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THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

JANUARY/FEBRUARY 2015 VOLUME 35, NUMBER 1

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www.PharmaceuticalEngineering.org

ISPE Global Headquarters
600 N. Westshore Blvd.
Suite 900
Tampa, Florida 33609 USA
Tel +1-813-960-2105
Fax +1-813-264-2816
ask@ispe.org

www.ISPE.org

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JULY/AUGUST 2015
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Manuscripts Due: 11 March 2015
Publishes: 27 July 2015

AUGUST 2015 E-Supplement
Process Equipment, Packaging, and Automation (including Cloud Computing and Anti-Counterfeiting)
Manuscripts Due: 1 May 2015
Publishes: 19 August 2015

SEPTEMBER/OCTOBER 2015
Risks Associated with Product Performance
Manuscripts Due: 7 May 2015
Publishes: 21 September 2015

OCTOBER 2015 E-Supplement
Green / Sustainability
Manuscripts Due: 3 July 2015
Publishes: 21 October 2015

NOVEMBER/DECEMBER 2015
Risk-Based Regulatory Review
Manuscripts Due: 9 July 2015
Publishes: 23 November 2015

DECEMBER 2015 E-Supplement
Quality Metrics
Manuscripts Due: 21 August 2015
Publishes: 16 December 2015

Industry Hot Topics

In addition to the Departments, each issue will feature industry relevant hot topics, including biosimilars, breakthrough therapies, next generation manufacturing, quality metrics, quality risk management, supply chain integrity, and sustainability.

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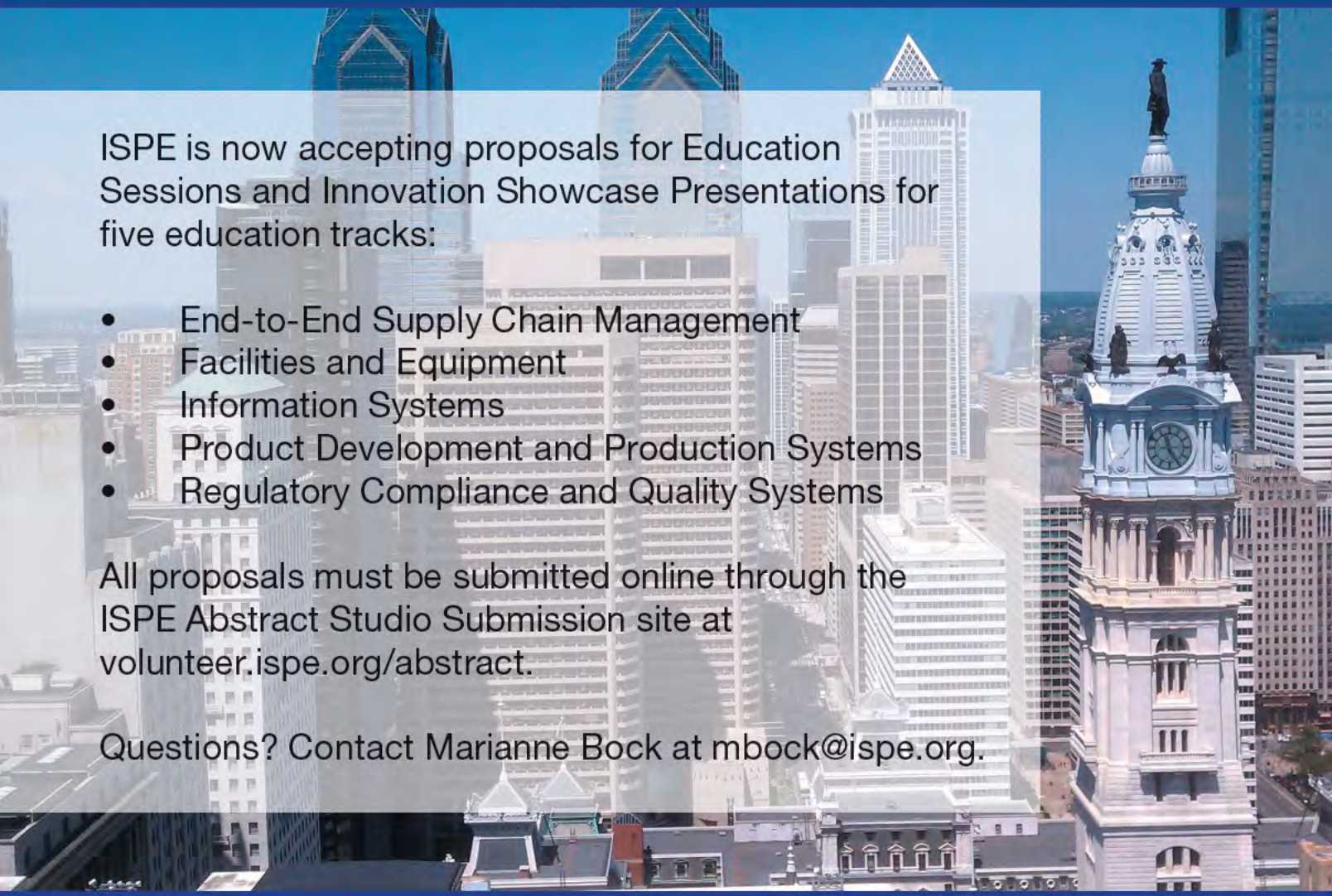

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Questions? Contact Marianne Bock at mbock@ispe.org.

