by virtue of the chemicals handled (flammability and toxicity), the operating conditions (pressure and temperature), and the inventory (volume or mass), as well as the construction (materials), the location of the plant, and the occupancy (personnel exposure).

If we consider a typical pharmaceutical process, it often handles dangerous materials, but generally does not operate at extreme pressures or temperatures, and in common with other batch processes, has a limited inventory which is typically the reactor capacity – but the volume of storage tanks should not be discounted as these can often be significant. However, the threat often comes from the manual or semi-automatic nature of many processes which require some operator intervention and thereby exposure to the hazards of the process as well as the potential for human error.

Process Hazard Analysis (PHA) is an established activity in all process industries, including life sciences. Commonly known as a Hazard and Operability (HAZOP) study,[6] a PHA is only the start of the safety journey – identifying what can go wrong – now we must evaluate and address it.

Allocation of Safety Functions to Protection Layers

Overall risk reduction is achieved by combinations of independent layers of protection. These layers may take many forms – mechanical, instrument/electrical, procedural, etc., and the standard shows typical risk reduction methods in process plants in terms of these "layers of protection" which are presented in Figure 2.

The Safety Instrumented System is one of many potential measures that can be taken at the "Prevention" level, as opposed to "Mitigation" (cure). Once a "tolerable" level of risk has been established, an analysis of the layers of protection should allow a function-by-function comparison of the hazardous event frequency.

Assuming this hazardous event frequency is lower than what is considered tolerable, no additional layers of protection will be required. Conversely, if the frequency is higher than the tolerable level set, then additional independent layers need to be applied. One of these layers may be a Safety Instrumented System.

Safety Integrity Levels (SIL) are order of magnitude bands of risk reduction. There are four levels defined in the standard ranging from SIL1 with the lowest level of risk to SIL4 that provides the highest (and rarest) level of risk reduction. These levels are documented in Table A according to the risk reduction that they provide.

For example, to achieve a tolerable risk of one death in 1,000,000 years (indicative value for illustrative purposes only) from a residual (i.e., with all other protection measures credited) risk of one death in 50,000 years, the Risk Reduction Factor (RRF) would be 20 (i.e., 1,000,000 ÷ 50,000) which lies in the SIL1 band. Therefore, we would require a Safety Instrumented Function with this integrity to achieve the required risk reduction.

Risk Reduction Factor	Safety Integrity Level
10000 – 100000	4
1000 – 10000	3
100 – 1000	2
10 – 100	1

Table A. Risk reduction and safety integrity levels.

Note that the standard suggests that applications which require the use of a single safety instrumented function of SIL 4 are rare in the process industry and that they shall be avoided where reasonably practicable by reviewing the process design to implement more reliable and (wherever possible) inherently-safe non-instrumented protection measures.

There are various methods of determining the Safety Integrity Level for a particular hazardous scenario and these are generally classified into two types:

- Qualitative
- Quantitative

Qualitative methods group numerical targets into more broad categories of risk reduction, while Quantitative methods give specific numerical targets for risk. Often qualitative methods are used for quick initial screening with quantitative meth-

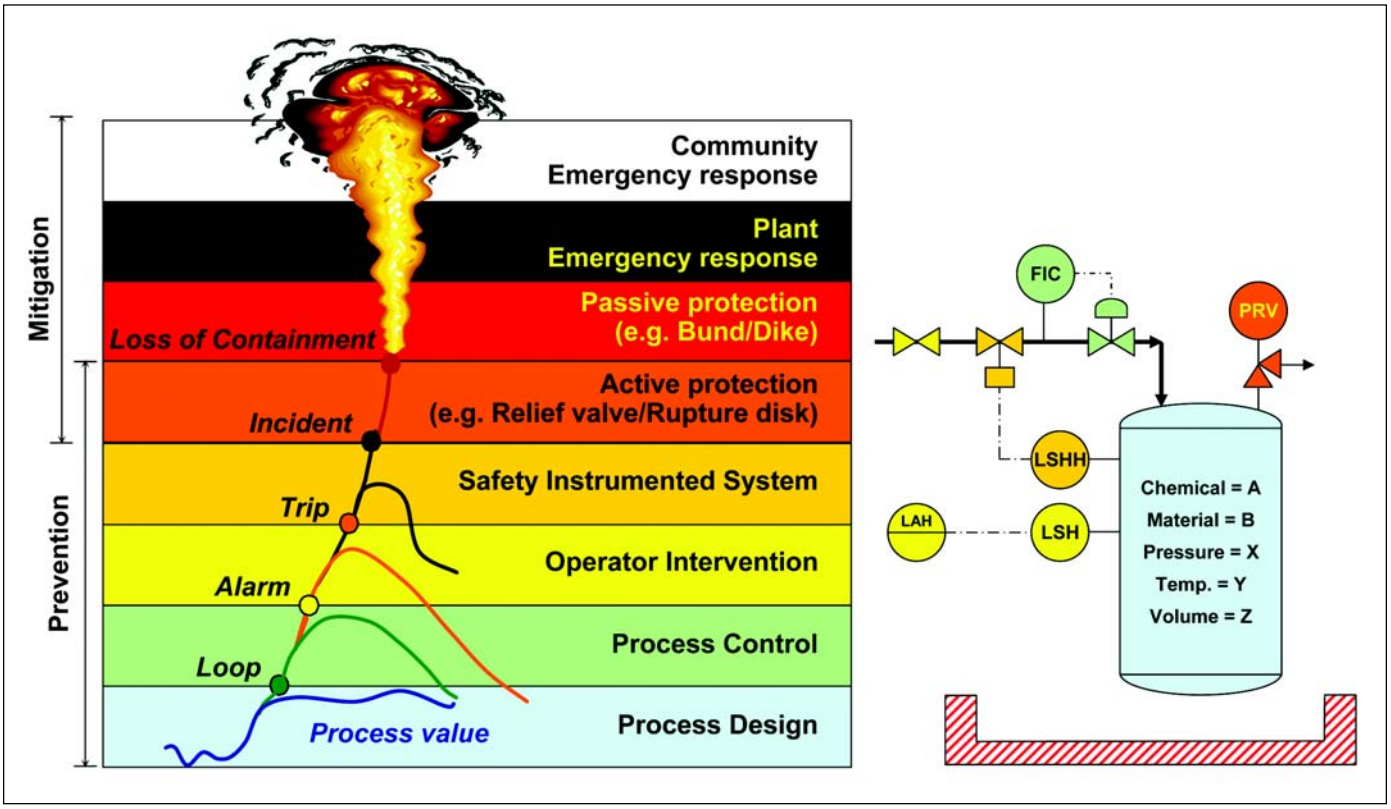

Figure 2. Typical protection layers.

Event Likelihood				
	High	2	3	4
	Moderate	1	2	3
	Low	–	1	2
		Minor	Serious	Extensive
		Hazardous Event Severity Rating		

Table B. Risk matrix (EXAMPLE).

ods reserved for higher risk scenarios that require more detailed investigation and evaluation.

Two basic types of qualitative Safety Integrity Level selection are commonly used in the process industry:

- Safety Matrix
- Risk Graph

The Safety Matrix example in Table B considers the severity of a specific hazardous event (X-axis) against the likelihood that the hazardous event will occur when all other credited protection layers have failed (Y-axis). The intersection of severity and likelihood gives a grade of risk reduction (or Safety Integrity Level) that the Safety Instrumented Function (specific to this hazard) must achieve.

The Risk Graph is a development of the safety matrix with a similar severity (Consequence) grading on the Y-axis and then consideration of three elements (Exposure, Avoidance, and Demand) that make up the likelihood X-axis of the hazardous event. Both safety matrix and risk graph methods produce a Safety Integrity Level, not a specific Risk Reduction Factor.

Quantitative methods are more powerful, but require more information. They enable the user to perform sensitivity analysis on all the risk reduction measures, allowing them to identify the weaker protection layers, which may require more attention.

One of the most common quantitative methods of Risk Reduction Factor determination (and therefore Safety Integrity Level selection) is Layer of Protection Analysis (LOPA) as shown in Table C.

This method is used to calculate the risk reduction factor for a specific hazard based on the unmitigated risk of the hazard severity and initial likelihood, which is then reduced by taking credit for appropriate and independent protection layers, each with their own probability of failure (lower probability of failure means more reliable), to yield a residual risk which is then compared to the target tolerable risk. The strength of this method relies heavily on having adequate, appropriate, and accurate (not necessarily exact) data, preferably from the users own experience.

Further guidance on the determination of Safety Integrity Level is given in the ISA publication Safety Integrity Level Selection[7] as well as part 3 of IEC 61511 and the AIChE CCPS publication Layer of Protection Analysis.[8]

Safety Instrumented System Safety Requirements Specification

The concept of a User Requirement Specification (URS) is well understood by pharmaceutical companies who follow the principles of Good Automated Manufacturing Practice (GAMP). It is a document (or set of documents), which defines clearly, concisely, and unambiguously what the user requires and is provided to the supplier as the definitive statement of what the system must do. The URS details functional and non-functional requirements with the emphasis on the requirements themselves (i.e., what) and not the method of implementing these requirements (i.e., how).

The implementation of Safety Instrumented System is similarly documented in a Safety Requirement Specification (SRS), which defines the requirements for the Safety Instrumented Function(s) within the Safety Instrumented System. These requirements must cover the following three key areas of each function:

- Functionality – what it does
- Reliability – how well it does it
- Performance – how quickly it does it

The UK Health and Safety Executive conducted a survey[9] of failures of computer-based systems and the causes of these failures are summarized in Figure 3.

The findings show two key issues. First, nearly 60% of failures are already "in" the system before it even arrives on site. Second, failures can occur at any time within the lifetime of a system, it is not just problems that occur due to maloperation or wear and tear during service. Ironically, it is the initial stage of the lifecycle where one may expect more 'educated' personnel to be involved that is the weakest.

The Safety Requirement Specification captures what needs to be done to achieve functional safety and is often a contractual document, which is passed from the User to the Supplier who is responsible for implementing the Safety Instrumented System.

Safety Instrumented System Design and Engineering

A Safety Instrumented System is a system composed of sensor(s), for example, pressure transmitters, logic solver(s),

Hazardous Event	Severity	Initiating Cause	Initiating Likelihood	Protection Layers				Residual Risk	Tolerable Risk	RRF	SAFETY INTEGRITY LEVEL
				BPCS	*Alarms*	*Relief*	*Other*				
Reactor rupture	1 death	Loss of cooling water	0.05/year (1 in 20 yrs)	0.1	0.5	0.01	1	2.5×10^{-5} (1 death in 40,000 yrs)	1×10^{-6} (1 death in 1,000,000 yrs)	25	1

Table C. Layer of protection analysis (EXAMPLE).

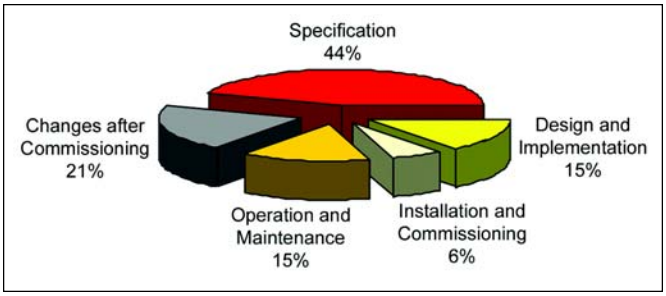

Figure 3. Failures of computer-based systems.

Risk Reduction Factor	Safety Integrity Level	Probability of Failure on Demand	Safety Reliability
10000 – 100000	4	0.0001 to 0.00001	99.99% to 99.999%
1000 – 10000	3	0.001 to 0.0001	99.9% to 99.99%
100 – 1000	2	0.01 to 0.001	99% to 99.9%
10 – 100	1	0.1 to 0.01	90% to 99%

Table D. Safety integrity levels and probability of failure on demand.

for example, Programmable Logic Controllers (PLC), and final element(s), for example, actuated valves, designed in such a way as to implement Safety Instrumented Functions.

The Safety Instrumented Functions are specified with a particular Safety Integrity Level in order to achieve a certain risk reduction for a defined hazardous event. This in turn sets the requirements for both hardware and software safety integrity of the sub elements in the safety loop by means of a target probability of failure.

We cannot predict exactly what will happen when, but we can make educated and well informed judgements regarding what is likely to happen both in terms of hazardous events and protective equipment failures. We consider that the worst-case scenario of a hazardous event occurring at the same time as the safety equipment is unavailable has a probability and that the greater this probability, the greater the likelihood of harm.

In order to address this challenge, we must aim to reduce the frequency of the hazardous event occurring and reduce the probability of the protective equipment failing. Everything will fail; some will fail sooner than others, but even then most 'reliable' equipment has the potential (however small) to fail when you really need it most.

If we develop Table A into Table D, we see that the higher the required risk reduction (i.e., the more 'unsafe' the process) then we require a Safety Instrumented Function with a higher safety reliability (i.e., when we place a demand on the Safety Instrumented Function, there is increased confidence that it will do what is required).

Although the determination of required safety may be determined qualitatively (as a Safety Integrity Level) or quantitatively (as a Risk Reduction Factor), the determination of achievable safety can only be determined quantitatively as a probability of failure. These probability calculations are performed using a variety of techniques, but all are based on the following three basic considerations:

1. Reliability – the quality of the equipment used within the Safety Instrumented Function in terms of failures
2. Redundancy – the quantity of equipment used within the Safety Instrumented Function in terms of voting and diversity
3 Repairability – how often and how thoroughly each Safety Instrumented Function is tested and faults repaired

Therefore, to achieve a Safety Instrumented Function with the lowest probability of failure, we should use the best equipment with multiple combinations and test it as often as practical. This obviously has a commercial impact, as the best equipment will often come at a higher price and frequent testing involves significant maintenance costs as well as production interruption with the associated loss of revenue.

Very generic sources of equipment failure data have existed for years in the oil and gas industries, but more manufacturer data is now being collected, assessed, and published by independent evaluation companies and bodies. The most accurate failure data comes from your own plant records that reflect actual devices in actual processes under actual maintenance regimes.

Further guidance on the confirmation of Safety Integrity Level and reliability calculations is given in the ISA publication Safety Integrity Systems Verification.[10]

Safety Instrumented System Installation and Commissioning

Installation and Commissioning of a Safety Instrumented System is similar to a system within a pharmaceutically validated process.

Installation Qualification (IQ) is defined as "***the documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications and are correctly installed.***"

For Safety Instrumented Systems, we could simply replace "product quality" with "process safety" and then consider the IQ to include aspects such as undamaged delivery to site, mechanical completion, and cold (power off) loop checking.

Operational Qualification (OQ) is defined as "***the documented verification that all aspects of a facility, utility or equipment that can affect product quality operate as intended throughout all anticipated ranges.***"

For Safety Instrumented Systems, we could consider the OQ to include aspects such as hot (power on) loop checking to ensure that individual sensors can sense/measure correctly and individual final elements function correctly.

Safety Instrumented System Safety Validation

Safety validation of the Safety Instrumented System is vital to ensure that all the Safety Instrumented Functions perform as required to achieve the necessary risk reduction. This activity is also known as Site Acceptance Testing (SAT) or a

Pre-Start-up Acceptance Test (PSAT).

Performance Qualification (PQ) is defined as "***the documented verification that all aspects of a facility, utility or equipment that can affect product quality perform as intended meeting predetermined acceptance criteria.***"

The acceptance criteria for PQ of a Safety Instrumented System would typically include the confirmation of:

- logical relationships between sensors and final elements (e.g., a deviation detected by a specific input initiates a response from a related output)
- time of response between initial detection and final action (albeit in initially clean/ideal service on day one)

Safety Instrumented System Operation and Maintenance

Safety validation of the Safety Instrumented System must be completed before the hazards are introduced and the system is put into service. This demonstration that the Safety Instrumented System can reduce risk is only the first step in a journey that may last for decades to ensure that the risks are reduced to the defined tolerable level while the facility and its protected processes and equipment are in operation (and therefore continue to present a threat of harm to personnel).

Regular maintenance of equipment is vital to ensure that the Safety Instrumented Function is available and capable as and when required and this involves routine inspection and cleaning as well as properly executed proof testing.

The purpose of the proof test is to find component failures that are otherwise hidden and make any repairs to restore the Safety Instrumented System to its fully functional state. It is often assumed that if it works properly, it has not failed and a conventional approach is to check to see if the Safety Instrumented Function operates and the equipment has not failed. This is only true for the most part since many proof test procedures do not completely test all of the equipment used in the Safety Instrumented System.

Regular and effective proof testing is a key element in sustaining functional safety and should be considered as early as possible within the design of each Safety Instrumented Function.

Safety Instrumented System Modification and Decommissioning

As with all quality aspects of regulated facilities, proper management of change is vital to ensure that safety is not compromised by uncontrolled or unevaluated modifications to the physical (hardware) or functional (software) attributes of a Safety Instrumented System.

Since the purpose of a Safety Instrumented Function is to reduce risk, any change to the risk it must reduce or its capability to reduce that risk will affect the safety it provides. It is important to note that these changes must include differences between the performance of equipment estimated during the analysis and design phases relative to its actual performance in the field.

- Hazard severity – If effects are worse than predicted, the risk reduction requirement is greater.
- Hazard likelihood – If more frequent than predicted, the risk reduction requirement is greater.
- Equipment reliability – If equipment fails more frequently than assumed, the risk reduction capability is less.
- Equipment redundancy – If equipment redundancy is reduced, the risk reduction capability is less.
- Equipment repairability – If equipment is tested less frequently than declared, the risk reduction capability is less.

Any of these changes must be properly evaluated, documented, and implemented to ensure that the functional safety protection is not weakened or eliminated.

The multi-product nature of many pharmaceutical facilities means that the same equipment may handle a variety of chemical regimes with process pressure and temperatures that change according to the recipes and production phases used. Therefore, it is essential that the risk reduction requirements and capabilities are properly evaluated for each plant and processes within that plant.

Decommissioning a Safety Instrumented Function or a complete Safety Instrumented System is an extreme form of modification. The key consideration for decommissioning is to assess the effects of removing some or all of the risk reduction and to ensure that other Safety Instrumented Function or non-instrumented protection layers are not compromised or expected to provide a greater level of risk reduction than they are capable of.

Conclusions

Functional safety mirrors the principles of process quality and can be summarized as follows:

- What can go wrong? (HAZOP or PHA)
- How bad can it be? (Risk Analysis)
- What can be done about it? (Safety Integrity Level Selection and Safety Requirement Specification)
- How reliable will it be? (Safety Integrity Level Verification)
- How do I stay safe? (Safety Integrity Level Sustain)

It is vital to know how much safety is actually required and what measures are available to achieve it before embarking on the expensive implementation of Safety Instrumented Systems, which may actually be unnecessary.

If they are necessary, then Safety Instrumented Functions must be appropriately designed, implemented, installed, operated, maintained, and regularly tested in order to optimally achieve and continue to achieve the required risk reduction throughout their life.

Appropriate management must be exercised with competent personnel, accurate data, and proven methods to support the analysis, realization, and sustainment of functional safety.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2008, Vol. 28 No. 5

This article discusses the future of API Manufacturing and the role ISPE can play in driving industry innovation.

Innovations in Process Technology for Manufacture of APIs and BPCs

by John Nichols

Introduction

This article presents a glimpse at some of the transformational changes impacting the technology and processes for manufacturing Active Pharmaceutical Ingredients (APIs). My main problem in writing this article was to convey in words the excitement I feel at seeing these changes starting to take place.

The ISPE API Community of Practice has formed a Process Technology Subcommittee with a mission to drive innovations in process technology for manufacture of APIs and Bulk Pharmaceutical Chemicals (BPCs) by the identification of subject matter experts, interaction and partnership with related groups; by support and input to the education program; the promotion/marketing of new innovations in process technology; and input to industry guidelines and best practice documents. I am Co-Chair of this subcommittee and together we have recruited thought leaders from industry and academia to help define this direction and drive this change.

The API COP Process Technology Subcommittee sponsored a conference in Copenhagen in April of 2008 on **Innovations in API/BPC Manufacture**. This article summarizes the various presentations which gave us a glimpse of this future in the following areas:

- Efficient Processing Implementation (e.g., Continuous)
- New Technology/Equipment
- ISPE/ASTM Enabling Activities

Change is Needed and is Coming

For many years, APIs/BPCs manufacturing has generally existed on batch unit operations with little difference in principle from those found in 3000 to 4000BC. However, things are starting to change.