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Welcome to the first 2015 edition of *Pharmaceutical Engineering*. Our main theme this year will be risk, considering the nature and potential sources of risk and how risk can best be controlled to protect product quality and patient safety. To provide context, this edition contains an overview of science-based quality risk management, as described in ICH Q9, which also gives examples of how risk is considered in various ISPE Guides.

The issue starts off with an opinion article by Brady which provides a perspective on the practical application of risk assessment, how to adopt a scientific approach to the risk management process, and simple and pragmatic advice on enhancing the process. It reminds us that risk management is a creative process that must be both facilitated and stimulated, and that organizations should create a culture of engaging with and including everyone in the risk management process.

While risk management is often associated with scientific and technical aspects of the product lifecycle, Falce, Girani, and Morreale present a case study showing the application of these concepts to factors of human behaviour. A case study shows a risk analysis conducted by a pharmaceutical company with the objective of improving quality and reducing deviations linked to human error. It describes the improvement derived from the analysis, which led to a more customized training plan, enhancement to documentation, and a direct impact on work activities.

Risk-based approaches also figure in the article by Thostesen, et al, which discuss the impact on Chemistry, Manufacturing and Control (CMC) part of a development project when a project is assigned Breakthrough Therapy (BT) status as defined by the US FDA. Such a designation poses many challenges, which a sponsor and the FDA need to address using a risk-based approach to assure sufficient information available to support approval and supply of high quality product, demonstrating "substantial improvement over existing therapies to patients" for serious diseases or conditions.

Also in the area of research and development Scalva, Buckingham and Bader's article is based on a presentation given at the 2013 ISPE Annual Meeting. It presents an overview of a novel quantitative method which by utilizing imaging software combined with tightly controlled variables in lighting, angle, and distance, quantifies the amount of process residue on a surface using high-resolution photographs. The accurate and repeatable experimental data generated using this method on a laboratory scale shows promising potential to eventually translate to full-scale process area applications.

Jin presents a comparison of different column designs for Expanded Bed Adsorption (EBA) in chromatography, which concludes that while EBA may not be a universal solution for direct processing of all particulate containing stocks, it is well fitted to most of the modern applications where the feed stocks are relatively clean and non-aggregating.

Gardner considers how Type I errors when using statistical process controls (i.e., concluding that the process is out of control when in fact it is in control) can negatively impact quality systems effectiveness, and what steps can be taken to reduce this impact.

As life sciences industries seek to implement Quality by Design (QbD) concepts in practice, there is an opportunity to apply existing tools such as Manufacturing Execution System (MES) software and related systems to enable the required knowledge and risk management aspects. Choi, et al, show how these opportunities include configuring MES as a knowledge repository, utilizing MES as a continual improvement tool for manufacturing, and using MES as a tool to allow knowledge gained from manufacturing to be systematically collected and made available to improve process design and development of a control strategy.

As always, I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
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Risk Assessment: Issues and Challenges

by Joe Brady, PhD

This article presents an opinion and a perspective on the practical application of risk assessment, on how to adopt a scientific approach to the risk management process, and also informally dispenses some simple and pragmatic advice that may enhance a risk exercise.

Risk can be defined as the effect of uncertainty on objectives.[1] Risk assessment is considered to be the overall process of risk identification, risk analysis and risk evaluation.[2] The risk management process is the overall and systematic application of management policies, procedures and practices to the activities of communicating, consulting, establishing the context, and identifying, analyzing, evaluating, treating, monitoring and reviewing risk.[1]

To be effective, the risk assessment and risk management processes both need to be properly understood, focused, transparent and clearly communicated. If a harmful event occurs, yet a risk assessment predicted that such an event was unlikely, everybody will want to know what went wrong. If risks cannot be properly evaluated, risk assessment itself becomes the biggest risk.[3] Therefore, the processes need assurances that they work.

A failed risk management process will inevitably leave a lot of questions to be answered, by the victims, those who were discommoded, or by the media. Types of questions asked will almost be universal. Who participated? Why were certain decisions taken? Why did it seemingly not work? Did anyone check the predicted outcomes before implementation? What confidence testing was done at the time to ensure that the assumptions were held to be true? These sound much like the same type of questions one would ask about a dubious scientific model.

This article is primarily focused on conducting an effective risk assessment, and then on the principles of risk review. Risk assessment is that part of risk management which provides a structured process that identifies how objectives may be affected, and analyzes the risk in terms of consequences and their probabilities before deciding on whether further treatment is required.[2] Risk review involves reviewing the output and results of the risk management process to take into account new and ongoing knowledge and experience.[4]

Risk Management Process

Risk assessment can be considered a mechanism to unlock wisdom not yet experienced, upon encountering a new system. A typical risk management process, as per the hypothetical worked example outlined in Table A, is generally considered to broadly encompass the following sequence of activities:[1,4,5,6]

1. A team of subject matter experts creatively identify risks (faults/failures/hazards) associated with a new and unfamiliar system.
2. The identified risks are analyzed and evaluated. The acceptability of each risk is determined.
3. Risks that are considered unacceptable are treated by the selection of appropriate mitigation strategies that are both robust and cost effective. The mitigation strategies and controls themselves are analyzed and evaluated to affirm where residual risk is deemed acceptable. Suitable controls are subsequently implemented.
4. Risks are subsequently reviewed post system implementation. Every day that passes, every batch manufactured, every customer complaint received, all contribute to new

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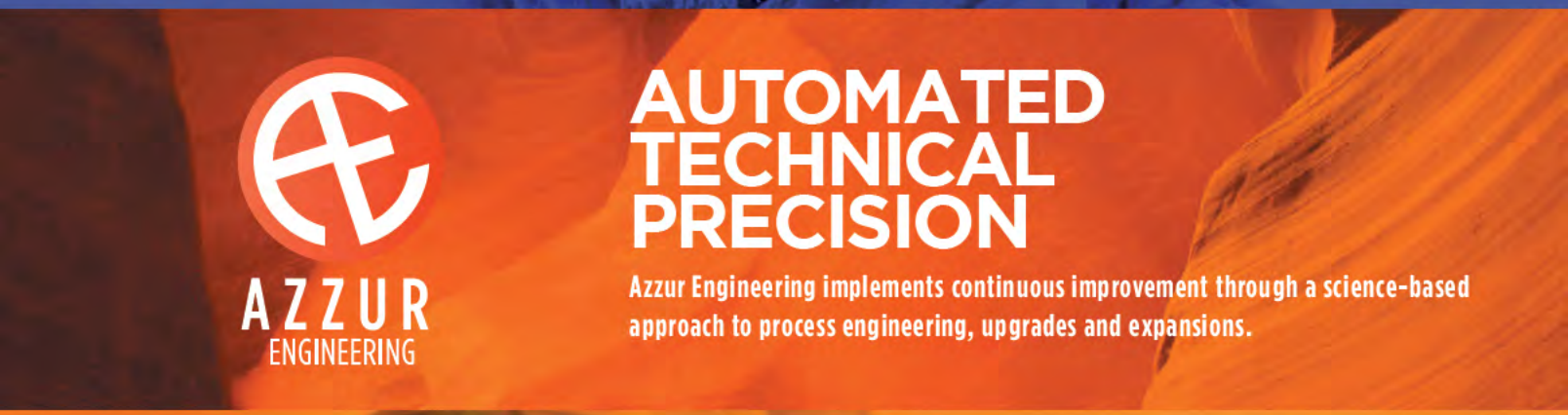

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knowledge and this results in more experience with the now familiar system. The benefit of this now first-hand experience and wisdom not only assists with the identification of new risks, but also with the adjustment of the existing risk controls. New knowledge is used to keep the risk assessment current, relevant and robust.

Subject Matter Experts

Selecting a team of subject matter experts to participate in a robust risk assessment process is about ensuring that the

During the concept-phase* of a hypothetical project, an initial design specification is proposed and corresponding preliminary process flow diagrams and process descriptions are generated. The project team now take a risk management approach to assessing the robustness of the design specification, prior to the formal generation of user requirement specifications and the subsequent issuing to vendors with requests-for-quotations. The general sequence of risk management activities for this hypothetical scenario might look like the following:

Step #	Description
1	**Initiate the Risk Management Process, and Define Inputs**
1.1	The risk management facilitator is appointed.
1.2	**Input-1:** The objective of this particular risk assessment is four-fold: a. Ensure that critical process elements specific to product quality, patient safety and data integrity have been identified. b. Identify any opportunities for the implementation of technically sound improvements. c. Postulate a performance and functionality verification testing strategy focusing on the identified critical elements. d. Propose an appropriate and robust structure for the detailed design documents, so that they may be confidently used both for systems implementation and as the basis for developing robust verification test scripts.
1.3	**Input-2:** A team of subject matter experts is assembled and attends the risk assessment exercise. The team comprises of experts with both product and process understanding, and also of subject matter experts who are conversant in the applicable regulatory expectations and with the conventions of the company's internal quality management system.
1.4	**Input-3:** The above listed subject matter experts are made familiar with the project approach, contracts, project methods, cost controls, and project timelines.
1.5	**Input-4:** Descriptions of the manufacturing systems are presented to the team, as follows: • Unit operations and the integrated manufacturing process. • Intended clinical use of the product (pharmaceutical, medical device, or combinational product). • IT infrastructure, topology, components and system architecture, and an overview of the various functions of the range of software applications. • Proposed lifecycle documentation hierarchy (for specification, design and verification documents).
2	**Risk Identification**
2.1	The team is organized into multiple groups, in the interest of either grouping or balancing the presence of certain expertise within the individual groups.
2.2	The risk statement/problem/enhancement is unambiguously communicated by the facilitator to the team, and is based on potential manufacturing system failures that could negatively impact on product quality, patient safety and data integrity.
2.3	During the risk identification phase, each team identifies potential faults (risks/failures/hazards) associated with the manufacturing systems, using creative fault finding tools, based on individual and combined subject matter expertise.
2.4	At the end of the risk identification phase, the facilitator collects the list of risks generated by each team. In this hypothetical scenario, the facilitator transcribes and collates a combined list of one hundred and thirty (130) faults into a risk identification report. Typically there will be significant overlap between observations amongst the various groups, so eventually the facilitator whittles down the overall list to one hundred (100) unique faults. Now a list of one hundred faults exists, the next step is to analyze and evaluate them.
3	**Analyze and Evaluate Risks**
3.1	Here the team starts with a list of one hundred identified faults. Remember, it will always cost time, money and resources to mitigate against a risk. Straightaway, it is obvious that all the faults cannot have the same priority (it would be unusual if they did). The next step now is to analyze and evaluate each and every fault and rate them against one another so that they can all be arranged in some order of priority. At a minimum, it is recommended to assign a risk-score to each fault based on the estimated product of the probability-of-occurrence and the severity of that occurrence should it occur (other categories could be included to finely-tune the priority order, such as assigning values for GxP impact, complexity, novelty, GAMP® software and hardware category, and detectability, for example).
3.2	The list of the one hundred identified faults is now rearranged, where the higher priority faults are organized towards the top of the list, and with the lower priority faults at the bottom. Ultimately, the priority order is in the context of product quality, patient safety and data integrity.
3.3	Now risk acceptability decisions have to be taken. A risk-acceptance line needs to be drawn in somewhere on that list. Below that line are the potential faults that the team can currently accept and live with. In other words, they are satisfied that the probability of occurrence is so low that the event might never be experienced over the lifecycle of the system, or that they would be able to recover relatively unscathed should the event ever occur in the first place, or both. Above that line, however, the risk-score is deemed to be too high, and thus unacceptable. For the prioritized faults above the line, risk control and treatment strategies will now have to be devised to reduce the risk-score to a more acceptable residual level. This will require a design change or a procedural change, or both. In this hypothetical scenario, the team decides that seventy (70) of the faults fall below the risk-acceptance line, with thirty (30) remaining above. The team now needs to decide upon creative risk controls and treatments for these top thirty high priority faults.