If we are looking for the point at which this started, we would most probably identify that as 2003 with the FDA's cGMPs for the 21st Century (announced originally August 2002) and PAT initiative as the obvious critical initiators. One of their objectives was to encourage early adoption of new technological advances by the industry.[9] Emer Cooke as Head of Sector, Inspections EMEA confirmed[11] Europe's similar view. The timing of these initiatives also combined with an external business environment of cost/price pressures,[10] social pressures for "greener" processes, and improved operator health and safety which has accentuated the opportunity. Companies have been hesitant to change until the new way is seen as "Industry" practice - a "Catch 22" situation. The regulators were to that point "seen" as the inhibitors of "change," but here they were saying the opposite. Often quoted is a statement by Janet Woodcock of the FDA that the desired state is: "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight," along with various comments on the poor efficiency of the pharmaceutical industry compared to others. Benchmarking the pharmaceutical industry against others suggests that there is huge potential to increase manufacturing performance with lower new investment.[18,19]

Most recently we have seen the Product Quality Lifecycle Implementation (PQLI) initiative[4] bringing together a Quality by Design (QbD) approach based on scientific understanding, the perfect basis for developing a process and technology targeted to the needs of the molecular transformations.

A Vision of the Future

Processes may be designed to be fully 'continuous,' i.e., material continually flows through an

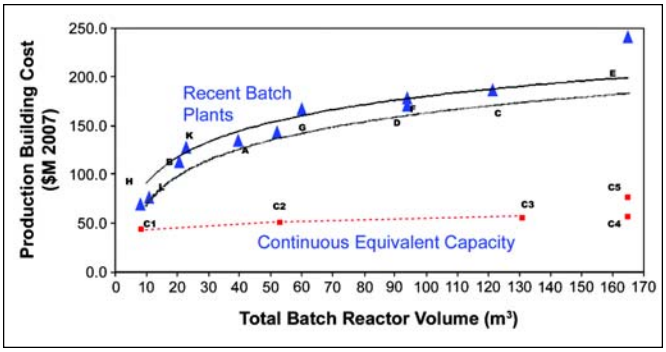

Figure 1. Economics of continuous plants. (Courtesy of Foster Wheeler)

integrated system of unit operations without a break. 'Hybrid' operation also is possible with some continuous operations as part of a batch process.

Process Intensification is the use of understanding of fundamental science (e.g., heat transfer, mass transfer, effect of gravity) to design highly efficient cost effective small equipment, e.g., compact heat exchangers/microreactors.

The concept of targeted processes is simple: understand the required transformations and what drives them in the desired direction, take a holistic view and select the best pathway, and design the process and technology to best meet those objectives.[7] However, to have that understanding, there needs to be a different approach to product and process development, a different approach to the use of PAT, and strong interaction and cohesion between the development chemists and the engineers. These are points developed in the PQLI philosophy, noted by many of the speakers at Copenhagen, and well presented in References 12 and 16.

In Reference 2, Roger Benson discusses Lean Manufacturing as an alternative to "Offshoring," an issue of prime current interest. Some of the particularly relevant principles of lean manufacture are listed below.[5] We can use these as a basis for looking at alternative technologies and means of processing.

- The customer's needs – price, quality, delivery
- Simplicity – ease of control
- Waste – elimination
- Flow – integrated synchronized operations
- Postponement – delay activities to the last possible time
- Time – reduce time to produce
- Variation reduction
- Thinking small – specify smallest machine and build in increments.
- Knowledge – build and distribute
- To these is added "agility"

The following discussion looks at how targeted production, continuous operation, hybrid batch/continuous, or process intensified operation can help achieve these objectives:

- The operating cost is reduced (see reduced waste below) and new facilities are smaller and have lower capital cost giving reduced product cost - *Figure 1.*
- Steady state operation in continuous manufacture and targeted production giving less by-products eases control, improves quality, and reduces variation.
- Reduced inventory in continuous or intensified manufacture gives improved delivery, more agility, and reduced waste.
- Intensified Equipment can be designed to give agility.[8]
- Steady state gives reduced raw materials (higher yield), utilities and environmental emissions, reduced waste. Reference 15 gives a methodology to factor these into decision making.
- Targeted production gives less by-product waste.
- Continuous or intensified facilities are typically smaller.
- In order to have a targeted design, we need scientific understanding of the transformations, improved knowledge. This article does not cover knowledge handling, but readers could refer to Reference 17 for a general discussion.
- Better control and better scientific understanding will lead to less "bad" batches, better quality.
- The scale of continuous or intensified processes is such that that the laboratory proof of concept plant, kilo laboratory, pilot plant, and clinical trials plant can become one and the same, the only difference is the duration for which they are run. Increase in production can then simply and flexibly be made by adding a second line. This enables early production, a critical feature for many pharmaceutical compounds.[13]

In addition, techniques such as continuous processing and process intensification by their nature enable the use of processes that would be impossible or difficult to control in a batch plant.[3] From the safety and health point of view, these improved techniques can reduce inventory, improve integration, thereby reducing handling, and give better control.

While not applicable to every process due to the nature of the transformations necessary, it has been seen that to adopt these techniques can be very beneficial in a substantial percentage of cases.

Innovations in API/BPC Manufacture – Copenhagen Conference 2008

The ISPE Copenhagen Conference covered a wide range of issues pertinent to current and future innovation in API/BPC manufacture. The Conference showcased the significant opportunities for improvement in operating efficiency being implemented in different areas, including:

- demonstrating where Genzyme, Novartis, and Pfizer are in implementing these new technologies
- highlighting new, available equipment technology
- featuring the work being done by ISPE and ASTM to facilitate this new technology implementation

Efficient Processing Implementation

Understanding the Factors Involved – Huw Thomas, Foster Wheeler

Thomas covered the business case for innovation, particu-

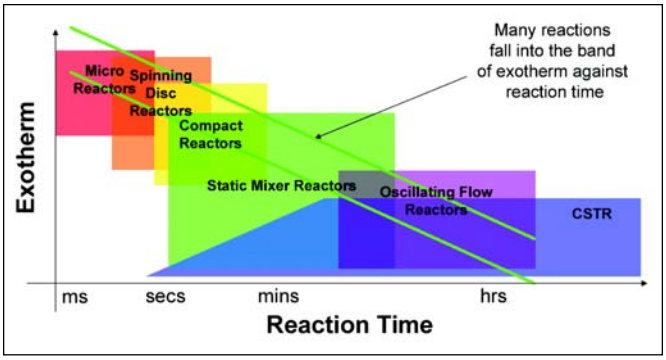

Figure 2. Equipment selection – reactor technology. (Courtesy of Foster Wheeler)

larly continuous processing, based on work already completed – *Figure 1*. He discussed the implications on process development, plant and process design, qualification, and operation.[6]

Aspects to consider are:

- How to chase the money
- What is the meaning of scale and scale-up for a continuous process
- Targeted equipment selection - *Figure 2*
- Hybrid implementation
- The challenges of small scale equipment
- Plant control and the need for buffering
- The implications on environmental and safety issues, qualification, and plant culture.

Continuous Processing, An Overview of Opportunities and Challenges – Paul Sharratt, Manchester University

Continuous processing promises more robust processing and smaller, more efficient plants for both primary and secondary manufacturing. Sharratt's presentation discussed:

- The nature of the benefits of continuous processing – both technical and commercial
- The changes in skill base necessary to access continuous processing

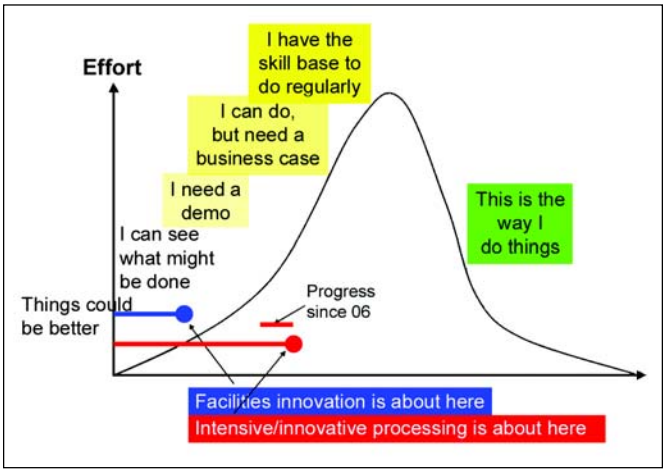

Figure 3. The innovation process.

- The challenges that continuous processing presents to organization and management - *Figure 3*
- Examples of individual continuous technologies and whole continuous process.

Challenges in the Validation of Continuous Processing – Peter McDonnell, Genzyme

The pharmaceutical industry has been slow to adopt continuous processing methods in comparison to other process industries. Recent FDA led initiatives have opened the door to examining ways of reducing manufacturing costs and increasing process understanding through implementation of Quality by Design principles.

Continuous processing with appropriate controls, offers the possibility of exercising exquisite levels of control and managing variability of inputs to give consistently high quality products - *Figure 4*. McDonnell summarized Genzyme's experience in the validation of their continuous manufacturing process for an API and how they have confronted unfamiliar challenges.

Continuous Manufacturing; The Ultra Lean Way of Manufacturing – Walter Bisson, Novartis

Traditional batch manufacturing has been very successfully optimized and offers in the future limited opportunities to drive significant efficiency gains. Transformation from batch to continuous, end to end processing will unlock significant efficiency gains. Together with academia, a blue sky vision has been formulated by Novartis, which Bisson described and discussed. He presented a view of the more distant future with a totally integrated end to end process conducted to meet ultra lean and high quality attributes.

API Process Technology, Improving the Productivity of the Manufacturing Process – Sarah Mancini, Pfizer

Use of new technology is being driven by strong cost pressures in the industry. Manufacturing processes need to achieve very high productivity, i.e., having both low cash and processing costs. While past cost improvement efforts have utilized new, more efficient chemical routes to reduce cost, application of new technology opens up the possibility to directly address processing cost. This will change process development from adjusting the process to function in existing equipment, to selecting equipment to meet processing demands. The resulting processes will have improved process control, maximized yields, minimized unwanted reactions, increased throughput, and decreased waste.

From new chemical entities to marketed products, efforts are underway to implement new technologies into batch processes and to implement fully continuous processes. Pfizer is implementing new technology as part of their process intensification efforts from implementing platform technology into batch processes to fully continuous process implementation. Mancini's presentation covered how processes are selected for technology enhancements and provided an overview of the key technologies that Pfizer is taking forward

for implementation into its manufacturing processes. This was followed by a presentation of the facilities that are available within Pfizer for new technology development - *Figure 5,* and the challenges they are encountering as they move forward with the implementation of new technologies.

New Technology/Equipment

New Technologies for Safe and Contained Powder Handling in the Bulk Pharmaceutical Industry – Frederic Dietrich, Dietrich Engineering

Dietrich's presentation introduced various requirements for and aspects of operating an API plant in regard to powder handling, and presented various technologies and examples of technologies, which can be implemented in order to optimize a production facility and decrease the operating costs.

The presentation elaborated on a number of points including:

- comparison of traditional operation with new powder handling technologies
- criteria for selecting proper technologies respecting the various aspects of containment, safety, and quality control requirement.
- impact of technologies on the productivity of a plant and how to decrease the process downtime (faster product changes for multipurpose operation)
- improvement of processes from batch to semi-continuous processes
- technology to handle powders as if they were fluids
- design for multipurpose operations in order to adapt quickly to the market/process requirements. The design of production units should allow fast changes of the process by using mobile and modular technologies.

The presentation introduced various ways to answer to these challenges and show how the selection of the appropriate concept for the powder handling in an API plant can have a large impact on the productivity of a plant and can lead to high cost saving when selected properly.

Batch Reactor Innovations – Jean-Marie Eslinger, De Dietrich

Glass-lined equipment have many well known advantages in API manufacturing because the glass is chemically resistant, non contaminating, and easy to clean thanks to the smoothness of the finish.

On the other hand, glass-lining manufacturing technology implies restrictions in the equipment design, mainly minimum radius of curvature, that create dead zones and retention areas that can be problematic in terms of cleaning and cleanability and poor mixing.

New technologies and products were presented, answering the needs of mixing, cleanliness, and cleaning validation in the field of glass-lined equipment, for example:

- new generation of reactors with baffles integrated onto the wall that delete dead zones that are difficult to rinse, and free up all the nozzles for process or cleaning devices installation
- glass-lined batch reactors that are no more under-baffled and less efficient compared to metallic reactors
- new range of bottom outlet flush valves equipped with cleaning additional port and retractable spray device
- new design of valve seats, avoiding cross contamination
- integration of sight glasses directly into the equipment, without gasket
- new type of nozzle flanges, deleting dead zones of traditional nozzles
- glass-lined stainless steel, for a better outside cleanliness (no painting but polishing)

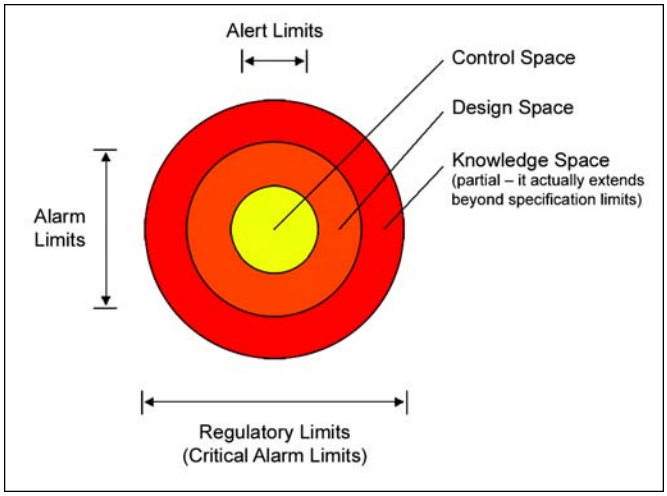

Figure 4. Design space and alerts/alarms.

Continuous Crystallization using Oscillatory Baffled Crystallizer – Xiong-Wei Ni, Nitech/ Herriott Watt.

In his presentation, Ni reviewed the fundamental theories in solution crystallization and outlined the challenges in industrial batch crystallization. Since no complete theory is available to model nucleation/crystallization, their behaviors can only be anticipated by experimentation; accurate process measurements are essential in understanding crystallization processes. A number of techniques have been implemented to monitor crystallization/process variables at laboratory scale. [e.g., optical turbidometric UVvis probe for metastable zone width; X-Ray Diffraction (XRD) for polymorph; Fourier Transform Infrared spectroscopy (FTIR) for supersaturation; Ultra Sound Spectroscopy (USS) for crystal size; Focused Beam Reflectance Measurement (FBRM) for online chord length of crystals and crystal size distribution; differential scanning calorimetry for phase transition; Particle Vision Measurement (PVM) for online crystal shape, Particle Image Velocimetry (PIV) for local velocity]

These techniques/measurements have promoted significant advances in understanding lab scale batch crystallization and have assisted in designing better crystallization processes. However these advances have not been matched by an equivalent increase in our ability and understanding in

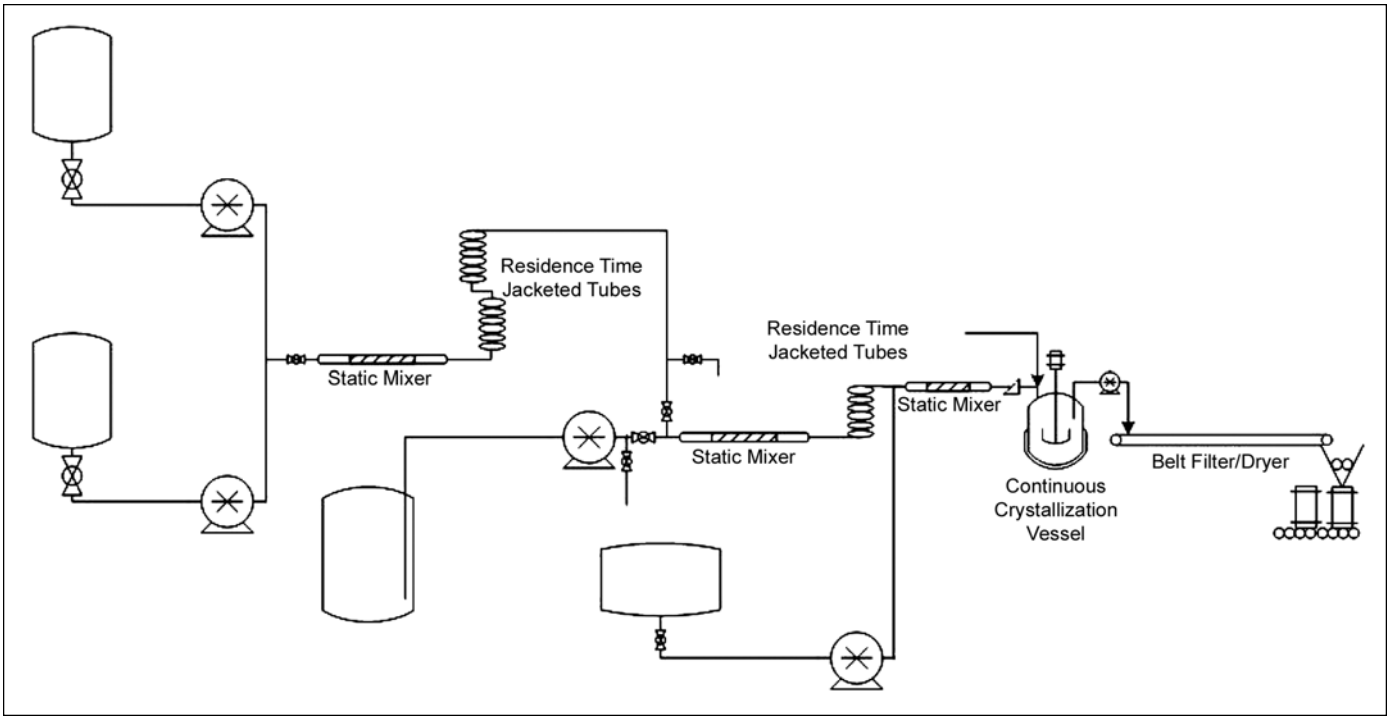

Figure 5. Technology development facilities.

scaling up STR, the workhorse of industrial crystallization. The simple example is that the LINEAR cooling profile has been identified as one of the key operational parameters in solution crystallization, while it is fairly easy to achieve such profiles in small STR, but is still a near impossible mission in industrial scale batch STR with huge volume, inherited non-uniform mixing, and significant velocity/temperature gradients.

He introduced the novel continuous crystallization technology, the Continuous Oscillatory Baffled Crystallizer (COBC), that offers near plug flow conditions under laminar flows with near perfect controllable radial mixing and excellent heat transfer coefficient. He noted that it provides controllable LINEAR cooling profiles that cannot be achieved in large batch operations, allowing well-defined continuous crystallization.

He then used real relevant specialty chemical and pharmaceutical examples of industrial crystallization in COBC to demonstrate the significant benefits obtained, e.g., consistent crystal morphology and size; better filterability; significantly reduced crystallization time, space usage, utility, and energy consumption.

Innovative Blending and Drying Technology – Jean-Francois Demeyre, Triaprocess

Demeyre presented an example of a new innovative piece of equipment, the Triaxe, for mixing and granulation processes. The Triaxe is a completely spherical mixer with a novel gyrating and rotating mixing blades, originally developed in 1998 for achieving homogeneity in jam.

Demeyre introduced the history of this mixer to date, general theory of mixing, and details of the machine and its peculiarities.

He then presented the mixing results in mixing viscous fluids, powders, and in granulation.

Results showed:

- It compares favorably against other equipment types, e.g., ribbon mixer.
- It is a very polyvalent system (interesting if you want to mix some products with changing properties).
- Ability to realize recipes that are not possible in other equipment.
- Very short mixing time to achieve homogeneity.
- Low power consumption.
- Capable of effective granulation.
- Size, distribution of size, shape, and mechanical strength can be altered by altering operating conditions.

ISPE/ASTM Activities

ISPE Activities, the API Community of Practice – John Nichols, ISPE

The presentation began with an explanation of how ISPE activities associated with the API Community of Practice (COP) fit into the current industry strategic environment, and parallel European industry initiatives for improvement in efficiency/process intensification, in particular how you can help make a paradigm shift in the API industry's application of new technologies, details of the new COP Process Technology Subgroup, its current work and its aims, and how input to the ASTM standards has been enabled.

The main messages of the presentation were:

- There is a real opportunity for API manufacture to reduce its costs, and ensure its future.

- To do this, multidiscipline interaction between development science, engineering, and quality disciplines is essential.
- There are lessons available to be learned from similar industries.
- We also need to note that some of the old paradigms no longer apply, circumstances have changed. For example: "Production Rates: Plants having a capacity of greater than 10×10^6 lb/yr (approx. 5000 T/yr) are usually continuous, whereas plants having a capacity of less than 1×10^6 lb/yr are normally batch types," etc.[1] For the pharmaceutical and specialty chemical industries, this ***is no longer true***.
- There is a lot of activity currently to make these improvements and various industry bodies are involved.
- Based on sound scientific, engineering, and business principles, Product Quality Lifecycle Implementation (PQLI) provides a technical framework for the implementation of Quality by Design (QbD). PQLI helps craft a pragmatic approach to implementing Q8 and Q8R, Q9, and Q10, using a risk-based approach to the lifecycle of a product – from regulatory submission, to end of life migration. Uniquely, PQLI involves worldwide regulators in the development and implementation of this critical thinking.
- The ISPE API COP is a good place to get the necessary support and action.
- The new Process Technology Group is specifically dedicated to making these paradigm shifts. Support it. It can help you. Only by working together will we get most synergy.
- We should not be afraid of making a change.

Developing a Consensus Standard for the Application of Continuous Processing Pharmaceutical Industry (9192) – Trevor Page, Niro Pharma Systems/ASTM

Page introduced his reasons for being involved in this initiative as: a passion for the concepts of lean thinking and a belief that applying continuous processing to pharmaceutical production has the potential to generate huge benefits.

He explained the background to ASTM, why it is relevant to the pharmaceutical industry, what is E55, what the new standard on continuous processing addresses, how ISPE has been involved in this, and the next steps for the ASTM standard.

Important messages were:

- ASTM has a proven track record of developing and delivering common sense standards.
- The standard is being encouraged and supported by the FDA, it meets the objectives of the "cGMPs for the 21st Century Initiative."
- The FDA believes it should not be developing its own government specific standard, but should be participating with voluntary consensus standards bodies.
- E55 has now been in operation for nearly four years and its role is broader than PAT. It includes various interlinked pharmaceutical standards.
- Continuous Processing is defined as:
  - Materials are fed into the system at the same time as product is removed from the system.
  - Material condition is a function of its position within the process as it flows from inlet to outlet.
  - The quantity of product produced is a function of the duration for which the process is operated and the throughput rate of the process.
- The standard is addressing key aspects (that may inhibit innovation implementation) for example:
  - Process Understanding (how to achieve necessary level of understanding, the desired state, residence time distribution, process dynamics/mixing, process control)
  - Material Traceability (e.g., lot identification, batch definition, composition)
  - Cleaning (e.g., degradation, microbiological)
- ISPE is involved in providing comment via the API Community of Practice.
- New draft of standard 9192 expected Summer 2008. Aim to get 60 percent positive vote by December 2008.

The Way Forward

In looking at the way forward, we see that we are at the stage of early adopters taking action to improve the position, but it is going to need proof of these concepts, general publicity of the benefits, and sharing of experience before the movement

Prof. Prabir Basu	Pharma Engineering, Britest, NIPTE	Purdue Univ
Carol Bye	Senior Dir. Head API Quality Operations	Pfizer
Nigel Fletcher	API Design	Foster Wheeler UK
Prof. Brian Glennon	Scale-up of Chemical and Bioprocesses	Dublin
Benny Goosen	Chemist, Process Development	Janssen
Ruth Hardy	Technical Support Pilot Plant	Pfizer
Dr. Barry Johnson	Equipment Development	Alfa Laval
Rick McCabe	Proj. Manager Innovative Projects	Pfizer
Dr. Peter McDonnell	Implementing Cont. Processing	Genzyme
Stan Newberger	Pilot Plant, API Design	CE & IC
John Nichols	Cont. Fine Chem. Operation, API Design	
Prof. Åke C Rasmuson	Crystallization in Pharma Processes	KTH/Royal Institute of Technology
Dr. Raf Reintjens	Coordinator for PI	DSM
Prof. Paul Sharratt	Prof of Sustainable Processing	Manchester Univ and Britest
Prof. Andrzej Stankiewicz	Chair EFCE PI Working Party	Delft TU
Prof. Bernhardt Trout	Dir. Novartis-MIT Cont. Man. Centre	MIT
Prof. Xiong Wei Ni	OFR Science and Development	Herriott Watt Univ/ Nitech

Table A. Membership of the API Process Technology Subcommittee.

becomes more widespread. ***Knowledge is nothing if it is not shared.***

Corporate culture can be one of the biggest inhibitors to innovation and we need to overcome this. Innovation is fostered by flexibility, commitment, communication, and creativity.[14] We have a great opportunity at the moment, we need to work together, and should not be afraid to grasp the opportunity.

One enabler for this, a vehicle for this communication is the ISPE API COP and in particular, its Process Technology Subcommittee.

The API Process Technology Subcommittee is currently working on a roadmap identifying all the main issues inhibiting the introduction of these new technologies, plus some enabling tools and tabling a path forward. The roadmap also will include an appendix of potential technologies. In addition, the team will maintain its ongoing input to the ASTM Continuous Processing Standard development. The group also has future plans to generate a white paper covering in more details the particular areas of compliance/quality assurance and control associated with continuous processing.

Future educational offerings will build on this work at US and EU conferences in 2008 and 2009, and there are long term plans to expand the API Baseline Guide with sections on process intensification/continuous processing and small volume/high potency manufacture.

This collaboration between industry and top-level academics highlights the role ISPE can play in advancing manufacturing technology, and building these strategic partnerships.

For further information, visit ISPE's Web site under Communities of Practice (www.ISPE.org).

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About the Author

John Nichols has more than 35 years of experience in the chemical engineering field, and is an expert in the areas of high containment and process design having facilitated and coordinated multi-national teams for biochemical, fine chemical, and pharmaceutical API projects. He recently retired from his role as Director of Pharmaceutical Technology at Foster Wheeler after more than 25 years. In this role, he was responsible for global technology coordination and consulting to API facilities for specific clients and projects, as well as being a Director of Britest. Previously, Nichols was a Director of Carlisle Consulting and Engineering Director for Extract Technology Ltd. a manufacturer of a wide variety of containment equipment. He is also former Manager of Pharmaceutical Engineering for Foster Wheeler's Reading Office, where he was responsible for the staff involved in the design of bulk pharmaceuticals, biochemicals, and secondary finishing facilities. Prior to that, he had 10 years experience in design, commissioning, and plant management of various

batch and continuous fine chemical facilities. Nichols is a Chartered Chemical Engineer and a Fellow of the Institution of Chemical Engineers. He has a BSc in chemical engineering from Imperial College, London, and a Diploma in management from Thames Polytechnic, London. He is a member of ISPE's International Board of Directors, Co-Chairman of the API COP Subcommittee on Process Technology, and a member of the EFCE Working Party on Process Intensification. He can be contacted by email: johnjenichols@aol.com.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2008, Vol. 28 No. 5

ISPE Baseline® Pharmaceutical Engineering Guide for New and Renovated Facilities Volume 2: Oral Solid Dosage Forms (Revision) – Executive Summary

This executive summary provides an overview of the second edition of the ISPE Baseline® Guide: Oral Solid Dosage Forms. The revision of the Guide was prompted by a number of developments within the industry requiring the guidance to be realigned and refreshed.

Visit www.ISPE.org for additional information about this Guide and other technical documents available from ISPE.

1 Introduction

1.1 Background

The design, construction, commissioning, operations, and qualification of Oral Solid Dosage (OSD) facilities are significant challenges for manufacturers, engineering professionals, and equipment suppliers. These facilities should meet Current Good Manufacturing Practice (cGMP) regulations while complying with all other governing codes, laws, and regulations.

The cost of bringing these facilities on-line has been rising, in many cases due to inconsistent interpretation of regulatory requirements. ISPE and engineering design and construction professionals from the pharmaceutical industry have entered into a partnership with the Food and Drug Administration (FDA) and European Agency for Evaluation of Medicinal Products (EMEA) to jointly develop a common understanding and interpretation of GMP requirements for production facilities. This Guide is intended to offer a consistent framework for interpretation, while still allowing a flexible and innovative approach to facility design, construction, commissioning, and qualification. This approach will allow manufacturers to better serve their customers by helping to reduce production cost and maintenance, and improve product quality, thus make more funds available for the discovery of new and innovative medicines. Additionally, this Guide will provide an overview of potential new technologies which are being applied selectively in the industry. The reader should consider this Guide as a tool to use in conjunction with design guides that are already available in the industry.

This is the revision to the ISPE Baseline® Guide, originally published in February 1998 for new and renovated OSD facilities. Aside from focusing on compliance with the current FDA cGMP regulatory expectations, where applicable this Guide also discusses the differences between the US, European, and Japanese practices. Some major changes to the Guide include:

- Addition of the new chapter on 'risk management and risk assessment.' This chapter discusses, at a high level, approaches relating to assessment and management of risks within the lifecycle of the facility design and construction project
- expanded definitions and discussion of product risk of contamination relating to the 'levels of protection' concept
- the chapter on 'product and processing considerations' has expanded to include emerging processing technologies, containment, MES, PAT, and cost considerations
- introduction of area definitions and zoning concepts with architectural detail
- updated the current philosophy of commissioning and qualification
- the appendices provide an overview of the risk assessment process as it pertains to non-GMP subjects such as HSE and controlled substances
- the facility cost section has been moved to the appendix, which will include information on lifecycle cost, and it will be referenced by appropriate chapters
- demonstrate and introduce methods to improve or maintain process
- deeper focus on quality and cost aspects

1.2 Scope of this Guide

This Guide may be used by industry for the planning, design, construction, and qualifica-

tion of new OSD facilities. It is neither a standard nor a commissioning design guide. It is not intended to supersede governing laws or regulations which apply to facilities of this type, nor is it intended to apply to existing facilities which may fall short of the baseline described. The use of this document for new facilities and major renovations of existing facilities is at the discretion of the facility manufacturer or operator and the current status of codes and standards may affect the appropriateness of certain design solutions.

The Guide covers pharmaceutical facilities for the manufacture of oral solid dosage forms including tablets, capsules, and powder. It may also be applied to clinical supply facilities. It is not intended to address the manufacture of dietary supplements, excipients, sterile products, topicals, oral liquids, or aerosols. Guidance on facility requirements for the manufacture of excipients can be found in the Baseline® Guide, Volume 1 – Active Pharmaceutical Ingredients (Second Edition), while sterile products, topicals, and oral liquids and aerosols are being addressed in the Baseline® Guide Volume 3 – Sterile Manufacturing Facilities. Wherever applicable, references are provided to existing Baseline® Guides for further detail on specific systems or operations.

Why a Revision?

This Guide has been revised both to reflect changes in regulations and industry practice, and refers to guidances such as ICH Q8 and ICH Q9.

It supports taking a risk-based approach and a new chapter on 'risk management and risk assessment' has been added to discuss, at a high level, approaches relating to assessment and management of risks within the lifecycle of the facility design and construction project.

The appendices now provide an overview of the risk assessment process as it pertains to non-GMP subjects, such as HSE and controlled substances.

The facility cost section includes information on lifecycle cost.

The chapter on 'product and processing considerations' has expanded to include emerging processing technologies, containment, MES, PAT, and cost considerations.

The Guide takes into account that several new ISPE Baseline® Guides have been developed and others revised. It relates closely to both the new Risk-Based Manufacture of Active Pharmaceutical Products (RiskMaPP) Baseline® Guide and the Good Engineering Practice (GEP) Good Practice Guide.

The Guide aims to define product protection requirements based on product risk factors and the discussion of product risk of contamination relating to the 'levels of protection' concept has been expanded.

New sections have been added to discuss area definitions and zoning concepts with architectural detail.

The Guide is intended primarily for facilities meeting the regulatory requirements to supply the United States (US) market, and follows US standards and references. Where applicable, pertinent European and other non-US standards are referenced in the appendices.

The concepts proposed constitute a Guide or base point from which to proceed. ISPE and FDA have agreed that this document is an acceptable guide to achieving regulatory compliance. Other applicable codes, standards, and governing laws still apply. These are mentioned for completeness, and for where they may impact upon GMP design issues.

1.3 Key Features of this Guide

The following key concepts are a basis for this Guide:

- proper application of facility design and procedures to assist with GMP compliance
- risk-based approach
- non-GMP technology and its impact upon facility design and costs
- contamination risk as assessed by the manufacturer
- design conditions versus operating range
- good engineering practice
- enhanced documentation

Proper Balance of Facility Design and Procedures: it is not necessary to address each GMP issue only by design; one or more of the following may be applied:

- procedural control
- facility layout
- containment and barrier technologies

This will allow the flexibility to design for appropriate levels of protection or containment, while avoiding costly designs that result in no significant improvement in quality, efficacy of the drug product, or protection of personnel. For example, based upon an assessment of contamination risk within a tableting room, one or more of the following may be applied to prevent contamination:

- airlocks
- multiple pressurization levels
- one-way personnel flow
- special gowning procedures
- special cleaning procedures

The risk-based approach involves using innovative manufacturing science and technology to assess, mitigate, and control the potential hazard in a manufacturing process that affect the quality of the drug product. As an example, utilizing statistical data analysis in conjunction with Process Analytical Technology (PAT) for continuous process monitoring and control will lead to higher quality product. Sharing such risk mitigation strategies with the FDA may be beneficial. (See Section 17, reference 1, ICH Q9 Quality Management System.)

Non-GMP Technologies: some facility design requirements arise from decisions made to address non-GMP issues or preferences of the manufacturer, such as operator safety or strategic operating decisions. These non-GMP driven technologies often affect facility design features aimed at achieving GMP compliance and are discussed in Chapter 10 of this Guide.

With proper planning, both GMP and non-GMP risk assessments may be completed in parallel so that key drivers for capital investment are included in the project scope.

The level of protection required is based upon the risk of contamination as assessed by the manufacturer, and assessment criteria include:

- The duration of product exposure
- The product mix and product changeover (product changeover is the frequency of change of product processed in a room or in a piece of equipment)
- The characteristics of those products, such as potency or toxicity
- Human activities performed during the manufacturing process
- Facility design and performance factors
- Environment in which the plant is located

Operating Conditions are based upon product acceptance criteria, while design set points and conditions are target values for the engineering designer to achieve. For example, a blending room may have a setpoint of 40% RH and a design range of 30 to 50% RH (Relative Humidity), but the product

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in that room may be unaffected by humidity in the range of 20 to 70% (validated product acceptance criteria). The acceptable operating range for the room is therefore 20% to 70%, not 30% to 50%. Additionally, non-product requirements, such as human comfort, are also criteria for the design. This is discussed further in Chapter 2 of this Guide.

Good Engineering Practice (GEP) is defined as engineering practices that are applied throughout the business to provide organization and control, balance risk and cost, and ultimately deliver appropriate and effective solutions.

The term GEP is used to describe an engineering management system that is expected in a pharmaceutical enterprise but not mandated by GxP regulations. GEP recognizes that all systems in a facility undergo some form of commissioning, which include inspection, testing, and documentation based on agreed protocols, while direct impact systems require enhanced documentation which include an enhanced design review, and Quality Assurance inspection and approval that are appropriate and acceptable to regulators. GEP capitalizes upon this by suggesting that manufacturers engage all stakeholders (engineers, managers, operators, Quality Assurance experts, and others) very early in the planning, design, construction, and commissioning and qualification phases to ensure that systems are documented only once. This is discussed further in Chapter 6 and Chapter 11 of this Guide.

A key element of good engineering practice is to develop appropriate documentation throughout the life of the project to ensure that the equipment and facility is fit for its intended use. The documentation should be reviewed, approved by appropriate subject matter experts, updated in a timely fashion, and stored in a secured location for retrieval.

1.4 How to Use this Guide

This Guide for Oral Solid Dosage Forms facility design is organized in a format similar to that followed by other ISPE Baseline® Guides.

Chapter 2 'Concept and Regulatory Philosophy' provides a general overview of regulatory expectations for OSD facilities, and identifies key design requirements for regulatory compliance. Chapter 3 'Risk Management' discusses a high level approach relating to assessment, control, communication, and review of risks to the quality of the product within the lifecycle of the facility design and construction project. These two chapters provide the regulatory framework for the design model to follow.

Subsequent chapters provide guidance on engineering systems such as HVAC, material and equipment selection, and installation. Chapter 10 'Other Considerations' focuses on implementing risk assessment and risk management strategies in the design for compliance with appropriate Health, Safety, and Environment (HSE) regulations. Chapter 11 'Commissioning and Qualification' provides the approach for commissioning the facility to properly qualify the direct components of an OSD facility. This discussion provided in this chapter is in alignment with the Baseline® Guide Volume 5 'Commissioning and Qualification.' At this writing,

Type	Facility	Processing Methodology
1.	Dedicated	- Facility manufactures products from a single Active Pharmaceutical Ingredient (API) - Same API all the time - The equipment and facility are dedicated - Dedicated Operation
2.	Multi-Use	- Facility manufactures products from different APIs, but they use dedicated equipment - Facility has a mix of APIs - Dedicated equipment in a multi-use facility - Concurrent Operation
3.	Multi-Purpose	- Facility manufactures products from different APIs, but specific equipment is not dedicated to any product - Different products/changeover within the facility - Multi-purpose facility and multi-purpose equipment - Both concurrent and campaign operation

Table A. Facility designation.

Volume 5 is being revised to align with the new ASTM E2500, which focuses on risk-based approach for the verification process, 'a new umbrella term that encompasses commissioning and qualification'.

Four Appendices have been added to provide more detail on some relevant aspects related to OSD facilities:

- Appendix A contains discussion and guidance on the lifecycle cost analysis relating to optimizing the design of the facility and selection of equipment and system.
- Appendix B contains an summary of the quality risk management process for an OSD facility.
- Appendix C contains an example of risk assessment for an OSD facility.
- Appendix D contains HSE Regulatory and Consensus Standards, Codes, and Guidelines References from the United States, the EU, Canada, and Japan.

2 Concepts and Regulatory Philosophy

2.1 Introduction

This chapter is intended to provide guidance on regulatory philosophy as applied to the design of Oral Solid Dosage process systems and facilities. Understanding and interpretation of regulatory requirements and guidance is key, as the engineering solutions adopted will affect both the initial cost and operating costs throughout the life of the facility.

GEP can help to ensure that the products meet the required standards of quality and purity.

2.2 Regulatory Philosophy

Regulation of the pharmaceutical industry is conducted by national and international agencies, for example, the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA), and the Ministry of Health, Labour, and Welfare (MHLW) in Japan. A list of international and national regulatory agencies can be found on the FDA home page: http://www.fda.gov/oia/agencies.htm.

These agencies are empowered by legislation, such as the US Food, Drugs, and Cosmetics Act (FD&C Act), and the EU

Directive 2003/94/EC. The legislation requires the pharmaceutical industry to follow current Good Manufacturing Practice (cGMP), e.g.:

> The FD&C Act, Chapter V, subchapter A, section 501 states: "*A drug ..... shall be deemed to be adulterated — (B) if ..... the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; ...*"

Paragraph 1 of the EC directive states: "*All medicinal products for human use manufactured or imported into the (European) Community are to be manufactured in accordance with the principles and guidelines of good manufacturing practice.*"

CGMP is set out in US Code of Federal Regulations Title 21, referenced as 21CFR210 and 21CFR211. The Center for Drug Evaluation and Research (CDER) also issues guidance documents, which represent the FDA's current thinking on a particular subject.

In Europe, cGMP is set out in EUDRALEX Volume 4 – Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice. Chapter 3 covers premises and equipment.

In Japan, GMP is required for manufacturing and marketing approval under Article 14.2, paragraph 4 of the Pharmaceutical Affairs Law. GMP requirements for OSD facility design are in MHLW Ordinance 'Regulations for Buildings and Facilities for Pharmacies, etc.'

OSD facilities may be designed and constructed to operate under different production scenarios - *Table A*.

The products manufactured in OSD facilities may vary in dosage form and degree of product hazard. The equipment used to produce OSD forms can range from open-type manual processing to enclosed, highly automated processing. This can lead to numerous possible facility layouts, but all are governed by the same basic GMP requirements for the design, construction, and validation of OSD facilities and equipment:

- should be of suitable size, construction, and layout to allow all required manufacturing operations; personnel, product, and equipment movement; and permit effective cleaning and maintenance
- should be designed with adequate space and orderly flow to prevent product mix-ups and product cross-contamination
- should provide protection of the product from chemical, physical, microbiological, and all environmental contamination
- should be designed and operated with facilities for breaks, toilets, hand washing, and garment changing, provided as appropriate for product protection
- should include specific precautions to ensure that hazardous materials do not present an unacceptable level of product cross-contamination risk or a risk to personnel or the environment
- elements of the facility and equipment which are critical to product quality should be qualified

These general principles represent the regulatory philosophy that drives the basic requirements within OSD facilities to ensure product quality and operator safety during the manufacturing process.

OSD facilities have common issues across the different unit operations and product types encountered. Dust containment often presents a design challenge for OSD forms, where highly hazardous active ingredients are becoming more common. This Guide is intended to help establish consistent and minimum parameters for facility design, which address these concerns and meet GMP requirements.

This chapter outlines guidance on the following concepts, which are further developed in Chapters 3 through 12:

- risk-based approach
- product protection requirements
- design concepts for product protection
- process control concepts
- commissioning, qualification, and validation

Each manufacturer should define the level of control, protection, and validation appropriate to each manufacturing operation, based upon a sound understanding of the product and process critical parameters. They should determine the risk of product contamination to the product mix within each manufacturing area.