Table A. Example of general sequence of activities associated with a typical risk management process.

right questions are put to the most appropriate and competent individuals. Where a risk assessment goes awry in the pharmaceutical industry, the obvious questions from the regulatory authorities might include: Where was the design and development team? Were any test engineers or validation specialists involved? Where were the manufacturing teams such as operations, utilities and facilities? What about the whereabouts of packaging and labelling representa-

Step #	Description
4	**Risks Control and Treatments**
4.1	The team has a priority list of thirty unacceptable faults. The team now wishes to revisit and update the initial design specification and preliminary process flow diagrams and process descriptions.
4.2	Here the team creatively devises a number of control and treatment strategies for each fault. Remember, there will most likely be multiple possible solutions to correct every fault.
4.3	With multiple options now available, the next step is for the team to evaluate each and every option in terms of robustness and cost, and impact on the project schedule.
4.4	Once suitable options have been selected to correct what was initially deemed as thirty unacceptable faults, the team now has to re-assign a risk prioritization score and evaluate the residual risk. Hopefully, the new risk prioritization score will drop that particular hazard well below the risk-acceptance line on the original list (from Step-3.3, above). If it does, all well and good. If it doesn't, more options may need to be considered to further mitigate the problem until acceptable residual risk level is achieved, or a business decision may need to be taken to proceed or not proceed with the project in its current guise.
4.5	Assuming that suitable control and treatment strategies have been decided upon for the all thirty faults, the next step is for the team to implement the various options. This should lead to an updated design specification, along with the corresponding process flow diagrams and process descriptions.
5	**Risks Report, and Outputs**
5.1	A summary report of this risk-assessment exercise is written up, listing at a minimum the background to the exercise, the overall objectives, the list of attendees and all other inputs, the methods used to identify faults, and the all-important list of outputs.
5.2	**Output-1:** The first output is arguably a comprehensive list of identified critical process elements specific to product quality, patient safety and data integrity. A rationale should be included for each element as to why it is considered critical.
5.3	**Output-2:** A primary output for this risk assessment exercise is the updated design specification, and corresponding process flow diagrams and process descriptions. Decisions to update the specifications and implement technically sound improvements should be traceable to the faults being remediated, and the associated control and treatment strategies selected. All specification update decisions must be obvious, traceable and fully informed, and should ultimately be shown to result in clear and unambiguous enhancements to patient safety, product quality, and data integrity.
5.4	**Output-3:** Robust user requirement specifications can now be confidently generated and issued to the vendors with requests-for-quotations. The specific critical process elements should be clearly articulated for the appropriate vendors, so that they might best understand how best to prepare their proposed functional solutions.
5.5	**Output-4:** With all critical process elements identified and with robust user requirements now in place, the team can immediately start with planning an efficient validation strategy, beginning with generating integrated performance level verification tests.
5.6	**Output-5:** During the project phase,* once the vendors submit their proposed functional design solutions and the vendor selection process is complete, the team can immediately begin planning and generating functional and unit-operation verification tests. This can then influence the structure and layout of the vendors' detailed design documents, so that they may be unambiguously used both for systems implementation and as the basis for developing robust verification test scripts whilst maintaining a focus on the critical process elements.
6	**Risk Review**
6.1	Achieving compliance and fitness for intended use is the ultimate goal of the various risk management processes. But how does the team know that their risk management approach works? Across the entire systems lifecycle phases(*) there will be multiple opportunities for the application of risk-based decision making. Each and every risk assessment in sequence should reference and build upon the assessments that have gone before. A common sense, and non-onerous, administrative approach should link the various outputs of the evolving program of risk management exercises, and encourage a system of checks and balances amongst iterations.
6.2	As more experience is gained across the lifecycle, the resulting knowledge may lead to the identification of new critical process elements. Indeed this new knowledge could even lead to the downgrading of earlier identified critical process elements, with justification.
6.3	Ongoing system performance monitoring, incident management, corrective and preventive action and repair activities can intuitively be linked to evolving and iterative risk management exercises. This should result in continuous opportunities for the identification of technically sound improvements, more smart and intelligent verification testing, and maintenance of specification and design documents.
6.4	The risk review process can also be inextricably linked to the outputs and observations from both ongoing internal and external audits of the installed and implemented system.
*Reference Figure M3.3 from GAMP® 5, for an overview of the typical use of risk-based decision making across the system lifecycle.[7]	

Table A (continued). Example of general sequence of activities associated with a typical risk management process.

tives? Did the quality assurance and quality control teams contribute? Did any personnel associated with warehousing and distribution, and product monitored post-implantation play a part? Was there a need for healthcare professionals to participate?