When existing facility renovations or modifications are made or manufacturing procedures are changed, the nature of the changes should be evaluated in advance to determine how they may affect patient safety and product quality. Appropriate change control procedures should be followed in making any change to qualified equipment, systems or validated processes. In addition, depending upon the extent of the change and its potential to affect patient safety and product quality, the governing regulatory agency may require notification or prior-approval of a change before it is implemented. Understanding the potential impact of a proposed change and the corresponding regulatory requirements is critical to maintaining facilities, equipment, and processes in a qualified and validated state.

3 Product Protection

The ISPE Baseline® Guide: Risk-MaPP describes a scientific risk-based approach for the prevention of cross-contamination that will, on a case-by-case basis, determine the need for dedicated or segregated facilities in the manufacture of pharmaceutical products. For further information see section 2.4.4 of this Guide.

4 Product and Processing

This chapter presents a guide to process and equipment choices available that meet the demands for OSD forms in new or renovated pharmaceutical manufacturing, formulation development, and pilot plant operations. Aspects of commonly used technologies, unit operations, and associated equipment that are pertinent to product quality and facility design are reviewed. In addition, material characteristics and properties, material handling, cleaning, and maintenance are addressed. The application of PAT and Manufacturing Execution Systems (MESs) is considered.

Decision trees are used to guide the reader through the options to a baseline operation and equipment training selection for a variety of process requirements and material types. Differences between European, Japanese, and US practices are discussed. For further information, see the ISPE Baseline® Guides on Active Pharmaceutical Ingredients (API) and Packaging, Labeling, and Warehousing Facilities.

5 Architectural

This chapter provides a guide for requirements to be considered for OSD facility design and construction regarding building programs, building layouts, space definition, details, and finish materials. These aspects of the facility are developed in the context of cGMP, risk, and process requirements to establish baseline guidance and parameters.

6 Process Support and Utilities

This chapter discusses the categorization of mechanical systems used in OSD pharmaceutical manufacturing. There are two broad categories:

1. process support systems
2. utility systems

This chapter discusses the categorization of mechanical systems using a risk-based approach methodology. This provides a robust methodology for the identification of process support and utility systems. It also provides a method for the determination of system applications and the selection of resulting commissioning and qualification strategies. Examples for each type of system are discussed.

Other considerations which impact system design, including user requirements, engineering design elements, and start-up requirements also are addressed. The discussion also focuses on GEP for utility system design. Approaches for multiple-use requirement scenarios also are addressed.

A listing of typical OSD utility systems is provided with general descriptions and requirements for each system.

7 HVAC

This chapter focuses on the GMP requirements for HVAC systems. It provides guidance on the design of HVAC systems based upon clearly defined user requirements (e.g., level of product protection, product and process requirements, and architectural design). Non-GMP requirements, such as operator protection, expectations on monitoring, energy efficiency, and safety requirements also are addressed.

HVAC systems can help mitigate risks to both the product and the people who work around it. Their contributions include: GMP risks and non-GMP risks.

HVAC designers should understand cGMP regulatory requirements and also be familiar with industrial HVAC as defined in various documents by the:

- American Society of Heating, Refrigeration and Air-Conditioning Engineers (ASHRAE)
- American Conference of Governmental Industrial Hygienists (ACGIH)

Knowledge of all local construction codes, the National Fire Protection Association (NFPA) standards, environmental regulations, and Occupational Safety and Health Administration (OSHA) regulations is also assumed. The design and installation of the HVAC system should comply with these and all applicable building, safety, hygiene, and environmental regulations.

8 Electrical

From the electrical perspective, the most important issues to be addressed in an OSD facility include:

- cleanability of all exposed electrical equipment
- flush lighting should be used wherever possible
- all conduits and raceways should be hidden (not exposed) in the production areas

Although the degree may differ based upon the level of protection required, the cleanability of the exposed electrical equipment is the primary concern of electrical systems in an OSD facility.

Electrical power distribution systems do not directly affect the quality of Oral Solid Dosage (OSD) pharmaceutical drugs and hence are not critical systems and are not subject to regulatory oversight and validation requirements. The 'equipment,' which produces and controls the pharmaceutical processes and provides clean and controlled environments for the manufacturing areas for OSD pharmaceutical drugs, requires a source of electric power and an electrical power distribution system that are reliable and maintainable.

A properly designed electrical distribution system should provide reliable electricity to the OSD pharmaceutical equipment. This Guide provides design and maintenance criteria to assist in the proper design of an electrical system to provide reliable electrical service.

9 Control and Instrumentation

This chapter considers Control and Instrumentation (C&I) systems for OSD manufacturing facilities and focuses on:

- those facility and environment controls which affect patient safety and product quality

- the major topics that drive decisions regarding the design and set-up of Process Control Systems (PCSs)

The objective is to provide design guidance, which results in cost-effective system designs, capable of being qualified.

C&I systems are used in many facility systems. They may be deemed to affect patient safety and product quality if they control, monitor, or record a CPP or directly affect a CQA. Components of C&I systems may also be considered critical if they come into direct physical contact with the product.

The functions described may be combined within a single C&I system, or be performed by several independent systems.

Specific design advice has been given where possible, but it is stressed that different operational preferences and priorities will influence the preferred solution.

The designer also should consider other relevant design criteria, such as safety, reliability, and design for maintenance.

Process Control Systems encompass a wide variety of systems such as, PLC, SCADA, DCS, and MES. For further information see the GAMP Good Practice Guides on Validation of Process Control Systems (VPCS) and Manufacturing Execution Systems (MES) (see Section 17, reference 13).

Control systems may be complex and validation strategies should be based on a defined risk-based approach. Testing strategy should be based on a predefined estimate of the level of risk, providing traceability and information allowing critical parameters to be determined.

Process Analytical Technology (PAT): the FDA published a PAT framework Guidance for Industry in 2004 (see Section 17, reference 28). The purpose is to foster innovation and efficiency in the pharmaceutical industry. The basis of PAT is process understanding and the application of appropriate control strategy for the critical process parameters to assure the quality of in-process material and final drug products. A robust control system is a key component to support a PAT system implementation.

Statistical Process Control (SPC) may be considered as a precursor to PAT.

A control system should assist with:

- collection of process data (60% of an SPC implementation)
- transfer of process data to standard statistical tools
- eventually implement monitoring and later on control charts in a batch context

At the time of publication, PAT often is only in the inception phase and the objective is to provide an approach which fosters PAT implementation. The ability to connect PAT measurement devices with process control systems and to transfer related data to statistical tools is required before filing for PAT. This is considered to be an important early step in the process.

10 Other Considerations

This chapter provides an overview of HSE and controlled substances considerations, which should be considered during a comprehensive risk assessment (described in Chapter 3 of this Guide). Non-cGMP risks that should be considered are summarized and an overview of the basic technical and procedural approaches that may be used to mitigate these risks is provided. In addition to information provided in this chapter, project teams should be aware of local requirements and facility policies.

This chapter is intended for use as a guide to the types of non-cGMP information that should be gathered as part of an organization's risk assessment and mitigation process.

See Chapter 15 of this Guide for a comparison of safety regulations for the US, Canada, and the EU. A summary of Japanese requirements is provided separately.

11 Revision of the Commissioning and Qualification Baseline® Guide

In the *Final Report Pharmaceutical CGMPs For the 21st Century – A Risk-Based Approach,* FDA described how their objectives included the following:

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality management systems approaches, to all aspects of pharmaceutical production and quality assurance
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas

A revision of the Baseline® Guide Volume 5 is underway that seeks to support these objectives by describing an efficient and effective design, installation, and verification process that focuses on safeguarding product quality and public health. It is intended that risk management should underpin the specification, design, and verification process, and should be applied appropriately at each stage.

As part of this revision, Baseline® Guide Volume 5 is being aligned with ASTM standard E2500, which describes a risk-based and science-based approach to the specification, design, and verification of manufacturing systems and equipment that have the potential to affect product quality and patient safety.

12 Appendix A: Cost Factors In OSD Manufacturing

How much does it cost to build a new pharmaceutical manufacturing facility? The answer to this important question should be carefully considered. It will drive the mathematics of profit projections and has the potential to terminate a project at an early stage if incorrect.

Project funding decisions are usually based on the first cost alone and value engineering efforts to reduce first cost are a common element in project planning. Most project planners are familiar with the concept of Lifecycle Costing but are generally not tasked with or experienced in doing it.

During the beginning phases of a project, the cost involved

in owning and operating a new pharmaceutical manufacturing facility throughout its useful life should be considered. This cost has significant long term ramifications. The need for radical changes may not become apparent until they are too costly to implement.

Lifecycle Costing offers an opportunity for a much more informed decision making process and, if properly implemented, can deliver significant savings. During the selection of options that deliver the required functionality, Lifecycle Costing considers both initial costs *and* future operating costs.

13 Appendix B: Summary of Quality Risk Management Process

This chapter provides a summary, for both GMP and non-GMP elements, of the quality risk management process.

14 Appendix C: Risk Management Tools

This chapter provides an example showing a systematic approach to risk management for the design (e.g., new, retrofit), qualification, and maintenance of an OSD facility.

Several qualitative and quantitative risk management tools are available. Tools that are routinely used are listed below. Additional references include ICH Q9 'Quality Risk Management, and the ISPE Baseline® Guide on Risk-MaPP (in draft form at the time of this writing). Selection of a specific tool will depend on the level of rigor of the data and the criticality of the risk assessment (e.g., higher risks to patient safety may require a more in-depth risk analysis tool.)

- Failure Mode Effects Analysis (FMEA; EN ISO 9001:2000)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools
- Basic risk management facilitation methods (flowcharts, check sheets etc.)

15 Appendix D: Other Considerations

This chapter provides information on HSE regulatory and consensus standards, codes, and guidelines for the US, the EU, Canada, and Japan.

16 Glossary and Acronyms

A glossary of pharmaceutical industry terminology relevant to this Guide.

17 References

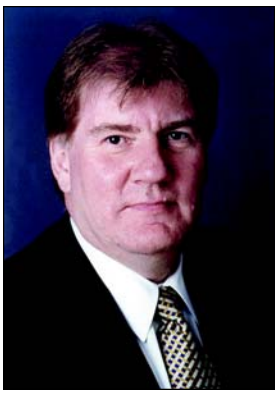
A list of publications referenced by the Guide which provides further reading on the topic of this Guide.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2008, Vol. 28 No. 5

PHARMACEUTICAL ENGINEERING Interviews Norman Winskill, Vice President, Global Technology, Pfizer Global Manufacturing and Kelvin Cooper, Senior Vice President, Pfizer Worldwide Pharmaceutical Sciences

by Rochelle Runas, ISPE Technical Writer

In this interview, Norman Winskill and Kelvin Cooper discuss how Pfizer manages the important interface between development and manufacturing. They also give insight into Pfizer's strategic thinking on QbD, lean approaches, outsourcing, new manufacturing technologies, and green chemistry.



Norman Winskill is the Vice President and Team Leader of Global Technology, Pfizer Global Manufacturing (PGM). His organization includes Pfizer Global Engineering, which has engineering responsibility for the whole of Pfizer; Right First Time, PGM's continuous improvement program; and Global Manufacturing Services (GMS), the manufacturing science and technology group of PGM. The main responsibility of GMS is the co-development (with Worldwide Pharmaceutical Sciences), scale up and launch of new products, process improvement and process optimization, and the development and implementation of new manufacturing technologies.

Winskill joined Pfizer Sandwich in 1975 as a biochemist in the International Process Development Group. In the next eight years, he held a number of positions in Manufacturing, Development, and PGRD before joining International Manufacturing in New York in 1984. By 1996, he was the group's Executive Director, Operations and Technology.

Winskill has a BSc in chemistry and a PhD in microbial chemistry from the University of Manchester, UK. Winskill is a Fellow of the Royal Society of Chemistry.

Kelvin Cooper is the Senior Vice President of Worldwide Pharmaceutical Sciences (PharmSci). Cooper led this organization since mid-2000 through the mergers and acquisitions of Warner-Lambert and Pharmacia.

Cooper joined Pfizer in 1981 as a medicinal chemist in the Sandwich Discovery Laboratories, where he worked in several different project areas, including anti-fungals, anti-bacterials, respiratory, urology, and exploratory medicinal chemistry. In 1991, Cooper transferred to the Discovery Laboratories in Groton, Connecticut to lead the inflammation, allergy, respiratory, and immunology medicinal chemistry programs and in 1994 became the Medicinal Chemistry Director of the cancer, inflammation, immunology, allergy, respiratory, and infectious disease programs. In 1998, Cooper led a new technology-based group encompassing large-scale synthesis, general pharmacology, drug metabolism technology development, and drug metabolism candidate support.

Cooper started his scientific career as a junior technician and analytical chemist in the drug metabolism department at Wellcome Research, Beckenham, England. He earned a bachelor's degree in chemistry, an honors degree in chemistry from Kingston University,

London, and his PhD from Nottingham University, where he conducted research in organic chemistry.

Cooper is a member of the Royal Society of Chemistry, the American Chemical Society, and a Fellow of the American Association for the Advancement of Science. Cooper is also a board member on the University of Connecticut Foundation.

Q The partnership between product development and manufacturing is an especially important one. How does Pfizer manage that important interface?

Winskill: The interface between these two key functions is one upon which Pfizer has worked for many years. We call this "co-development" and we manage it jointly between Pfizer Global Manufacturing (PGM) and Worldwide Pharmaceutical Science (WWPS). Though we've been practicing co-development for years, it became more rigorous and systematic when we acquired Warner-Lambert (2001) and then Pharmacia (2003) – forcing us to institutionalize and formalize our co-development procedures.

Our co-development process incorporates all of the elements of Quality by Design, lean manufacturing, green chemistry, and many other critical initiatives within Pfizer. What is interesting is how Pfizer manages this, with one core team comprised of colleagues from all relevant disciplines in both PGM and WWPS. We use a joint governance/joint procedures approach between the two organizations, built on mutual responsibility and mutual respect. We believe this is a competitive advantage. Others in our industry talk about doing this, but when we discuss this in detail with our peers in the field, it is evident that Pfizer is going beyond the kind of co-development happening in most other pharmaceutical companies right now.

Cooper: The structured co-development relationship emerged some six years ago, and was developed from an evolving relationship that had its roots some 15 to 20 years ago when we had more of a sharp interface between what had historically been considered to be two discreet functions. Just recently, the latest evolution in co-development adjusted the critical interface again and now we have a single team approach to technology development — through co-development. The result is a very smooth transition from R&D through commercial with no real handoffs and no sharp interfaces.

Norman Winskill and Kelvin Cooper, representing the strong partnership between Pfizer manufacturing and development.

Q Pfizer has been an active participant in the FDA's QbD pilot program with the first approval in that program. How does QbD fit into the future of pharmaceutical development and manufacturing?

Winskill: It's true that Pfizer has been very active in the area of Quality by Design. In fact, we had two out of the original nine applications in the pilot program, including the first approval in the program. We learned a great deal about our readiness and expectations on the part of the FDA from this pilot, and Pfizer shared its experiences extensively at AAPS, PhRMA, PDA, and ISPE meetings and other industry forums. Our second pilot program, demonstrating continuous improvement with lessons learned from the first, went even smoother. There is still a lot more to learn.

The industry is under enormous pressures, including cost control and product development. Trying to develop increasingly complicated technologies with fewer resources than were available in the past is a challenge. Within our co-development process, we started exploring how best to do more with less, and out of these efforts came our Right First Time (RFT) program, our terminology for Six Sigma. This evolved into QbD, something we were already partially doing when we learned of the FDA's intentions. We were quick to embrace the pilot program because of our long established co-development process. A QbD submission is now the standard for all new drug products in the Pfizer R&D pipeline. The application of QbD at Pfizer is a scientifically grounded, prospective, and risk oriented approach to development and we believe it will improve the understanding of our products and the processes that produce them and lead to increased innovation.

QbD has great potential benefits to the industry, and the FDA deserves enormous credit for its bold steps in this area and its willingness to share perspectives and feedback. Through the efforts of Dr. Janet Woodcock, Helen Winkle, Moheb Nasr, Joe Famulare, and others at the FDA, QbD is evolving in ways where the industry is able to learn how to implement the concept on a practical basis. It helps pharmaceutical companies focus on more critical, promising prod-

ucts and process areas. This will only become more important as pressures on the industry remain or increase over time. We greatly appreciate that EU and Japan regulators are actively engaged in the building and content of this program, people like Emer Cooke, Jean-Louis Robert, Jacques Morenas, and Yukio Hiyama. And we are hopeful that industry and regulators from emerging markets will participate in the near future.

Cooper: Our participation in the FDA QbD pilots was extremely useful for Pfizer, and demonstrated the potential to achieve much greater control and understanding about the process, which in turn ensures quality and enables greater flexibility.

The insights gained during the varenicline pilot, to give one example, enabled us to respond quickly and expertly when commercial demands far exceeded expectation. Because our response capability was already within our design space and our quality control parameters, we were confident we could increase volume very quickly and change things around as needed to meet the market demand. Measuring it another way, that quick response translated to somewhere in the area of a million patients getting on varenicline – without QbD and continuous improvement built on QbD (i.e., the old way) we'd have been stocked out within probably a month.

This benchmark collaboration between the FDA and industry has been very useful in taking the industry forward; it's my understanding that these QbD pilot programs are being used as templates for other pharmaceutical companies.

Q Are you familiar with ISPE's Product Quality Lifecycle Initiative (PQLI)? What role do you see this initiative playing in the future of pharmaceutical development and manufacturing?

Winskill: Yes, PQLI is an important program providing practical, consistent advice to companies trying to implement ICH guidance. Companies interpret guidance in different ways, leading to inconsistencies, confusion, and delays. PQLI aims to eliminate this confusion, thus leading to more rapid adoption.

Pfizer has been very active from the beginning with ISPE's PQLI initiative and our support is consistent with our desire to have global industry and regulatory discussions on best practices for implementing concepts of ICH Q8, Q9, and Q10. ISPE's strong reputation as a global educational and professional development organization makes the group ideally suited to run the PQLI program, and we think this initiative will play an important role in manufacturing and development in the future.

PQLI is a limited duration program, slated to run about five years. Hopefully, the guidelines it is helping to get implemented will become part of the industry's daily modus operandi. If successful, the ICH guidelines that underpin PQLI will be used more regularly and consistently in both development and manufacturing. PQLI also has been very successful assuring a global perspective on QbD.

Cooper: We've been very active in PQLI from the beginning — Pfizer colleagues serve on a number of teams, including quality, design space, criticality, legacy products, and control strategy, as well as on the steering committee. It's an important initiative that to a great degree is made possible by the support and collaboration of both the industry and regulators.

Q With cost pressures and the trend toward more outsourcing, how will Pfizer manage supply chain integrity and assure high product quality?

Winskill: We get asked this question a lot these days. The answer is "with care," as we always have done. The factors that affect Pfizer's decision to outsource include: sourcing flexibility, competitiveness, need for special technology, cost control, and site divestitures. However, whether we produce internally or outsource, a secure supply chain is paramount in protecting the patients who use Pfizer products.

There are several considerations in order to qualify a supplier for the intended purpose. Once a working relationship is established, many ongoing issues need to be addressed, including quality of product and services, practices, safety, regulatory compliance, reports, and metrics. Special considerations when working with suppliers in emerging markets include, first and foremost, product integrity and safety. Any potential supplier is evaluated on its ability to produce material in a manner that is fully compliant with all regulatory procedures. Pfizer has taken steps to educate, evaluate, and essentially, enforce appropriate quality standards with suppliers in emerging markets.

We partner with companies in low cost locations as needed. If there are issues, we will try to resolve them to our satisfaction. If necessary, we will walk away. It's important that we hold external members of our supply network to Pfizer's stringent standards. This is somewhat different from some companies who may still purchase from low cost locations, often from a broker, without much knowledge of the supplier's manufacturing conditions.

Cooper: Quality is number one here and dominates our processes both internal and external. We have a very, very strong internal quality system that includes extensive oversight of the supply chain whether it is Pfizer owned or not. Every partner that we consider working with goes through rigorous quality, scientific, financial, EHS, work practice, and related audits and must meet and work within Pfizer standards.

We're actually helping some external suppliers get into QbD via a sort of mentoring process. Suppliers that embrace QbD should have a competitive advantage in our industry in the future.

Q What are the new manufacturing technologies that will change the way pharmaceutical manufacturing is done from today?

Winskill: I'd prefer to answer the question in a broader context: 'How will pharmaceutical manufacturing

differ in the future?' I say this because there is more than just a technology difference involved; it is really a mindset change. In the past, our industry was largely compliance based. We internally benchmarked ourselves year on year, and considered that good enough. The industry was not prepared to push the envelope to find a better way of managing manufacturing and regulatory issues.

This is all changing rapidly with a number of factors leading to a significant increase in cost pressures. Almost every company in the industry has a need to be more competitive. The industry can learn a lot from other industries where cost has been an issue for many years. For example, companies like Pfizer are already looking sideways to see how cost-sensitive industries such as food or chemicals, for example, view production issues. True, technology is a part of it, but other factors are important.