What influences the decisions when selecting a team of subject matter experts to partake in a risk assessment process? Everyone has expertise on a plethora of subjects, but the actual degree of expertise in each case varies. The point here is that everyone could potentially contribute to nearly all risk assessments in the work place. Being selected or choosing to participate is primarily influenced by the extent of one's expertise. The risk assessment process is initiated with a clear and unambiguous problem statement, together with a clear study context. A crucial query for the risk assessment team at this point is who they would ideally like to have in attendance to brainstorm on the problem. What expertise would best contribute to the study?

The team organizing the risk assessment need to, with great dignity, determine the optimum degree of expertise available within the organization. Sometimes they may need to look outside their industry for a suitable degree of subject matter expertise. The organization needs some novel communication tools to let the employees know what risk assessments are currently being conducted, and those that are planned for the future. The presumption here is that all employees would enthusiastically be willing to contact the risk assessment team should they feel that they could contribute constructively to a particular exercise. The organizing team ought to remember to preserve dignity at all times, and respect all submissions and volunteers. If a volunteer at this point-in-time is not optimum for a study and is not selected, the chances are that at some point in the future they will be suitable for another. Nobody should ever feel discouraged before or after volunteering, regardless of it being their first time or not. The organizing team should be forever grateful and humble when someone offers to share the extent of their expertise. Everyone generally looks forward to sharing their knowledge in a collaborative and encouraging environment, and they need to be respected for this each and every time.

Perhaps, a novel user-friendly database of skills and expertise could be formally or informally maintained by the organization, and in particular be updated by the individuals themselves. The risk assessment teams would have access to this database which may help them identify key individuals for a particular study. Too often, individual expertise is completely overlooked in the workplace due to its invisibility, and such a database might be a contributor to making it more noticeable. The risk assessment team needs to be aware of any strong individual biases or ardent views that may skew the study, and try to carefully balance these out among the selected contributors. Different personalities and cultures are more assertive than others when it comes to declaring individual expertise. In this instance, a method may be needed so as to gently coax out individual strengths from the more introverted participants.

Finding Faults

There seems to be only one guarantee with risk assessment and that is all the risks will never be identified. Similarly, when a fault is identified it is not usually possible to identify all causes, so therefore total treatment and mitigation is seldom a reality. The most crucial ingredient to finding faults is to have the correct subject matter experts doing the brainstorming. Experienced and/or knowledgeable personnel thinking on the problem is a prerequisite. Risk assessment is used to identify potential hazards in advance, and subsequently put some treatments and mitigating safeguards in place to prevent the causes of their likely occurrence. Risk assessment can be considered an important supporting process to the product lifecycle.[7,8] This lifecycle support contributes to progressing innovations from design through to eventual implementation with the intent of manufacturing and distributing a safe and effective product.

The first stage of a risk assessment process is generally considered to consist of the creative identification of risks (faults/failures/hazards). Hopefully, the use of systematic tools will facilitate the participating subject matter experts to methodically, logically and objectively make risk observations. This stage of the risk assessment process requires intuition and creativity, and any or all of those practices that actively stimulate and promote intuition and creativity. It is about creative fault finding. Innate creativity is something that can be facilitated using systematic tools. Everyone has the capacity to be creative, but the conditions need to be suitable for it to manifest. Creative fault finding requires an enabling, stimulating, encouraging, challenging, and inspiring environment.

The risk assessment process is initiated with a problem statement and a study context. The desired subject matter expertise is ascertained and the relevant experts are selected to participate. The appointment of study facilitator should be given serious consideration. Ways to creatively stimulate the identification of faults should be developed. For example, a prototype may be presented, a mock-up built, or a computer model generated. Systematic risk assessment tools need to be selected to assist with, and drive forward, the brainstorming of faults.[2,5] These can be used either in a standalone capacity or adapted and combined for maximum flexibility.

Risk serves as a stimulant. When faced with something new in life, people tend to extrapolate past learnings, wisdom and experience, and apply it intuitively to any new system to try and predict where hazards might arise. Indisputably, many skills and proficiencies are immediately transferable between systems and industries. First and foremost,

intuition based on experience is central to identifying faults associated with a new and unfamiliar system. People can be emotional, impulsive, and at times can be somewhat predisposed to identifying arbitrary faults. Emotional impulses can be fuelled by, for example, fear, pride, prejudice, insecurity, or envy. These can lead to substantial and haphazard biases in people. Ideally, a good risk assessment process with systematic tools will help a participant to recognize and neutralize their own biases – both positive and negative – leading to methodical, logical and objective fault observations.

Fault Tree Analysis (FTA), cause and effect (Ishikawa/fish-bone) diagram, Preliminary Hazard Analysis (PHA), and Event Tree Analysis (ETA) are very intuitive systematic tools to identify faults with. They are relative easy to learn and to become proficient at using, and be systematic in their application. Another useful technique for finding faults is based on the first of the seven steps of the Hazard Analysis and Critical Control Points (HACCP) technique. The first step of HACCP is to conduct a hazard analysis for each step of a process and find faults based on a process description and on a straightforward high-level visual review of a process flow diagram (the first step of HACCP also includes the determination of preventive measures associated with the identified faults).