Today, Pfizer is benchmarking other industries, looking at best practices from a variety of fields. We are already well known for our PAT program; the fact is that many of our PAT applications were "borrowed" from other industries. As the industry's mindset changes, it will free up pharmaceutical companies to more boldly explore novel technologies and approaches like PAT, continuous processing, biocatalysis, and advanced process control systems. In the immediate future, the industry will be leaner, more agile, and certainly greener. The past mindset was to hide behind the regulators… 'They won't allow us to do this, so we won't ask.' Today, the industry is open to other ideas for moving forward.

Cooper: We are seeing a big trend away from just tablets and capsules as a way to present medicines and toward biologics in different delivery systems, more devices, and the potential to get into combination therapies. In addition, changes in technology will be enabled as a result of our investments in QbD. Understanding the design space in which you can operate makes it possible to start to build continuous manufacturing which allows you to completely change the way you manage manufacturing, and to do so with absolute confidence in quality and your ability to respond efficiently and effectively to market demand. The environmental benefits also will be significant; imagine the plant of the future as smaller and 'greener,' with fewer emissions, better energy utilization, less waste, and a correspondingly smaller footprint.

Q Six-sigma, Lean, and similar approaches have been strongly endorsed across the industry. How are they managed through the development to manufacturing continuum?

Winskill: Pfizer's co-development process is an ideal framework to assure our lean approaches and continuous improvement efforts can be carried out across a product's lifecycle, starting at the pre-filing stage while the compound is still under development. This builds a foundation for lifecycle feedback and continuous improvement that offers great benefits.

Several years ago we formally incorporated Right First Time (RFT) into the co-development process and created a jointly staffed RFT Program Office to incorporate Six Sigma and lean concepts into new products. This established a sound scientific basis for future continuous improvement throughout the lifecycle of a product. The boundaries between our WWPS and PGM organizations continue to blur, allowing us to more effectively manage company initiatives from development through manufacturing.

Cooper: RFT can be looked at as a structured risk assessment program that looks at the entire development/manufacturing process and devises strategies to minimize and mitigate risks. In PharmSci, we have invested heavily in a science of scale approach that aligns very well with RFT, thereby informing and bolstering a lean approach to understanding and applying the science involved.

Q How is Pfizer building a culture of continuous improvement? Can you provide some specific examples?

Winskill: When it comes to impact on culture, the most significant thing we have done is to recognize that to change the culture we had to get everyone in the organization to speak the same language, to understand the tools and how to use them. So training plays a huge part in culture change at Pfizer.

We have three levels of training in continuous improvement: Yellow, Green, and Black Belt. Our goal was to have 100% of PGM colleagues trained in Yellow Belt by 2008; 5% in Green Belt, and 1% in Black Belt. We are on target to reach this objective. Within R&D, more than half of the colleagues will be formally trained by year-end.

Of course, it's not enough to have our colleagues onboard solely through training. We stress that continuous improvement is everyone's responsibility, not just a select few. This inclusive spirit has resulted in thousands of successful projects (on average we complete more than one Green Belt or Black Belt project and countless Yellow Belt projects every day of the year) and the business benefits from the resulting savings.

There is broad-based management support within Pfizer for continuous improvement, evidenced by our reward and recognition program. We reward colleagues who use continuous improvement tools that make a real difference in how our business operates. And when quality or safety investigations are conducted, we expect colleagues to use the RFT tools and techniques.

About a year ago, Pfizer Inc. looked at PGM's program and decided to adopt continuous improvement as a company-wide strategy. They appointed John Scott as the Vice President in charge, the person who ran PGM's RFT initiative originally. Each part of Pfizer is now doing continuous improvement, though slightly differently to accommodate different business needs.

Cooper: Currently, we have nearly 100 continuous improvement programs going on at all levels across PharmSci. Yellow belt colleagues are encouraged

to apply that training to a specific project to demonstrate a good return on investment — such as cycle time reduction, eliminating several wasteful steps, all which contribute to driving the cost of the process down — and they are rewarded for doing so. The results have been impressive. The ultimate goal is not just to save time or eliminate steps, but for colleagues to be fully engaged in what they know best and to understand and evaluate the overall processes, and as appropriate, to suggest those changes that will achieve an optimum balance of effectiveness and efficiency.

One example that comes to mind is a project at our (Chesterfield, MO) biologics pilot plant to reduce cycle times and increase throughput for the manufacture of monoclonal antibodies (mAB)—the active ingredient in some biotherepeutics. This Black Belt project will increase our internal manufacturing capacity and save an estimated annual cost of $8 million due to decreased outsourcing expenditures.

Q Can you tell us about the Green Chemistry program at Pfizer and why Pfizer decided to implement such a program?

Winskill: Pfizer has been interested in Green Chemistry for a long time. About six years ago, we formally declared that it was the morally and socially responsible thing to preserve resources to the best of the company's ability. I can say confidently that we all feel that green initiatives are the right thing to do for the planet and the life on it. What is interesting is that initially the program was about minimizing resources. As we started to work on the details of Green Chemistry, Pfizer saw that there were important economic benefits as well. That fact alone will be helpful in getting Green Chemistry more widely adopted throughout the industry.

Cooper: Green chemistry is the design of efficient chemical processes that reduce energy use and reduce or eliminate the use of hazardous substances, reduce the use of solvents. Minimizing our environmental impact is key to Pfizer's mission of creating a healthier world. We have always committed to this concept and in 2006, we decided to further elevate our commitment organizationally. Pfizer appointed a green chemistry leader, Peter Dunn, who in turn created a cross divisional steering committee that integrates Green Chemistry into our research, development, and manufacturing organizations; is active in community and educational initiatives, including green chemistry education at high schools and colleges, and has established green chemistry awards within Pfizer.

In addition, we have received recognition for our environmental initiatives and accomplishments from organizations, including the U.S. Environmental Protection Agency. In 2002, Pfizer took first place in the EPA's Presidential Green Chemistry Challenge. In 2003, we were awarded the Crystal Faraday Award, and in 2006, we received the Astra Zeneca Award for Excellence in Green Chemistry.

Career Paths in Development and Manufacturing

Q What led you into or sparked your interest in a career in pharmaceutical manufacturing?

Winskill: What attracted me to Pfizer was the science. I was doing my PhD in the United Kingdom when I saw an ad for a company I had never heard of. I applied and joined Pfizer for a job co-located at their manufacturing site in Sandwich. That was 33 years ago.

Though I was involved in R&D, I got to work very closely with the manufacturing team. I spent eight years there and took various jobs shuffling back and forth between manufacturing and R&D. What finally drew me to stay with manufacturing was the realization that the manufacturing environment had very unique challenges, which were equally stimulating as those in research. But the big advantage was that the time frames were much smaller. I could see a tangible impact of my work whereas in the field of research you can work all your life and not work on a product that makes it to the marketplace.

Cooper: I never set out to be in pharmaceutical sciences or manufacturing; it kind of evolved with my career. I started with Pfizer as a discovery chemist trying to identify new medicines. As I attained leadership positions in that role, I got interested in the development phases for a medicine, which then got me interested in pharmaceutical sciences.

At the time of the Pfizer Warner-Lambert merger, I was asked if I would like to create the Pharmaceutical Sciences organization within Pfizer. I have been with Pfizer 27 years and in my current role for almost eight years. I have a PhD in organic chemistry, and started my career at Wellcome.

Q What kind of training and experience best prepared you for your current position?

Winskill: My experience in the R&D environment definitely helps me to better evaluate and understand science and technology. Also, I have had the opportunity to work on Animal Health, Chemicals, and Consumer Health products within Pfizer – all very cost-sensitive areas of the business. This is proving invaluable considering the direction in which the pharmaceutical business is now headed.

Cooper: What most prepared me for my current position were my chemistry education, essential in a chemistry-based organization such as PharmSci, and the training and development that I was privy to at Pfizer. For example, just learning the discovery and drug development business over the years has been an amazing experience.

Q What significant changes have you seen in manufacturing and what changes do you anticipate in the next few years?

Winskill: In 33 years, I've seen some key shifts in manufacturing. I remember a period of expansion when cost pressures were minimal and the emphasis was essentially on supply and

quality. This has changed and the industry is more competitive now. We need to get much closer to our customers and to be more agile in our responses. I envision this trend continuing, and in fact, increasing. Another feature of pharmaceutical manufacturing that is changing is the movement away from traditional products – like tablets, capsules, and small molecule APIs. In five years time, the industry will manage more complex technologies, more diversity of delivery systems, and more biological products.

Cooper: The changes I've seen in my 35 years in this industry have been absolutely incredible in terms of the science and technology now available. We are now gaining a good fundamental understanding of the science of formulation, a huge advance that brings us all the way back to science of scale and QbD again. Some of the science changes have been equally dramatic... going from simple tablets and capsules to much more complex medicines, and now all the way to the potential for stem cell therapies. The science of manufacturing stem cells under the rigorous quality standards Pfizer maintains is certainly a big challenge to think through.

Q What are some of the challenges you are currently dealing with in manufacturing?

Winskill: There are a great deal of challenges in this field today, including cost pressure, excess capacity, loss of exclusivity, pipeline issues, the exiting of some sites, and maintaining morale and motivation in the midst of it all. How to balance all this is a major issue. What will separate Pfizer from the rest is how we handle it.

Cooper: The business and financial challenges we are experiencing are similar to those being experienced across the industry. As demand for more complex medicines drives the cost of manufacturing up, there is pressure to cut costs to remain competitive. New kinds of therapies are emerging that present technical challenges; iRNA is just one example. We can design molecules that interfere with RNA, the protein synthesis machinery of the cell, but we cannot deliver these innovative new therapies using any of the conventional delivery systems at the present time. What will distinguish Pfizer is its pursuit of such innovative therapies, and as it has demonstrated throughout its history, where others see challenges, Pfizer envisions solutions.

PE would like to thank Jim Spavins for his contributions to the development of this interview.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2008, Vol. 28 No. 5

How to Make a Perforated Pan PAT-Compliant

by Davide Manca, Caterina Funaro, Fiorenzo Cembali, Giusi Mondelli, Giorgio Tarozzi, and PierAntonio Ragazzini

This article describes a PAT-approach to the coating process performed in a perforated pan. The main topics include process understanding, Quality by Design, and process regulation and control.

Introduction

Process Analytical Technology or PAT, is a set of systems for the analysis and control of manufacturing processes based on the measurement of critical quality parameters and the performance attributes of raw materials and in-process products to assure an acceptable end-product quality.[2] The PAT initiative promotes the process knowledge and understanding to integrate new manufacturing technologies into pharmaceutical production.[5] As reported by the FDA (2004) "the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner." Several current and new tools enable scientific, risk managed pharmaceutical development, manufacture, and quality assurance. Quoting from the FDA: "these tools, when used within a system can provide effective and efficient means for acquiring information to facilitate process understanding, develop risk-mitigation strategies, achieve continuous improvement, and share information and knowledge. A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process." As a result, it is possible to reduce production cycle times by using on-, in-, and/or at-line measurements and controls. It also is possible to prevent rejects, scrap, and re-processing, while achieving the so-called real time release. Process automation allows improved operator safety, while reducing human error.

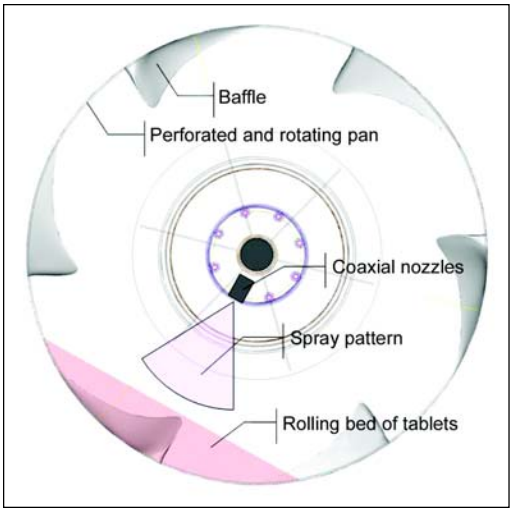


Figure 1. Frontal view of a perforated pan.

This article focuses on a perforated pan and on the effort played by the authors to move both equipment manufacturing and process operation from well-established and conventional knowledge toward the PAT-approach. This mindset change is not chosen, adopted, and covered because it is fashionable, but because it represents a challenge to uphold the current technological gap with competitors, while increasing the understanding of the process. This last point is of paramount importance for process management because working with a PAT compliant approach to process operation allows replacing the static and rigid approach utilized by conventional recipes to embrace an advanced process control that through measurement, process knowledge, and regulation of operating conditions permits achieving the real time release.

The PAT initiative attempts to move pharmaceutical manufacturing from a recipe driven approach toward a process control methodology. The process should not be managed according to a pre-established recipe, but instead a "measure and control" system should follow an optimal process trajectory. By doing so, the end-point problem would be upset. On one hand, the recipe assigns a predefined time bucket for every production stage of the pharmaceutical process; on the other hand, the "measure and control" system follows a completely different approach based

on product quality achievement. Once the process is thoroughly understood, the equipment is designed according to production demands, and a dedicated control system is setup, it is eventually possible to make the process follow an optimal process trajectory. By doing so, the end-point problem is automatically solved and production time is optimized against the external disturbances that make the process deviate from the design conditions.

Before addressing the model and control of the coating process, it is necessary to understand in-depth how a perforated pan works and what are the most important parameters that influence its operation.

Understanding the Perforated Pan

A perforated pan coater consists of a horizontal cylindrical drum that rotates around its axis - *Figure 1*. The tablets are loaded into the pan and the basket containing the tablets is perforated with holes smaller in dimension than the tablet in order to avoid any loss of cores.

Once the pan is loaded, the basket begins to rotate and a flow of hot, dry air passes through the perforated basket and the rolling bed of tablets. The metal basket comprises some baffles that increase the mixing of the tablets within the rolling bed. A number of nozzles spray a liquid solution of polymer and solvent (usually water) to the surface of the tablets. The air flowrate dries the wet tablets and an increasing polymer thickness covers the cores. Once the optimal coating thickness and the residual moisture content meet the process specifications, the coating process stops and the tablets are unloaded.

Several parameters condition the coating process. Three distinct categories can be identified: the design specification, the static process conditions, and the dynamic process variables. Some examples for each category are:

- design specifications: drum diameter, drum depth, number and geometry of the mixing baffles, number, pitch, and distance of the holes, geometry of air inlet and outlet ducts and their relative positions in respect to the drum
- static process conditions: number of nozzles, pan load (i.e., amount of tablets loaded), polymer/solvent ratio
- dynamic process variables: inlet air flowrate, inlet air temperature and moisture, pan speed, solution spray rate, nozzle patterns and operating pressure, nozzle angles and distance from the tablet bed (the dynamic angle of repose [i.e., the angle formed by the tablet bed in respect to a horizontal plane when the pan is rotating] changes with the pan speed).

Nominal size [l]	200
Min/Max pan capacity [l]	50-200
Pan diameter [mm]	1330
Pan engine power [kW]	4
Maximum air flowrate [m^3/h]	4000

Table A. Technical data of the perforated pan.

The geometrical dimensions and layout of the pan coater are of paramount importance in the scale-up of the process units. A deep understanding of the physical phenomena involved in tablet coating can be of real help in the design and scale-up of industrial units.

Static process conditions are adjustable parameters that must be set before the coating starts. A deep understanding of their action may significantly influence the quality and yield of the final product. Usually, it is up to the coating supervisor to assign these parameters as input data for the process recipe. Once again, a shared and validated knowledge of the impact of these parameters on the product quality helps in configuring the pan coater, while avoiding any misinterpretations by the operator.

The dynamic process variables allow the regulating and controlling of the coating process according to the product quality specifications. Instead of blindly implementing a predefined and static recipe, it is possible to configure a control system capable of driving the process through an optimal operative trajectory. The optimal product quality can be accomplished by continuously changing the operating conditions, while complying with the process constraints. The implementation of a control system permits attaining the product specifications, independently of the external disturbances that invalidate any predefined recipes.

Some Words about the Coating Process

Table A reports the technical and geometrical data of an industrial perforated pan.

We assume a partial load of the pan in terms of 100 kg of placebo tablets. The tablets are round, have a diameter of 11 mm, and each weigh 350 mg. The apparent tablet density (bulk density) is 800 kg/m^3. Consequently, the tablets take up a volume of 125 l, which is about 63% of the nominal pan size.

The mean coating weight increment is 4% in respect to the uncoated tablets. Since we have 100 kg of uncoated tablets, the solid coating weighs 4 kg. The sprayed suspension of polymer and excipients in water is 20% on a weight basis. Consequently, the liquid solution weighs 20 kg (16 kg of water and 4 kg of solids). The spraying period takes about one hour, and according to the pan speed (usually 6 to 10 rpm), the sprayed flowrate is 250 to 350 ml/min.

Figure 2 shows the spray guns. Usually, for a 100 kg batch, there are four nozzles, which are aligned with the drum axis. The bore diameter for each nozzle is 1.2 mm, and the atomization air pressure is 1.5 to 2.0 bar. The distance between the

Total number of tablets	285,714
Droplet mean volume [m^3]	6.37063E-15
Mean flight time [s]	0.013
Total number of sprayed droplets	3.139409E+12
Number of droplets sprayed in 1 s	872,057,988
Total number of droplets sprayed on a tablet	10,987,931
Number of droplets sprayed on a tablet in 1 s	3,052

Table B. Mean operating data of a pan coater based on 100 kg tablets load.

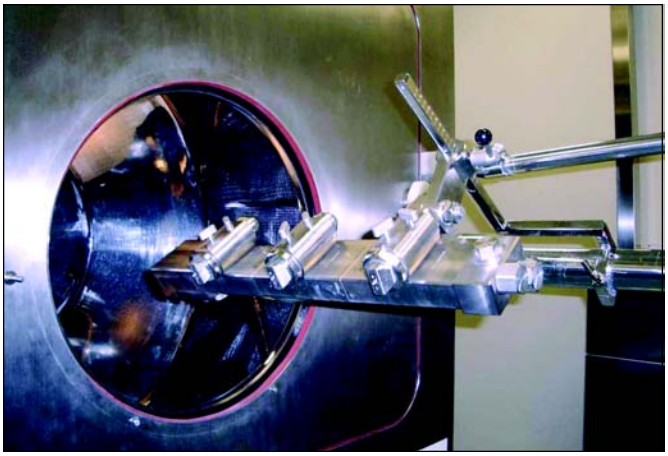


Figure 2. Spray guns applied on the perforated pan.

nozzle and the rolling bed is about 200 mm according to the pan load and this gives rise to a spray breadth of about 160 mm. The nozzle manufacturer performed a number of experiments to measure the spray pattern as well as the mean diameter and velocity of the droplets.

Typical droplet diameters are 18 to 28 mm and droplet velocities are 7 to 24 m/s according to the emission angle of the droplet in respect to the nozzle axis. Based on these mean data, it is straightforward to compute the average operating values reported in Table B.

The droplet mean volume (in the order of picoliters) and the number of sprayed droplets (teradrops, i.e., thousands of billions of drops) are quite impressive values. It also is amazing the average number of droplets that hit a tablet in only one second (some thousands). Actually, the coating process is even more complex.

Spray Pattern and Droplet Drying

As per the aforementioned, a nozzle sprays an endless number of droplets through its bore. Two streams of compressed air separately feed the spray gun. The former atomizes the sprayed liquid; the latter moulds the spray and is called *pattern air*. Usually, the flowrate and pressure of the atomization air are larger than those of the pattern air. The pattern air drives the sprayed droplets toward the rolling tablets and avoids any losses on the pan walls. As reported in Table B, the flight time of a droplet is quite short. During its flight, the droplet dries due to evaporation. While it flies in an almost straight line (gravity does not play a significant role due to the high initial velocity and short flight distance), the droplet crosses a hot and parallel airflow. The hot air flowrate plays a dual role: it partially dries the flying droplets and the sprayed tablets within the rolling bed. Its velocity is significantly lower than the sprayed droplets. While the droplet decreases its water content, the exsiccating air increases its moisture content. The droplet does not evaporate completely, but a certain amount of water is still present when it impinges the tablet surface. This water content is of paramount importance for the coating process. Actually, if the droplet has excessive water content then the tablet gets soaked and this may compromise its integrity and that of the active principle. Conversely, if the droplet is too dry then it does not stick on the tablet surface and the coating turns into dust that is lost through the perforated cylinder. Consequently, there is an optimal operating range for the hot air flowrate and its inlet moisture content.[14] Due to the spray breadth and the different flight times (as a function of the launch angle in respect to the normal bore direction), it is possible to adjust the pattern air pressure to either narrow or widen the spray pattern in order to achieve a convenient final distribution of the droplet diameters (i.e., droplet moisture).