Hazard and Operability Analysis (HAZOP) tools can be used to identify operational faults as a result of deviations from design intent. The HAZOP tool is very structured and formal. It can be very time consuming and resource-heavy, and it may take the team a little time to master how to use it effectively. The Failure Mode Effect Analysis (FMEA) tool is used to determine causes and effects of pre-established faults. A range of faults must first be established (using one of the earlier tools described above, for example) and inputted into the FMEA spreadsheet. The spreadsheet technique will then facilitate the brainstorming of related causes and effects. Training a team of individuals how to use FMEA effectively and consistently can be a bit of a challenge. The FMEA team may have a tendency to deviate on tangents outside the frame of reference for the study, so it is perhaps important that a FMEA study be carefully coordinated by the appointment of a facilitator.

For fault identification purposes, FTA, cause and effect diagrams, PHA, ETA and HACCP can be deployed and used throughout all the lifecycle phases of a manufacturing system (see GAMP® 5 for a description of the lifecycle phases.[7]) They are particularly effective during the earlier phases of a project, such as the concept, planning and the functional-design-specification phases where there is limited information on design details or operating procedures. Often the outputs from these studies act as a precursor to further studies, such as FMEA; however, both HAZOP and FMEA can be considered particularly formal, time consuming and resource-heavy tools. Both are perhaps best used during the detailed design phase of project, prior to a design being official issued for construction.

During the risk assessment process, equal importance should be allocated to everyone's views. The facilitator may find themselves constantly moderating the forthright individuals, while at the same time patiently encouraging and coaxing contributions from the more timid characters. Robust debate is encouraged to refine ideas, but a culture of 'respect for all' must prevail. The momentum between the introverts and extroverts on the team must be balanced and fair. Fault finding is not a competitive sport, and it is quality over quantity every time.

During a risk assessment, groupthink should be eliminated as much as possible as it can lead to biases and irrational decision making. In a respectful and tactful manner, the potentially destructive effects of company hierarchies also must be minimized. The hierarchical perception of 'the boss is always right' can have an inhibitory effect on creative flow throughout the entire risk assessment process. If their ideas remain unchallenged, submissive conformity may lead to substantial biases in the overall process and invariably skew the resultant model. Certain cultural sensitivities may require, or leave no other option than to, segregate and group hierarchies according to their status and rank, where each organizational level embarks upon their own separate risk assessment process.

Everyone should be encouraged to participate in the process to the fullest possible extent. Individual thoughts and knowledge are only useful when they are shared. Concepts evolve, expand and flourish with robust debate. Without the entire team dynamic, the foundation of many ideas would simply not transpire; therefore, no one individual can ever lay exclusive claim to an idea. The facilitator should collate and combine all identified faults into a logical preliminary report that compliments the study question. The risk assessment process may then proceed to the next stage, where the team of subject matter experts will now analyze and evaluate the risks. It may be a good idea for the team to have a rest or recreational period before progressing into this next stage, so that they might recharge their creativity energy.

Analyzing and Evaluating Risks

Once a list of risks is available, they can now be analyzed and evaluated with respect to one another. The acceptability of each risk is determined. Which are the risks that are tolerable? Which are the risks that are not tolerable and require treatment? One way to do this is to compare one risk against another and come up with some type of ranking system.

A traditional ranking system for risks is based on the product of probability and severity. Here a quantitative value or qualitative hierarchy is assigned to each risk based on the probability of their likely occurrence, coupled with the severity of that event should it occur. The risk assessment team

will probably always feel that they do not have enough information to assign a probability and severity value or establish a hierarchy. A complete information set, regrettably, will most likely never exist; therefore, every judgment will only be an estimation based on the limited information at hand. This is usually a good enough place from where to start the risk assessment process, and commence formulating the risk evaluation model. Assurances that the evaluation model is effective will be based on a continuous iterative risk-review process.

For both probability and severity, quantitative point-scales are often used, with the scale one to five (1-5) getting frequent usage. The value for both probability and severity are multiplied together to give a risk score. Simple stratification methods are often used. These typically use red-yellow-green or low-medium-high rating scales so that risk likelihoods can be displayed on a two-dimensional heat-map[3,7] (see Figure M3.5 in GAMP® 5 for an example of a heat-map.[7])

Severity, for example, in the pharmaceutical industry is generally in the context of patient harm. Descriptors for severity might include: 1. low, medium or high, 2. minor, critical, major or catastrophic, and 3. worry, acute illness, hospitalization or death. Once a range of risks has been identified, a relative severity rating is assigned in the context of the overall risk question. If a risk is determined as fatal, that severity cannot be reduced by treatment. However, what can be done is to reduce the probability of that risk occurring in the first place, by the implementation of suitable treatment and mitigation strategies.

Descriptors for probability might include: 1. very low, low, medium, high or very high and 2. frequent, probable, occasional, remote or improbable. In many instances there may be no scientific or statistical basis on which to form any calculable probability whatsoever. However, there is more to assessing risk probability than statistics.[9] A risk assessment is not an attempt to precisely establish absolute probability from the onset, but like the severity rating, merely to rate a predicted risk against another in the context of the specific risk question. For example, two separate studies with seemingly unrelated contexts may identify the same type of risk, but there is no guarantee that the risk will be assigned the same relative probability rating. The rating of one risk is relative to the others identified in the same study, and is context specific. It may not be a good idea to carry probability determinations from one study into another. Perhaps as various risk evaluation models mature, one may indeed be able to build up a general rating system for common risks that may be exchangeable between various studies. Probability and severity ratings, although subjective, are relative in the context of a specific study. Risk practitioners need to be careful, as momentum can be lost if the teams get mired down in making these determinations, particularly in the case of probability.