The Moisture Balance

With reference to the perforated pan, it is possible to write an overall dynamic balance for the process water. The main reason for this water mass balance is sketching out the process moisture content. Actually, the main task of a perforated pan is producing tablets with optimal coating thickness and uniformity, and optimal moisture content. Usually, the coating thickness and uniformity are measured at-line by an operator who, at predefined time intervals, weighs a certain number of tablets withdrawn from the rotating basket, and visually checks the surface for irregularities. The moisture content of the coated tablets is more difficult and expensive to measure (in terms of required time). It is usually performed afterward, in a laboratory, by measuring the moisture fraction of a number of tablets whose coating has been scratched out in advance. These tablets are withdrawn from the pan at predefined time-intervals. Consequently, the dynamics of the tablet moisture content may only be determined at the end of the coating process. This measure is not desirable from an on-line point of view. It is used only to verify *a posteriori* the product specifications. Conversely, if the tablet coating moisture was measured on-line and in real time, it could be used to identify the end-point condition.

Figure 3 shows the experimental set-up, which helps to conclude the moisture content of the tablets. If one measures the inlet and outlet water factors, it is possible to write a rather simple dynamic mass balance for the water crossing the perforated pan. We have to evaluate four quantities.

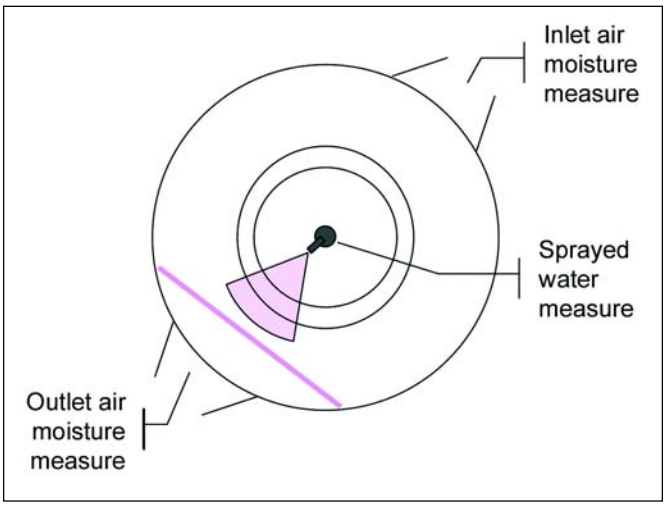


Figure 3. Simplified experimental setup for measuring the moisture content in the perforated pan.

Two are relative to the moisture content of the inlet and outlet air flowrates ($\rho_w^{in} x_w^{in} Q_a^{in}$ and $\rho_w^{out} x_w^{out} Q_a^{out}$). The third quantity is the inlet water flowrate sprayed by the nozzles on the tablet bed ($\omega_w^{spray} W_{sol}^{spray}$). The fourth is the moisture content of the atomization and pattern air flowrates to the nozzles.

The overall water mass balance is: $\frac{dM_w^{pan}}{dt} =$

$$\rho_w^{in} x_w^{in} Q_a^{in} - \rho_w^{out} x_w^{out} Q_a^{out} + \omega_w^{spray} W_{sol}^{spray} + \rho_w^{nozzle} x_w^{nozzle} (Q_a^{pattern} + Q_a^{atom})$$

where M_w^{pan} is the total water amount inside the perforated pan. More specifically, we can assume that $M_w^{pan} = M_w^{tab}$, *i.e.,* the water amount inside the pan moistens the tablets.

This hypothesis is reasonable since the vapor condensates neither on the rotating basket nor on the outlet metallic duct. Moreover, the spray guns control the pattern in order to avoid any droplets spraying on the pan walls. Therefore, it is sufficient to add two moisture probes to the inlet and outlet hot air ducts since the inlet sprayed solution is measured either volumetrically (peristaltic pump) or massively (dedicated flowmeter). The water fraction in the sprayed solution is constant as the polymer solution is continuously stirred. The same can be said for the compressed air fed to the nozzles. Finally, the remaining overall water mass allows the estimation of the mean moisture content of the tablets. This estimated measure is almost instantaneous as the moisture probes and the flowmeter give a quick response. Therefore, it is possible to speak of a soft-sensor determined according to the PAT directives. The mean moisture content of the tablet bed is of paramount importance since it allows the identification of the end-point condition of the coating process. It also can be used for on-line control of the coating process. Let us suppose that a parametric design of experiments has identified an optimal exsiccation trajectory, which is a compromise between tablets that are either too wet or too dry (to preserve both mechanical integrity of tablets and active principle degradation.)[11,15] The on-line controller, based on the tablet moisture soft sensor, will regulate the operation of the coating process (e.g., inlet air flowrate and temperature, sprayed flowrate, pan speed) to follow the process optimal trajectory. It is worth mentioning that once the spraying is over the coating process proceeds with the exsiccation stage where the hot air stream reduces further the tablet moisture to the desired value. In this case, as well, we have an optimal trajectory problem where the end-point time is unknown and varies from batch to batch along with the spray features and history. In reality, very often, the coating process is managed in a more conventional way where the recipe dictates its aprioristic rules. Actually, the exsiccation period is assigned *a priori* and is kept constant, but this approach does not match the PAT methodology that supports the trajectory tracking and end-point achievement.

Tablets Trajectory

The homogeneous mixing of tablets during the coating process is a prerequisite for good coating uniformity. This feature is significantly influenced by pan speed, spray rate, inlet air temperature and flowrate, tablet shape, and baffle geometry.[1,3,8,10] Therefore, understanding the tablet motion in a perforated pan may lead to an improved coating process.

As reported, several attempts were made to understand and record particle motion using a variety of particle tracking techniques, such as video imaging, particle imaging velocimetry, positron emission, and photometry.[9,12,13] Leaver showed that the surface time (the time that the tablet spends on the surface of the bed) is directly related to the pan speed and load.[4] In contrast, the circulation time distribution is only affected by the pan design and mainly by the baffles presence/absence. Wilson and Crossman showed that coating uniformity increases with pan speed.[16]

According to Mehta, the optimization of pan coating operations may involve more than 20 design and process variables.[6] This set of variables would require a too demanding experimental effort. This is one of the reasons for simulating the motion of particles in the pan and to develop models to simulate the coating dynamics. Turton and coauthors discussed extensively the tablet kinematics in a pan-coating device,[7,9,12] using an imaging technique to sample in real-time the tablet motion. A few variables give an overall picture of the tablet kinematics: the time spent by a tablet in the bulk of the bed also called circulation time (t_{circ}), the time spent on the surface of the bed (t_{surf}), the projected area exposed to the spray (A_{proj}), and the surface velocity (v_{surf}). Actually, the tablet surfs and rolls on the bed surface for short times, while it travels and shuffles in the bed bulk for longer times. When the tablet floats on the bed surface, it receives the droplets sprayed by the nozzles. Since the tablet rolls and tumbles, the area exposed to the jet stream keeps on changing in a random way.

With reference to the circulation time (t_{circ}), the experiments showed that:

- There is a decrease in t_{circ} as the pan speed increases (since the tablet residence time inside the bed decreases when the pan rotates more rapidly).
- Under the same operating conditions (*i.e.,* pan speed and load), larger tablets are characterized by lower t_{circ}.
- t_{circ} increases with the pan load (the more the tablets, the higher the residence time inside the bed. This is due to the fact that, when the pan load is higher, the bed is thicker and the tablets have to cross a larger volume).
- The baffles promote the tablet motion and reduce the dead zones. As a consequence, the coating uniformity is promoted by baffles and t_{circ} is slightly reduced.

With reference to the surface time (t_{surf}), the experiments showed that:

- t_{surf} decreases when the pan speed increases
- t_{surf} decreases when the pan load increases
- The influence of the tablet dimensions on t_{surf} is negligible.

With reference to the projected surface area (A_{proj}), the experiments showed that:

- A_{proj} decreases when the pan speed increases
- A_{proj} increases with the dimensions of the tablet

Finally, with reference to the tablet surface velocity, Sandadi showed that its horizontal component has a null mean value due to the random collisions among tablets.[12] Conversely, the vertical component of the surface velocity (v_Y^{surf}) has a gaussian-like distribution, whose mean value is positive (in the downhill direction). Turton and coworkers (2004) observed that this component increases with the pan load. This is due to the direct proportionality between the pan load and the wall-tablet friction (the friction term increases the dynamic angle of repose of the rolling tablets).[4,7] Consequently, the higher slope of the bed surface makes the tablets move at a higher velocity. This point also explains the reduction of t_{surf} when the pan load increases. On the other hand, v_Y^{surf} is rather independent of the tablet dimensions.

Mueller and Kleinebudde (2007) showed that the peripheral pan speed is not a valid scale-up criterion for design purposes.[7] Actually, the most important parameter is the surface time, which measures the amount of sprayed solution received, while the tablet moves inside the pan. As previously shown, there is a direct dependency between t_{surf} and v_Y^{surf}. Mueller and Kleinebudde showed that, under constant pan loads and peripheral pan speeds, the tablet surface velocity is not constant, but may change significantly.[7] They proposed a scale-up parameter (ξ_{pan}) that allows for the determination of the surface velocity when passing from lab-scale to pilot-scale and even to an industrial-scale pan:

$$v_{pan_2} = \xi_{pan} \sqrt[3]{\frac{d_2}{d_1}}\, v_{pan_1}$$

where d is the diameter of the basket, and ξ_{pan} may be determined by measuring the main process variables.

All these considerations delineate the complex world of pan coating: a non-linear sum of effects, conditions, and parameters that is necessary to account for and to understand deeply the process sensitivity before addressing the regulation and control themes.

Control Framework

This section is devoted to the analysis of the regulation and control of the coating process inside a perforated pan. Before addressing individually the control topics, we would like to set clearly the boundary line between regulation and control.

The term regulation means the modification and adjustment of a process variable by means of another process variable. This adjustment is based on a recipe, which is assigned *a priori*. An example follows: when the pan speed increases from 6 to 8 rpm then the spray rate is increased from 300 to 350 ml/min. This regulation is performed independently of the real process conditions that should account for the disturbances either measurable or immeasurable. As far as the regulation is concerned, we do not assign any setpoints, we do not define any controlled variables, we neither setup nor configure any control loops, and we do not even define any pairings among manipulated and controlled variables. Actually, we have only some rules that are dictated by the recipe. When these rules are implemented, the regulator adjusts the manipulated variables to the new recipe settings (this also is known as actuator device).

On the other hand, the classical term for control refers to the pairing existing between manipulated and controlled variables. The operator assigns a setpoint value to the controlled variable and the controller adjusts the manipulated variable accordingly in order to avoid possible offsets produced either by external disturbances or by process variability.

Process Regulation in a Perforated Pan

With reference to a typical pharmaceutical recipe, we can say that the coating process is usually split into a few time buckets where the manipulated variables are kept constant. These variables change value at the end of every time bucket. Consequently, we have the typical step-like dynamics that contributes to process discontinuities. An example is given by the pan speed that, according to the recipe, is usually adjusted three times by predefined increments. Instead of step-changing the process variables, we suggest adopting a smoother approach to process regulation. The step function that describes the dynamics of a manipulated variable can be substituted by a continuous interpolating function, which is a sounder approach to process stability. A cubic spline interpolation is a good compromise between simplicity and flexibility without compromising the process robustness. To preserve the same impact of the manipulated variable on the process dynamics, it is possible to assume the conservation of its integral action.

With reference to the perforated pan, the main manipulated variables that are usually adjusted at predefined time intervals are the pan speed (ω_{pan}), the sprayed flowrate (Q_{spray}), the inlet hot air temperature (T_a^{in}), and seldom the angle of the spray gun in respect to the bed tablets (φ_{spray}). To acutely understand the regulation and control framework, it is necessary to give a short explanation of the role played by these manipulated variables. There is a direct proportionality between the pan speed and the degree of mixing required of the tablets within the bed. We have already reported that an increase in the pan speed means a decrease of time spent by the tablet inside the bed, and an increase of the number of sprayed droplets that collide with the tablet surface in the time unit. At early stages, when the tablet is still uncoated, the pan speed should not be excessive to avoid the tablet crumbling due to heavy mechanical friction. The coating, besides preserving the active principle from external agents, also enhances the mechanical strength of the tablet. Therefore, it is then possible to increase progressively the pan speed and the degree of mixing within the bed. This allows the increase of the spray flowrate while reducing the total processing time. Therefore, to support the increment of sprayed flowrate and coating moisture, it is recommended to increase the inlet air temperature. The dynamic angle of the tablet bed is a function of the pan speed. A clever operator adjusts the spray gun angle to keep the longitudinal spray axis perpen-

	Controlled variable	Manipulated variable
Loop #1	Bulk temperature of the tablets	Inlet air temperature
Loop #2	Moisture content of the tablets	Inlet air flowrate

Table C. Pairing between the manipulated and controlled variables of the control loops.

dicular to the tablet bed. According to these considerations, it is then possible to define the following hierarchical dependencies: $Q_{spray}(\omega_{pan}(t))$, $T_a^{in}(\omega_{pan}(t))$, and possibly $\varphi_{spray}(\omega_{pan}(t))$.

Conversely, the inlet air flowrate is kept constant to avoid the tablets sticking to the pan walls, due to the resistance exerted by the gas flowing through the perforated basket of the pan. Primarily, its value depends on the total tablet load and only secondarily on the sprayed flowrate.

Process Control in a Perforated Pan

From the aforementioned arguments, it might look as no more manipulated variables are available for control purposes. This is not true. In fact, it is possible to set-up a control loop for the bulk temperature of the tablet bed where the most suitable manipulated variable is the inlet air temperature. The reason for choosing the bed temperature as a controlled variable is the coating quality and integrity. Actually, if the bed temperature is too low then the tablets are too wet (even soaked) and they stick together. This phenomenon also is known as *twinning*. Conversely, if the bed temperature is too high, besides the danger of compromising the active principle, the coating uniformity decreases. For too high tablet temperatures, common phenomena are the so-called orange-peel effect as well as a manifest roughness of the coating (with chinks and polymer detaching).

When this control loop is implemented, the process operator assigns an optimal bulk temperature belonging to the interval between the lower and upper bounds that define the attainment of the process quality. It is quite easy to measure the bulk temperature of the tablet bed by means of either a thermocouple or a PT-100 probe. It is worth mentioning that, due to the size of the pan, the temperature probe does not affect significantly the bed flow and the mixing degree of the tablets.

To make the control framework more complex and flexible, it also is possible to use the inferred measure of the moisture content of the tablets. In this case, a possible manipulated variable is the inlet air flowrate. Formerly, we wrote that the process operator prefers to keep the inlet air flowrate constant. This happens because pharmaceutical processes are usually under-controlled and a number of process variables are kept constant to reduce both the degrees of freedom and complexity of the process. This is particularly true when the process is operated manually. Conversely, a robust control system allows the increase of the operative elements, while making the process more flexible and responsive. As a matter of fact, a new control loop, based on the mean moisture content of the tablets (controlled variable) and the inlet air flowrate (manipulated variable) may be implemented and coupled to the previous one (see Table C for more details on the variables pairing).

Conclusions

This article discussed the PAT approach to the coating process carried out in a perforated pan. In respect to the conventional process operation, which is based on the recipe paradigm, the PAT approach is a significant change to this well-established practice.

One of the main achievements is process understanding. This is the basis for further innovative procedures such as online process regulation and control. The optimal trajectory problem, disturbance rejection, and constrained processing are distinctive features of PAT. Actually, they are quite challenging for the pharmaceutical world, which is restrained by the inflexibility of the recipe paradigm. At the same time, the proposed PAT features open pharmaceutical manufactures to new frontiers and high quality control.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2008, Vol. 28 No. 5

Doxorubicin Loaded Contrast Agents for Ultrasound Triggered Drug Delivery: Importance of Process Parameters

by John Eisenbrey, Phyllis Huang, Michael Soulen, and Margaret Wheatley

This article discusses research contributing to the development of a drug delivery platform that has the potential to greatly reduce systemic toxicity commonly associated with chemotherapy, while increasing the concentration of the drug at a tumor site.

First presented by John Eisenbrey at the 2007 ISPE Delaware Valley Student Poster Competition, this research went on to win the Graduate Level award at the ISPE International Student Poster Competition in Las Vegas, NV later that year.

Introduction

Traditional chemotherapy relies on a systemic dosage of a highly toxic agent with hopes that a small proportion of the drug will be delivered to the actual site of need. This approach to cancer treatments has led to the well known debilitating side effects commonly associated with chemotherapy. Additionally, this approach leads to a relatively low therapeutic level at the actual tumor site, greatly reducing the potency of the drug. While this approach has had success with some forms of cancer, it has been woefully unsuccessful in the treatment of liver cancer. In 2006, roughly 1.3 million new cases of primary liver cancer were reported worldwide with a five year survival rate of 7%.[1] Two of the salient problems facing treatment of liver cancer are the low early detection rate and the inability to gauge tumor size,[2] both of which could be solved using a delivery platform capable of improving imaging contrast as well as delivering drug. Additionally, many other forms of more treatable cancer metastasize to the liver and become fatal.

Doxorubicin (Dox) is one of the few chemotherapeutics that has shown clinical efficacy against liver cancer.[3] However, its use brings with it severe side effects, including cardiotoxicity and congestive heart failure.[4,5] This effectiveness coupled with its systemic side effects makes it an ideal candidate for a targeted drug delivery platform. The proposed platform currently being developed in our lab uses ultrasound sensitive carriers injected intravenously, while ultrasound is being applied to a particular treatment area with the goal to provide a systemic dosage of carrier, but a localized delivery of chemotherapeutic drug.

Ultrasound has many advantages as an imaging modality because it is relatively inexpensive, portable, real time, uses non-ionizing radiation, and is readily available.[6] Ultrasound uses the transmission and reflection of generated pressure waves to create an image. Depending on insonation frequency and acoustic pressure, it can be focused on areas smaller than one cm^2 at any depth in the body.[7] Despite the technical advances within ultrasound,[8] the modality continues to have trouble distinguishing between healthy and diseased tissue, making cancer detection difficult.

These shortcomings in detection have given rise to development of ultrasound Contrast Agents (CA), which increase image contrast by upwards of 20 dB.[9] CA consist of a core microbubble (generally a non toxic, relatively inert gas such as air, sulfur hexafluoride of perfluorocarbon) stabilized with an outer shell. A CA must be intravenously injectable, stable enough to last the duration of the imaging session, non-toxic, non-carcinogenic, and smaller than 8 µm in order to freely pass through the capillary beds during circulation. These agents have been successfully synthesized from polymers, proteins, surfactants, and lipids.[10] It has been shown that ultrasound imaging has become sensitive enough to detect a single CA in circulation.[11] A method for producing hollow, stable, echogenic microbubbles from both poly lactic and poly lactic-co-glycolic acids has been developed in our lab, giving ultrasound en-

hancement of more than 20 dB both in vitro and in vivo.[12,13] These agents show a tight size distribution with a mean size of 1.23 +/- 0.62 µm. It also has been shown that these agents are completely biodegradable after use and break down due to hydrolysis.[14]

The development of CA for targeted drug delivery has progressed along two paths: the loading of drug onto and within the CA, and the addition of tumor specific ligands to the surface of the CA in order to provide a higher binding affinity of the agent to the area of need. While the majority of research in these areas has remained separate, the two approaches are expected to merge, eventually creating a CA with a high affinity to solid tumors that also can release chemotherapeutics when triggered with ultrasound.

Several labs have had success with adhesion of tumor specific ligands to the surface to CA. Poly-lactic-acid CA have been developed with the $\alpha_v\beta_3$ integrin specific Arg-Gly-Asp (RGD) ligand on the surface. These agents were shown to demonstrate a significantly greater affinity for cancer cells expressing the $\alpha_v\beta_3$ integrin than non-targeted CA.[15] Other groups have shown that targeting α_v-Integrins is a viable means for assessing angiogenesis using ultrasound.[16] Research such as this reinforces the importance of the CA drug delivery platform for use for both diagnosis and therapy.

Additionally, several labs have shown the potential for drug-loaded CA. Huang and MacDonald have shown that it is possible to encapsulate drugs within acoustically active liposomes.[17] Using calcein as a model, the group was able to achieve an encapsulation efficiency of roughly 14% without sacrificing ultrasound enhancement of the agent. In vitro, the agents showed a 60% release when insonated and almost no release when stirred in solution.[17] Pong et al. have shown that it is possible to use ultrasound to mediate leakage from large, acoustically sensitive phospholipid vesicles, again triggering high release amounts in vitro with low frequency ultrasound.[18] High-Intensity Focused Ultrasound (HIFU) has been used as a source of hyperthermia together with injected thermosensitive liposomes to enhance delivery and efficacy of doxorubicin in tumors.[19] It has been shown that HIFU can be used to induce tumor ablation through heating.[20] HIFU also has been used in conjunction with magnetic resonance imaging which is used for in situ target definition and identification of nearby healthy tissue that is to be spared.[21] In addition to the use of ultrasound to disrupt drug-loaded agents and for ablation, the use of the platform also may be beneficial due to the well documented effects of ultrasound with traditional systemic drug delivery. Ultrasound has been shown to lead to increased efficacy at the area of insonation through increased drug retention at the tumor site. Several studies have been done showing that systemic administration of doxorubicin combined with low intensity ultrasound (0.25-2 W.cm2) leads to increased drug efficacy.[22,23] These therapeutic benefits of ultrasound with chemotherapy become even more significant in the presence of CA. Higher intensity ultrasound can be used to rupture CA in circulation by inducing inertial or collapse cavitation.[24] This cavitation has been shown to result in higher membrane permeability, increasing drug uptake at the site of insonation.[25] Clearly, many advantages exist using a drug delivery platform of targeted, drug-loaded CA compared to traditional chemotherapy.