Risk Control and Treatment

The idea for the implementation of one or more control and treatment actions is that it may stop a trigger event from causing a fault in the first place.[9] Risk treatment, according to ISO 31010, can involve:[2]

- Avoiding the risk by deciding not to start or continue with the activity that gives rise to the risk
- Taking or increasing risk in order to pursue an opportunity
- Removing the risk source
- Changing the likelihood
- Changing the consequences
- Sharing the risk with another party or parties
- Retaining the risk by informed decision

Additional control and treatment measures typically employed by manufacturers include:[5]

- Eliminating the risk completely
- Substituting one thing with another that is more acceptable (substitute one solvent for another)
- Uncoupling, loosely coupling, or modularizing a process to prevent a problem from escalating and impacting on an entire process (confine an event to a single unit operation)
- Applying engineering controls (automation interlocks)
- Isolating a process or product to prevent contamination, and/or protect operators and the environment from accidental exposure
- Providing information (drug contraindications on the container and on the patient leaflet)
- Validation (for example, providing documented test evidence of the robustness of all the cold-chain management steps for a temperature sensitive vaccine formulation)
- Duplicating the asset (having two smaller production sites instead of just one large one, in case one site has a catastrophe)
- Proceduralizing a process by providing specialized information
- Training as both a preventative and protecting control measure
- Monitoring a process to identify an event and initiate appropriate controls

Risk Review

It is somewhat obvious lately that risk assessment doesn't always work, leaving behind a regrettable aftermath of devastation, loss and human hardship. Financial institutions lose money regardless of their complex multivariate risk algorithms devised by physicists and mathematicians. Defenses to natural disasters are breached because levees and sea-walls are simply not tall enough or strong enough

to withstand rare storm surge or tidal wave events. Unusually, civilian aircraft are confronted with the hazard of not being diverted away from conflict zones and are left susceptible to a military strike. Therefore, a continuous, weary and conspicuous eye should be cast over each and every risk evaluation and risk based decision.

ISO 31010 recommends that monitoring and performing reviews should be established as part of the risk management process. Risks and controls should be monitored and reviewed on a regular basis to verify that:[2]

- Assumptions about risks remain valid.
- Assumptions on which the risk assessment is based, including the external and internal context, remain valid.

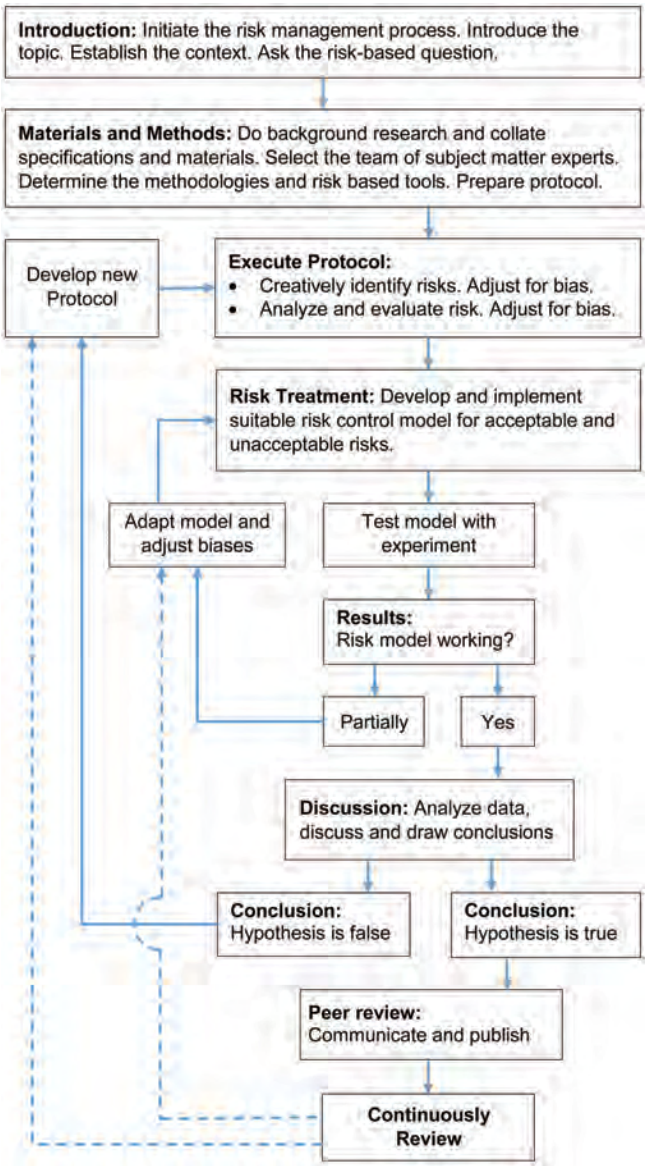

Figure 1. Application of the scientific method to the risk management process.

- Expected results are being achieved.
- Results of risk assessment are in line with actual experience.
- Risk assessment techniques are being properly applied.
- Risk treatments are effective.