Several methods of loading Dox in PLA CA have been developed within our lab. Drug has successfully been loaded both on the surface and within the shell of these agents without sacrificing the acoustic performance of the original agent.[26] The successful synthesis of these agents has shown the feasibility of a drug delivery system using CA and resulted in several optimization studies. This paper will examine the optimization of one particular method, dry surface adsorption, in which Dox is applied to the surface of the CA after synthesis. Effects of temperature and adsorption time will be examined. Both in vivo and in vitro results are included showing the method's feasibility for both ultrasound enhancement and targeted drug delivery.

Materials

Poly-lactic-acid (PLA) (MW = 83 kDa) was purchased from Lakeshore Biomaterials. Poly (vinyl alcohol), 88% mole hydrolyzed, with a MW of 25 kDa, Dox, and camphor were purchased from Sigma-Aldrich. Ammonium carbonate was purchased from J.T. Baker. All other chemicals were reagent grade from Fisher Scientific.

Methods

Microbubble Preparation

PLA CA were prepared using a double emulsion method (W/O)/W developed in our lab.[12] Briefly, 0.5 g of PLA combined with 0.05 g of camphor were dissolved in 10 ml of methylene chloride. One ml of ammonium carbonate (4% w/v) was added and the mixture sonicated at 110 Watts for 30 seconds at three seconds on and one second off using a Misonix Inc. sonicator probe. After sonication, the resulting (W/O) emulsion was poured into 50 ml of 4°C, 5% polyvinyl alcohol within a 600 ml beaker and homogenized for five minutes at 9000 rpm. CA were then collected by centrifugation and washed with hexane. After hexane evaporation, the capsules were flash frozen and lyophilized for 48 hours. During this process, ammonium carbonate and camphor sublime out of the capsule, leaving a void in their place that later fills with air after being exposed to atmospheric pressure. All dry samples are then stored in a desicator at -20°C until used.

Drug Loading

Several methods for loading Dox onto the CA have been developed in our lab. For this study, we focus on adsorption, were Dox is adsorbed to the surface of pre- fabricated CA. An electrostatic attraction between the drug and polymer results in a strong adhesion between the two. One hundred mg of dry agent was added to 3 ml of 3% Dox (w/v). The sample was then shaken end over end for varying time periods at varying temperatures. Drug adsorption was done at 20°C and 4°C with loading times of five and 30 minutes, one, two, and 24 hours. After addition of Dox to the shell surface, the CA was centrifuged and washed three times to remove any excess

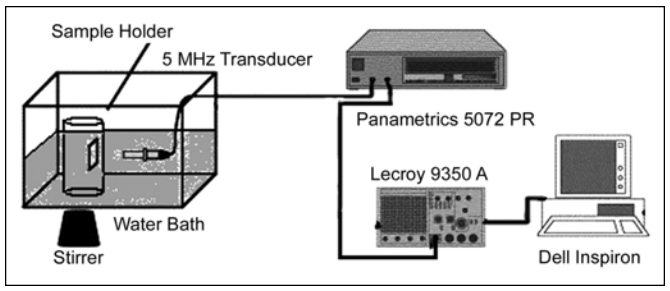

Figure 1. Acoustic setup used to test ultrasound enhancement, stability, and in vitro drug release under ultrasonic conditions.

drug that had not adsorbed to the surface. After centrifugation, samples were flash frozen and lyophilized for 48 hours. All samples were then stored in a desicator at 20°C to avoid degradation through hydrolysis.

Particle Sizing

Particle size was measured on a Malvern Nano ZS Particle Sizer in order to characterize the mean size and distribution of the agent. Roughly one mg of dry sample was suspended in 1 ml of deionized water. Each sample was measured three times and the results averaged.

Scanning Electron Microscopy (SEM) Imaging

Drug loaded agent was imaged using an environmental scanning electron microscope. Freeze dried agent was sputter coated with platinum for 60 seconds prior to imaging. All images were taken at a magnification of 6000x with an accelerating voltage of 3.0 kV. All electron microscopy was done at the Drexel University Materials Characterization Facility.

Acoustic Testing

Ultrasound enhancement, stability, size distribution over time, and drug release were all measured in vitro to determine the agent's feasibility as a platform for drug delivery. Acoustic enhancement and stability under ultrasonic conditions were both measured in vitro to determine microbubble performance as a CA as well as sensitivity to ultrasound. These properties were characterized using the setup shown in Figure 1.

A 12.7 mm diameter, 5 MHz transducer with a focal length of 50.8 mm, 6 dB bandwidth of 91% and a pulse length of 1.2 mm was placed in a water tank filled with 37°C, 18.6 MΩ-cm deionized water. These acoustic parameters are all well within current ultrasound imaging standards.[7] The ultrasound transducer was focused through an acoustically transparent window in the sample holder onto the sample volume. A pulser-receiver generated an acoustic wave with a pulse repetition frequency of 100 Hz. The reflected signal from the CA was detected by the transducer and amplified 40 dB before being read by an oscilloscope. Data was then acquired and values calculated using Lab View 7 Express and stored on a CPU.

Ultrasound Contrast Enhancement

Backscattering enhancing was measured as a function of CA dosage in order to gauge both ultrasound contrast enhancement as well as the agent's sensitivity to ultrasound. The sample holder shown in Figure 1 was filled with 50 ml of PBS at 37°C. Three mg of dry agent was suspended in 800 µl of PBS. Samples were pipetted into the holder in incremental dosages from 0-16 µg/ml. The agent was allowed to mix for 10 seconds before readings were taken to ensure homogeneous sample volume. Sixty readings of each individual sample were taken using LabView. All final values were based on an average of three readings from three individual samples.

Physical Effects of Insonation on CA

In vitro insonation experiments were all performed in the acoustic setup shown in Figure 1 in order to assess the agent's behavior in the sound field, and hence its suitability as a platform for triggered drug delivery. Ten mg of sample were added to 50 ml of 37°C PBS within the sample holder. The agent was then insonated using the 5 MHz transducer at 0.68 MPa pressure. At varying time intervals, one ml of mixture

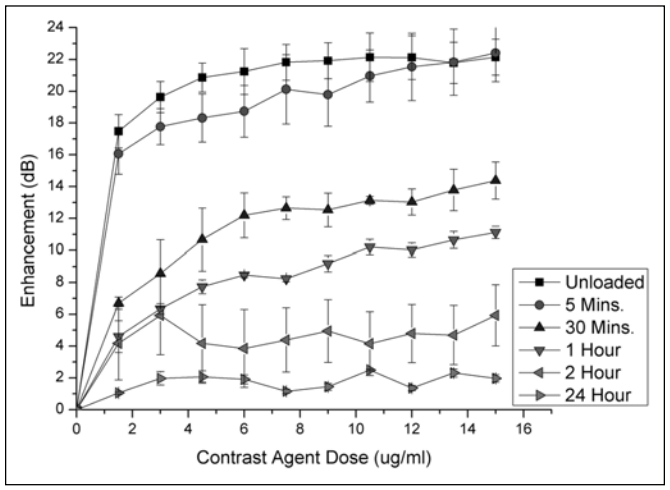

Figure 2. Ultrasound enhancement as a function of CA dosage for agent loaded for varying time intervals at 20°C. Beyond 30 minutes of loading at room temperature, the agent does not provide enough enhancement to be used as a CA.

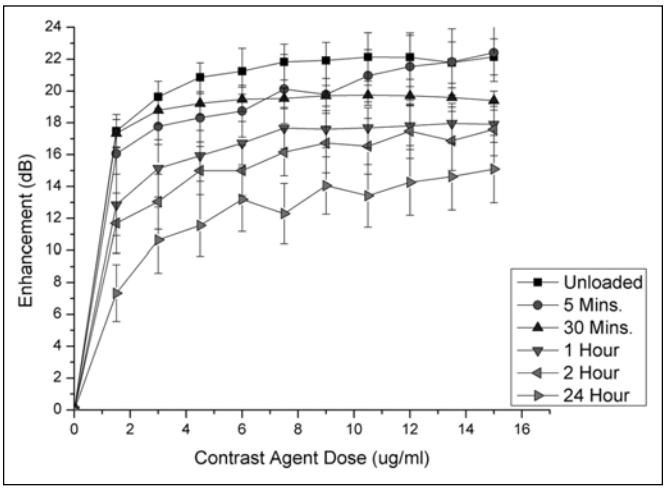

Figure 3. Ultrasound enhancement as a function of CA dosage for agent loaded at varying time intervals at 4°C. After 24 hours of loading at 4°C, the agent still provides enough enhancement to be used as a CA.

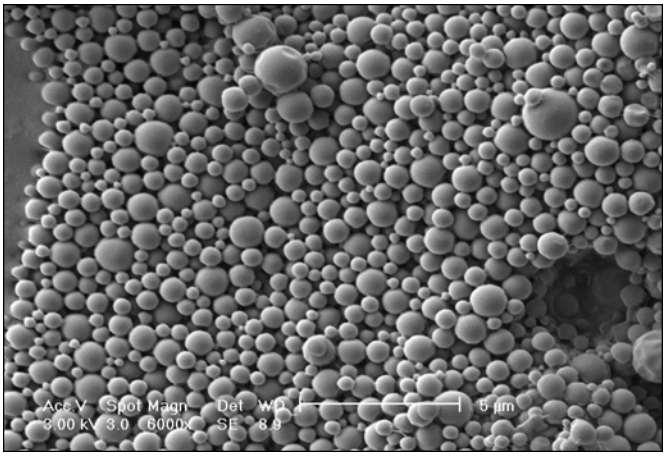

Figure 4. SEM image of CA population at 6000x. (Size bar = 5μm, Accelerating voltage = 3 kV).

was taken using reverse pippeting. CA size distributions were then measured using the particle sizer. Controls were performed using the same setup and time scale, but without insonation.

In Vivo Imaging

In vivo imaging was performed in New Zealand rabbits with 2 to 3 cm^2 VX2 tumors implanted within the liver in order to determine ultrasound enhancement and the agent's ability to penetrate within a vascular tumor model. Seventy mg of agent suspended in 510 ml of physiological saline were injected intravenously through an auricular line and the tumor was imaged continuously both before and after injection. Doppler ultrasound was used to image the solid tumor at a frequency of 5 MHz at a mechanical index of 1.0 for a total of 20 minutes. All images were saved and digitized for later processing.

Statistical Analysis

A one-way ANOVA was used to determine statistical significance and was performed using Prism 3.0. Statistical significance was determined using $\alpha = 0.05$. A Newman-Keuls test was performed as a post test to determine significant variance between groups.

Results and Discussion

Optimization of Drug Adsorption Parameters

Longer loading times result in higher encapsulation efficiency, but jeopardize the CA's sensitivity to ultrasound. Thus, after drug loading, ultrasound enhancement of the CA was measured to ensure that the agent was both still usable as a CA and still sensitive enough to be used as an ultrasound sensitive carrier.

Figure 2 shows the ultrasound enhancement of the agents loaded for various times at 20°C, while Figure 3 shows the same loading times at 4°C.

Figures 2 and 3 show the importance of loading temperature on the acoustic properties of the CA. Enhancement for each loading time was found to be significantly higher when loaded at 4°C compared to 20°C ($\alpha = 0.05$).

Drug loading at 4°C for 24 hours produces a drug loaded CA that provides more ultrasound enhancement than an agent loaded for one hour at 20°C. High enhancement is an important characteristic of the CA in order for the agent to provide good contrast enhancement during the scan, and also for triggering drug release.

As mentioned previously, longer loading times are needed to improve encapsulation efficiency. Encapsulation efficiency was not statistically different between the two loading temperatures, with both methods giving an efficiency of 62 +/- 8% after 24 hours. Thus, the optimal loading technique within our lab has shown to be at 4°C over 24 hours. SEM image of these agents is shown in Figure 4. The agents show smooth surface morphology, a mean size of 1.3 µm and a relatively tight size distribution. Drug loading of the CA could further be optimized by performing adsorptions at lower temperatures at mediums with freezing points below zero.

Physical Effects of Insonation on CA In Vitro

Additionally, the size distribution of the drug loaded CA was examined over the course of insonation as described in the methods section. Figure 5 shows the change in size distribution of the CA over time with and without insonation.

Figure 5 shows the manner in which the CA population changes when in solution over time. Notice over the course of 15 minutes with no insonation, the agent swells slightly, becoming 10% larger. However, when ultrasound is applied to the sample, the agent population decreases drastically. CA have been shown to rupture when insonated and others lose their gas cores, causing them to shrivel.[27] These findings are confirmed by our results. After 15 minutes of insonation, we see a population size reduction of almost 200% with the final population having a mean size of roughly 300 nm. These differences were found to be statistically significant with a final size small enough for particles to exit through the

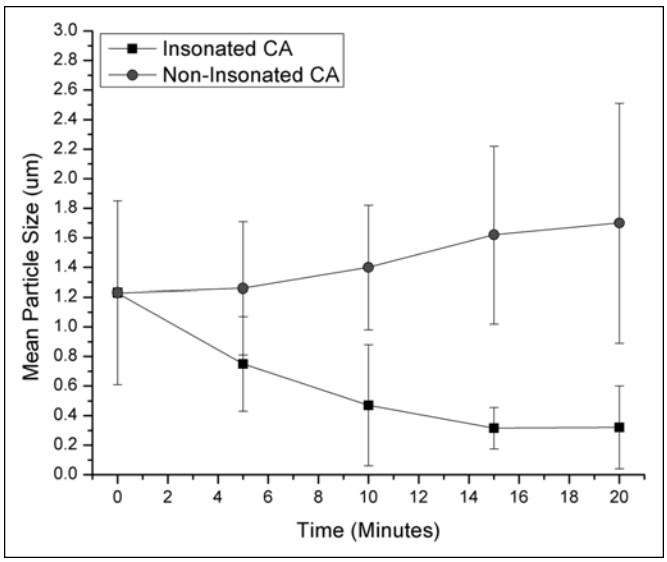

Figure 5. Size distributions of the CA population over time are shown for samples under insonation, and samples under no insonation while circulating in the sample holder described in Figure 1.

vasculature within the tumor and deliver their contents on the cellular level.

Results from preliminary studies show great promise for a drug loaded CA to be injected intravenously and with localized drug delivery initiated through focused ultrasound. We have seen that our agent gets excellent penetration into a solid tumor, and after insonation becomes small enough to escape out of the vasculature and initiate change on the cellular level. Thus, the platform can provide a primary release of drug within the solid tumor as well as a carry drug out of the vasculature and to the cancer cells after insonation.

In Vivo Imaging and Tumor Penetration

In vivo experiments were conducted showing the agent's potential to both provide enhancement during ultrasound scans, and penetrate into the vasculature of a solid tumor. Doppler ultrasound was used to image the solid tumor at a frequency of 5 MHz at a mechanical index of 1.0. This corresponds to pressures that have been shown to cause destruction of polymer shelled CA,[27] a potential mode of triggering drug release**.** Figure 6 shows Doppler images of the tumor pre and post injection of the CA.

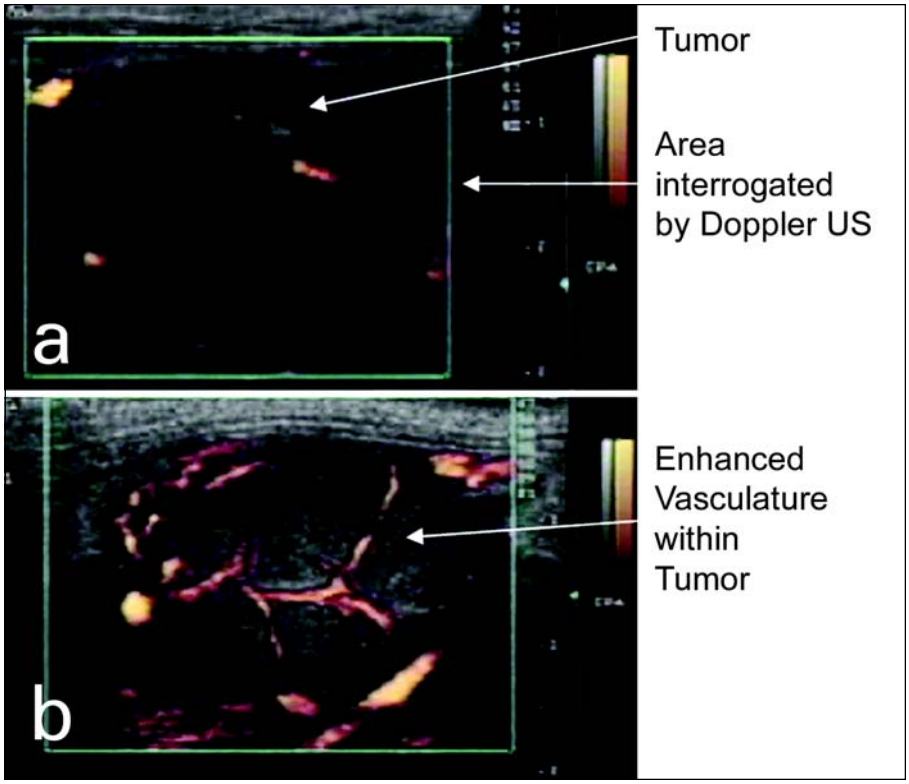

Figure 6. Power Doppler image of an implanted VX2 tumor within the liver of a 2-3 kg New Zealand Rabbit, a) pre injection, b) post injection. The upper left oval shows the solid tumor within the liver. Notice that after injection, CA penetrates well into the tumor as well as in the tumor feeding vessels surrounding it. Both Doppler and grey scale images are enhanced after injection, with the tumor mass showing much greater detail. 179 × 154 mm (72 × 72 DPI).

Results from imaging studies with our agent show that the CA penetrates well into the solid tumor and the in vitro studies indicate that focused ultrasound can be used to cause destruction of the microbubbles in an isolated region. For drug release studies in vivo, the ultrasound beam can be focused entirely within the solid tumor (1-2 cm^2), initiating destruction of the CA primarily within the tumor.

Conclusions

A drug delivery platform has been developed in conjunction with an ultrasound contrast agent, and parameters have been identified which do not destroy the echogenicity of the CA, which can be administered systemically. This type of platform can greatly reduce systemic toxicity commonly associated with chemotherapy, while increasing the concentration of the drug at the tumor site. The process parameters of adsorbing drug to the surface of the CA have been optimized with a loading time of 24 hours at 4°C resulting in an encapsulation efficiency of 62 +/- 8%, with loss of roughly only 25% in echogenicity. These agents respond well to ultrasound, show smooth surface morphology, and a tight size distribution. Preliminary drug delivery studies show the platform is detectable by ultrasound in vivo and provides good tumor penetration. In vitro, the size distribution of the agent under ultrasound was shown to become small enough to escape out of the vasculature which would cause contact of the drug with the cancer at the cellular level. This work, combined with research on the addition of tumor specific ligands to the surface of CA may ultimately result in a drug delivery platform in which drug carriers with a higher affinity for solid tumors carry drug through the body and release their contents at a desired location when triggered with focused ultrasound.

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Acknowledgments

In vivo imaging studies were performed at The University of Pennsylvania with help from Susan Schultz. Electron Microscopy was done at Drexel University's Materials Characterization Institute with the help of Kelleny Oum. Funding was provided through NIH grants HL 52901 and CA 52823, and The Coulter Foundation.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2008, Vol. 28 No. 5

API COP Forms Subcommittee to Drive Innovation in Process Technology

by Rochelle Runas, ISPE Technical Writer

Taking a lead role in the future of Active Pharmaceutical Ingredient (API) manufacturing, the API Community of Practice (COP) has formed a Process Technology Subcommittee.

"We are seeing a period of change catalyzed by the FDA's GMPs for the 21st Century and Industry initiatives to reduce the cost of drugs," says the Subcommittee's draft mission statement. "This is generating many new concepts based on the strength of scientific understanding, for example, QbD, risk-based approach, PAT application, PQLI, etc. leading to a potential revolution in the way that we approach the process development, technology utilization, and facility design."

"There is a real opportunity for API manufacture to reduce its costs and ensure its future," said John Nichols, Co-Chair of the new Subcommittee, at the ISPE Copenhagen Conference in April. "To do this, multidiscipline interaction between development science, engineering, and quality disciplines is essential."

The API COP Process Technology Subcommittee's mission is to drive innovations in process technology for manufacture of APIs and BPCs by the identification of subject matter experts, interaction and partnership with related groups, by support and input to the education program, the promotion/marketing of new innovations in process technology, and input to industry guidelines and best practice documents.

"We also need to note that some of the old paradigms no longer apply, circumstances have changed," Nichols said. For example: "Production Rates: Plants having a capacity of greater than 10×10^6 lb/yr (approx. 5000 T/yr) are usually continuous, whereas plants having a capacity of less than 1×10^6 lb/yr are normally batch types," etc.[1] For the pharmaceutical industry and specialty chemical industries, this is no longer true."

Nichols said currently there is a lot of activity both in the US and Europe toward making such paradigm shifts. For further details about these activities, see "Innovations in Process Technology for Manufacture of APIs and BPCs" by Nichols (pgs. 24 – 34). The article summarizes presentations from the ISPE Copenhagen Conference, giving a glimpse into the future of efficient processing implementation (e.g., continuous), new technology/equipment, and ISPE/ASTM enabling activities.

In addition to sponsoring the ISPE Copenhagen Conference seminar on Innovations in API/BPC Manufacture, the Subcommittee has recruited thought leaders from academia, API manufacturers, and equipment and services suppliers to further help define the group's direction and drive change.

The Subcommittee is currently working on an appendix of potential technologies; a roadmap identifying main issues inhibiting the introduction of new technologies; and is maintaining its ongoing input to the ASTM Continuous Processing Standard development. The Subcommittee also has future plans to generate a white paper covering in more detail the particular areas of compliance/quality assurance and control associated with continuous processing. Future educational offerings will build on this work at US and EU conferences, and there are long term plans to expand the API Baseline Guide with sections on process intensification/continuous processing and small volume/high potency manufacture, said Nichols.

To join the Subcommittee and for further information on the group, visit the API Community of Practice site at www.ISPE.org.

The API COP is one of 17 ISPE Communities of Practice (COPs). ISPE's COPs enable like-minded professionals to connect through an interactive online community. Through professional networking and peer collaboration, ISPE's COPs produce discipline-specific content that deepens members' knowledge and expertise, increases quality and continuous improvement in the industry, and help to achieve ISPE's core purpose of leading global innovation. Current COPs are:

- Active Pharmaceutical Ingredients (API)
- Biotechnology
- Commissioning and Qualification (C&Q)
- Containment
- Critical Utilities (CU)
- Disposables
- Engineering Standards Benchmarking
- Good Automated Manufacturing Practice (GAMP)
- Good Control Laboratory Practices (GCLP)
- Heating, Ventilation, and Air Conditioning (HVAC)
- Investigational Products (IP)
- Packaging
- Process Analytical Technology (PAT)
- Process/Product Development (PPD)
- Project Management (PM)
- Sterile Products Processing (SPP)
- Sustainable Facilities

Joining an ISPE COP is easy, free, and open to both Members and nonmembers. Visit www.ISPE.org under the People and Groups heading for further information.

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Annual Meeting to Help Navigate Horizon of Industry Change

The industry compass continues to point toward a horizon of change that includes more science- and risk-based approaches, lean and flexible manufacturing, and complex technologies. To help navigate this horizon, the educational sessions planned for the 2008 ISPE Annual Meeting (26 – 29 October, Boca Raton, Florida, USA) have been tailored to address these and other emerging trends and practices.

The following are highlights of what to expect at the Keynote Session and in seven educational tracks:

Keynote Session

This year's Annual Meeting Keynote Speakers are:

- **Hans Rosling, MD, PhD**
  Professor of International Health, Karolinska Institute and Director of Gapminder Foundation, Stockholm, Sweden

- **Janet Woodcock, MD**
  Director, Center for Drug Evaluation and Research, US FDA

- **Patrick Y. Yang, PhD**
  Executive Vice President, Product Operations, Genentech, USA

Regulatory Track

More than a dozen regulators have been invited to speak and are confirming now. This track is for anyone who deals with regulatory compliance or quality issues and focuses on the following topics:

- Product Quality Lifecycle Implementation (PQLI) and a practical approach to global implementation of ICH documents
- Lessons learned from use of Process Analytical Technology (PAT) and how to apply them to your own fast-track PAT program
- Risk-MaPP and the use of risk-based techniques to manage cross contamination – key regulatory agencies present
- Financial, legal, technical, and regulatory issues facing biosimilars
- Regulatory compliance and quality issues as related to quality laboratory facilities and an update on the much anticipated Baseline® Guide for Quality Laboratory Facilities scheduled for publication during first quarter 2009

Innovation Track

The industry faces many challenges that require companies to develop products faster and at less cost. Manufacturing is tasked to reduce costs and become more lean and flexible, while meeting compliance in an increasing global environment. This track examines how today's leaders are meeting some of these challenges, including:

- Continuous and high throughput processes for everything from APIs to biologics and innovative processes to increase the downstream efficiency in biotechnology
- Implementing PQLI, Quality by Design (QbD), and other initiatives to reduce time and cost for developing new products
- Vaccines, from pre-pandemic vaccines to current manufacturing challenges
- How nanotechnology can be applied and developed
- Changes in regulatory thoughts on GMPs
- A special session probes the idea of innovation and how it can be/is being taught and practiced in and out of our industry

Manufacturing Operations Track

This session will address real concerns, including:

- Higher costs requiring increased efficiencies
- Decisions on internal production versus outsourcing opportunities
- Ways to be more productive and faster using ideas from other industries
- Trouble-shooting your aseptic process

Engineering Design Track

This track presents a unique opportunity to see and hear in a few hours what the experts have devoted many years developing and improving through application of innovation and response to demands of a dynamic industry. Delegates will have a chance to review developing technologies and techniques and practical solutions, including:

- Working details of systems in the transfer technologies field, options in the selection of equipment, and analysis of competing systems
- Facilities retrofit design processes, available choices between retrofitting and new construction, and construction logistics planning
- Project presentations by the Category Winners of the Facility of the Year Awards (FOYA) program for 2008
- Energy reduction techniques for critical utility applications and comparison with new, more efficient water and pure steam technologies
- Identification and description of new and developing equipment construction standards and current trends in their generation
- Function and importance of kilo labs and pilot plants, in addition to cost and scheduling of related projects

Investigational Products Track

Education sessions are offered from two perspectives of critical importance for today's clinical supply chain professional: operations and management.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Annual Meeting...

Continued from page 82.

Sessions in the operations track include business process management; supply pooling through protocol interpretation; distribution; management of controlled substances; and comparator strategy. Sessions in the management track review business process management; developing and engaging talent; successful partnerships; delivering supplies to emerging markets; and applying six sigma concepts to study supply planning. In the general session, recognized experts will talk about the future of clinical supplies; removing use-by dates from clinical trial materials in Europe; and clinical research perspective on handling/managing clinical supplies.

Project Management Track

In today's troubled economic times, the demands to deliver projects ahead of schedule and under budget force project managers to adopt innovative methodologies. While classic tools and programs will never be abandoned, the industry is demanding an out-of-the-box mindset, and this is most often affected by analyzing lessons learned from both previous success and failure.

This interactive track will analyze current, real world, applied innovations in project delivery and take advantage of insights from industry experts discussing how current and future trends can be used to transform current projects and help shape future project success. There will be discussions on successful project execution on a wide variety of project types; management of risk and innovation; the differences between projects of different size and scope; and the human side of managing projects.

Efficient and Effective Compliance Track

Attendees of this track will have the opportunity to learn from the early adopters of the new approaches to compliance. The program covers a broad array of key topics, such as project management challenges; best practice approaches to Computer System Validation (CSV); and incorporation of new approaches to compliance in facilities, utilities, and manufacturing systems. Case studies provide insight on how companies are refining project approaches through cooperative efforts of quality, IT, and engineering. Discussions will include:

- ASTM E2500 – Practical examples of a science- and risk-based approach

Concludes on page 4.

ISPE and CCPIE Work Together to Bring Learning Opportunities to China

As part of a pioneering relationship between an American not-for-profit organization and the Chinese government, the China Center for Pharmaceutical International Exchange (CCPIE) has invited ISPE to collaborate with them in bringing a first-of-its-kind learning opportunity to Chinese pharmaceutical professionals.

The 2008 ISPE Conference in China will take place 11-12 November 2008 in conjunction with the 13th China International Pharmaceutical Industry Exhibition (12-14 November) at the China International Exhibition Center in Beijing, China.

The CCPIE acts as the conduit between professional organizations and the SFDA, China's pharmaceutical regulatory agency. The collaboration between ISPE and CCPIE is as pivotal as it is historic, as the CCPIE also trains members of the SFDA.

The keynote session on the first day of the conference will provide delegates with insights on China's GMP regulations, perspectives of the China State Food and Drug Administration (SFDA), and the US Food and Drug Administration (FDA).

The second day of the conference consists of the following three parallel tracks and their respective track leaders:

- GAMP® 5 – Sion Wyn, Director, Conformity Ltd.
- Biotechnology – Ron Branning, VP Corporate QA, Gilead Sciences Inc.
- Validation – Steve Wisniewski, Senior Associate, Director of Compliance, IPS

Many other notable speakers will take the podium during the two-day conference, including:

- Robert Best, President and CEO, ISPE
- A representative from SFDA
- A representative from US FDA
- Zhao Yajun, Director, CCPIE
- Paul D'Eramo, Executive Director, Quality and Compliance Worldwide, Johnson & Johnson
- Professor Zheng Qiang, Director, Centre for Pharmaceutical Information and Engineering Research, Peking University
- Robert Tribe, ISPE Asia-Pacific Regulatory Affairs Advisor

To review the conference agenda, speakers' biographies, and to download a registration form, please visit www.ISPE.org.cn or email: china@ispe.org.

Knowledge Briefs to Offer Snapshots of Industry Issues, Processes, and Technologies

ISPE has established the Knowledge Brief publication program to provide access to general information on issues, processes, and technologies impacting the contemporary pharmaceutical industry. Presented in levels of Basic, Intermediate, and Advanced, a Knowledge Brief is intended to provide an overview written in such a manner that the non-technical reader can understand the context, substance, and relevance of the subject.

Each Knowledge Brief will include links to technical documents, Pharmaceutical Engineering articles, Communities of Practice, seminars, and the like to provide readers access to more specific and detailed information on the subject.

Knowledge Briefs are free to ISPE Members and $5 US/€ 3 to nonmembers and are available for immediate download from the ISPE Web site:

Biotechnology Basics

Level: Basic

Adapted from the ISPE Training Course on Biotech Basics, this Knowledge Brief provides basic concepts explaining the science of biotechnology and how science and process are combined to lead to the manufacture of a human therapeutic product.

Commissioning and Qualification of Biopharmaceutical Facilities

Level: Intermediate

This Knowledge Brief summarizes the considerations involved in the commissioning and qualification of a biopharmaceutical manufacturing facility. The information contained in this Knowledge Brief was extracted from the ISPE Baseline® Guide: Biopharmaceutical Facilities.

Quality by Design

by John Berridge, PhD

Level: Intermediate

This Knowledge Brief provides and explains the basic elements of Quality by Design (QbD).

For information on submitting an article to the Knowledge Brief program, please contact Rochelle Runas, ISPE Technical Writer, by email: rrunas@ispe.org. Authorship recognition will be provided to all individuals whose Knowledge Brief is published. Publications emanating from COPs or technical documents will reflect authorship by those groups, rather than by individual. Prospective authors are encouraged to review currently available Knowledge Briefs to better understand the type of document being sought.

Annual Meeting...

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for specification, design, and verification of facilities and equipment
- Process validation – Hear from confirmed regulatory speaker Rick Friedman, US FDA
- Computer System Validation (CSV) – Benchmarking your current practices and solving your real questions
- Case studies for transitioning to the new verification models
- Best practice case studies in CSV
- Project information management – Lessons learned and recommendations from case study projects
- C&Q Baseline® Guide updates – Review status of Volume 12, a science- and risk-based approach to verification, and contribute to content for the revision the original Commissioning and Qualification Baseline Guide (5.1)

COMING SOON:

Downloadable Glossary of Pharmaceutical and Biotechnology Terms

In fall 2008, ISPE will introduce a portable PDF version of its acclaimed Glossary of Pharmaceutical and Biotechnology Terminology for ISPE Members only. The Glossary contains more than 5,800 abbreviations, acronyms, and terms focusing on specific areas in biotechnology and pharmaceutical science and manufacturing, such as computer technology, manufacturing processes, water treatment, welding, metallurgy, HVAC, medicine, biology, chemistry, and many other subjects. This tool is designed to help industry professionals with daily job functions, understand terminology used in ISPE's technical documents and education seminars, and standardize industry terms around the globe.

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South America

Argentina

The Argentinian National Medicines, Food and Medical Technology Administration (ANMAT) has published new mandatory regulations (Anmat Disposición 2372/2008) for GMP inspectors to follow when gathering manufacturing process information. These regulations aid in standardizing the procedure for GMP investigators. There are two parts to the new regulation: the first covers inspections and the second offers the classification of GMP compliance deficiencies. The regulations cover: human resources, the plant and its general condition, water system, storage of raw materials, packaging materials, finished products, recalls, production documentation, batch registration procedure, and corrective measures for company deficiencies in these areas.[1]

Brazil

ANVISA requires that companies involved in the manufacture, importation, exportation, repackaging, storage, dispatch and distribution of APIs submit the details of their products to the regulatory authority so that these details are recorded in the national API databank. In cases when APIs are not directly obtained from the manufacturer, the ANVISA asks companies to submit detailed information about the suppliers and vendors in order to track for each specific API from the origin to the distribution chain. It is the responsibility of companies to keep this required information up to date. Therefore, where companies fail to provide detailed information about their APIs, ANVISA stated their APIs will no longer be marketed. Pharmaceutical companies will only need to submit details of imported APIs (i.e., without a distributor). Companies only involved in transporting APIs and compounding pharmacies are not meant to follow this new regulation.[2]

Asia/Pacific

Australia

As of 1 July 2008, the Therapeutic Goods Administration (TGA) requires that the manufacturer details and the formulation of Over-The-Counter (OTC) medicines in Australia be made available to sponsors. The regulatory agency explained that not doing this will prevent sponsors from fulfilling their obligations under the Therapeutic Goods Act 1989. The manufacturer details and the formulation of OTC medicines will be disclosed to sponsors through the three TGA's online services (the Australian Register of Therapeutic Goods, the Electronic Listing Facility, and the OTC Medicines Electronic Lodgement system). The TGA says the purpose of this regulation is to ensure the safety, quality, and efficacy of the OTC drugs, and to be able to fully investigate their adverse events.[3]

India

In an effort to improve the working relationships between the European Directorate for the Quality of Medicines and Healthcare (EDQM), the Indian Health Ministry and the Indian Pharmacopoeia Commission (IPC), Susanne Keitel, a Director in EDQM, said they would be in favor of an application from India for observer status at the European Pharmacopoeia Commission. The Indian officials said the IPC also would be keen on exchanging scientific expertise with their European counterparts. In the future, collaboration between Europe and India especially in joint inspections of manufacturing sites and scientific cooperation is expected to increase.[4]

Europe

In July 2008, the European Commission DG Entreprise published a summary of the public consultation on the provisions for certification of quality and non-clinical data for small and medium-sized enterprises (SMEs), pursuant to Article 18 of Regulation (EC) No 1394/2007. The summary outcome of the public consultation paper is now available.[5]

In addition, the Commission Regulation (EC) No 542/2008 of 16 June 2008 amended Annexes I and II to Council Regulation (EEC) No. 2377/90 laying down a Community procedure[6] for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin, as regards cyfluthrin and lectin extracted from red kidney beans.

In the course of the public consultation, the Commission has received 100 stakeholder responses from industry (pharmaceutical industry, wholesalers, pharmacies, companies producing authenticity features, etc.), 12 from civil society (patient groups, consumer associations, citizens), and three from Health Insurances and Health Care Centers. These responses are now available.[7]

The European Commission published an article on their Web site that summarized the opinion on the combat of counterfeit medicines in Europe. Most of the agencies agree to take urgent and decisive actions, but the challenge is to implement new stricter enforcement regulations without leading to a whole restructure of the already existing legal systems.[8] The European Federation of Pharmaceutical Industries and Associations said in its response that it supports the use of overt and covert authentication features (e.g., holograms, color shifting inks, taggants), but the technology choice should be specific to each manufacturer.[9] In addition, it wants these measures to be extended to all prescription drugs rather than implemented on a risk-based basis. In order to effectively combat the medicines counterfeit, the EGA agrees with the commission's proposals to make all participants in the distribution chain comply with existing pharmaceutical legislation (Directive 2001/83/EC, as amended).

The EMEA has published a report on the progress of the annual, "sampling and testing programs for centrally authorized medicines." Sampling and testing programs run by EDQM, the national laboratories and medicines authorities of EU, and EEA Member States are used to detect quality issues that need to be addressed, in the interest of protecting public and animal health. This report covering the period 1998-2007 shows the statistical data on medicines tested, the results obtained, the changes introduced to the programs over the years, and emphasizes involvement and cooperation

of partner organizations across Europe.[10]

A productive collaboration at the Transatlantic Economic Council (TEC) between the European Commission, the European Medicines Agency, and the U.S. Food and Drug Administration resulted with strengthening of transatlantic cooperation on medicines regulation.[11] The Commission/EMEA and the FDA will pilot joint inspections of companies manufacturing pharmaceuticals in the U.S. and in the EU and of companies manufacturing active pharmaceutical ingredients in third countries; pilot the exchange of inspection schedules results, and information on inspected manufacturing sites in order to attain more GMP inspection coverage collectively and to better identify manufacturing sites producing active pharmaceutical ingredients in third countries. Moreover, a collaboration to determine to what extent dedicated production facilities are necessary for certain pharmaceuticals taking into account a risk-based approach will be set up. The EMEA and the FDA also announced successes in their transatlantic work on biomarker development and validation for various product development purposes. Both parties will continue to work on this initiative with further biomarker development and validation.

The following meetings were held during the period covered by this update:

- The Committee for Orphan Medicinal Products (COMP) held its ninetieth plenary meeting on 13-14 May 2008.[12]

- The Committee on Herbal Medicinal Products (HMPC) held its 24th meeting at the EMEA on 2-3 July 2008.[13]

- The Committee for Orphan Medicinal Products (COMP) held its ninety-second plenary meeting on 8-9 July 2008.[14]

- The Paediatric Committee (PDCO) celebrated its first anniversary at its 2-4 July 2008 meeting.[15]

- The Committee for Medicinal Products for Human Use (CHMP) held its June plenary meeting from 23-26 June 2008.[16]

EMEA provides a Questions and Answer on Active Substance, European Pharmacopeia, Impurities, Manufacture of the medicinal products, Specific types of product, Stability, Water and Data submission topics.[17] EMEA provides a Questions and Answer on the Stability – Calculation of Expiration Dates topics.[18]

The following guidance documents are noteworthy:

- **Concept Paper on Development of a Guideline on Setting Specifications for Related Impurities in Antibiotics.**
  EMEA has published on their Web site the current thinking for "Setting Specifications for Related Impurities in Antibiotics."[19]

- **Explanatory note for clarification of the scope of the VICH Guideline 17 on Stability Testing of Biotechnological/Biological Veterinary Medicinal Products**
  EMEA has published an explanatory note clarifying the VICH Guideline 17 relating to the "Stability Testing of Biotechnological/Biological Veterinary Medicinal Products."[20]

- **ICH Topic Q10 Note for Guidance on Pharmaceutical Quality System**
  The International Conference on Harmonisation (ICH) Q10 document[21] on Pharmaceutical Quality System was adopted (Step 4) at the ICH Steering Committee meeting in June 2008. This describes a model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, and includes applicable Good Manufacturing Practice (GMP) regulations.

- **ICH Topic Q4B Annex 5**
  EMEA released this note on the evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on "Disintegration Test General Chapter."[22]

- **ICH Topic Q4B Annex 4C**
  This EMEA note is for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on tests for microbiological examination of non-sterile products: "Acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use."[23]

- **ICH Topic Q4B Annex 4B**
  This note follows the Annex 4A and is related to the evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for "Microbiological examination of non-sterile products: tests for specified micro-organisms."[24]

- **ICH Topic Q4B Annex 4A**
  This note from the EMEA is for "Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on microbiological examination of non-sterile products: micrological enumeration tests."[25]

- **ICH Topic Q4B Annex 3**
  This note from EMEA is for "Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for particulate contamination: sub-visible particles general chapter."[26]

- **ICH Topic Q4B Annex 2**
  This note from EMEA is for "Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for extractable volume of parenteral preparations general chapter."[27]

- **US**
  The new "Guidance for Industry cGMP for Phase 1 Investigational Drugs"[28] has been published in July 2008. This guidance mentions the current thinking of the Food and Drug Administration (FDA) on the Good Manufacturing Practice in the manufacture of most Investigational

New Drugs (INDs) used in phase I of clinical trials. This guidance does not establish enforceable responsibilities but should be viewed as recommendations.

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