Application of the Scientific Method to the Risk Management Process

Instinctively, resultant risk treatment and mitigation strategies will never be fully trusted, nor should they be. The point here is that risk analysis and evaluation is not supposed to be a one-time event. To say that a documented risk-based decision was taken once upon a time, and now the probability of hazard occurrence is under control is simply not true. The assumption that a once-off risk assessment resulted in hazard consequences that are indefinitely tolerable is false. An effective risk evaluation model should ultimately lead to logical and traceable decisions regarding ongoing treatment and control of potential risks. But like all models it needs to be proven that it actually works. This is what any competent authority will expect if they are presented with a risk based decision. Science purports to assist the risk assessment process, so therefore one must, like all good scientific investigations, ensure the risk evaluation

model robustly holds true within the context of the study question.

A risk evaluation model, perhaps, should be treated the same way as a model derived from the scientific method, as illustrated in Figure 1. Generally the scientific method begins with replicate experiments with controlled inputs to yield consistent observed outputs. This empirical output data is assessed and formulated to reveal novel correlations. The correlations are modelled to explain the empirical observations. Based on theoretical inputs, the corresponding outputs are then predicted using the model. To prove the validity of the model, replicate experiments are executed using the same theoretical inputs. The resultant empirical outputs are then compared against the predicted theoretical outputs. The robustness of the model is forevermore challenged and modified based on endless inputs and observed outputs. The same philosophy should hold for risk evaluation models in order to prove the risk assessment hypotheses is true.

Conclusion

Risk assessment is a method for the systematic analysis of uncertainties on the objectives of an organization. It is a creative process that must be both facilitated and stimulated. In an organization, a culture of engaging with and including everyone in the risk management processes should be developed. Every organization has numerous experts on all sorts of specific risks, and chances are that many of them are not in management. Some effort ought to be made to survey representatives at just about every job level in the firm, in terms of contribution.[3] The risk management process cannot take place in isolation, but needs to be supported by a culture and framework within the organization.[6]

The golden rule of any risk evaluation model should be to simply make sure that it works. Always have a healthy obsession with acquiring good quality data and evidence, using good scientific practices, to support the hypothesis that it does work. Examine any evidence objectively before making any judgment or decision. Recognize biases in order to make better decisions, and challenge all preconceptions (in a professional, diplomatic and sensitive way).

To paraphrase Peter L. Bernstein,[10] show the world how to understand risk, measure it, and weigh its consequences, then convert risk-taking into a prime catalyst to drive innovation.

References

1. ISO 31000, *Risk Management – Principles and Guidelines,* International Organization for Standardization, Geneva, Switzerland, 2009, www.iso.org.
2. ISO 31010, *Risk Management – Risk Assessment Techniques,* International Organization for Standardization, Geneva, Switzerland, 2009, www.iso.org.
3. Hubbard, D. W., *The Failure of Risk Management: Why It's Broken and How to Fix It,* John Wiley & Sons, Inc., 2009.
4. *ICH Q9 – Quality Risk Management,* International Conference on Harmonisation, Geneva, Switzerland, 2005, www.ich.org.
5. Vesper, J.L., *Risk Assessment and Risk Management in the Pharmaceutical Industry – Clear and Simple,* PDA/DHI, 2006, www.pda.org.
6. Hopkin, P., *Fundamentals of Risk Management – Understanding, Evaluating and Implementing Effective Risk Management,* Kogan Page Ltd., 2012.
7. *ISPE GAMP® 5: A Risk Based Approach to Compliant GxP Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), First Edition, January 2010, www.ispe.org.
8. *ASTM E2500 – Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment,* American Society for Testing and Materials, 2007, www.astm.org.
9. Fenton, N., and Neil, M., *Risk Assessment and Decision Analysis with Bayesian Networks,* CRC Press, Taylor & Francis Group, 2013.
10. Bernstein, P.L., *Against the Gods – The Remarkable Story of Risk,* John Wiley & Sons, Inc., 1998.

About the Author

Joe Brady is the Director of Global Compliance and Validation at Zenith Technologies. He has more than 17 years of project experience in the pharmaceutical, biopharmaceutical and medical device industries in Ireland, Singapore, China, the Netherlands, France and the USA. Brady is also an assistant lecturer with the Dublin Institute of Technology (DIT), Ireland, in the School of Chemical and Pharmaceutical Sciences. He lectures on the Masters programs in "Pharmaceutical Validation Technology" and "Pharmaceutical Quality Assurance." He can be contacted by email at: joe.brady@zenithtechnologies.com or joe.brady@dit.ie.

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CMC Considerations when a Drug Development Project is Assigned Breakthrough Therapy Status

by Earl S. Dye, PhD, John Groskoph, Brian Kelley, George Millili,PhD, Moheb Nasr, PhD, Christopher J. Potter PhD, Eric Thostesen, and Hans Vermeersch

This article discusses the impact on Chemistry, Manufacturing and Control (CMC) part of a development project when a project is assigned Breakthrough Therapy (BT) status as given in Food and Drug Administration Safety and Innovation Act (FDASIA)[1] and FDA Guidance on Expedited Programs for Serious Conditions.[2]

Assignment of Breakthrough Therapy (BT) designation could lead to accelerated clinical programs, which could be two or more years less than a "conventional" development program. Potential accelerated clinical development timelines could lead to insufficient time to complete all "traditional" CMC studies for approval and delivery to the patient within the boundaries of completing the clinical development program, for example:

- May have reduced real time stability for commercial material and need to leverage stability information from development studies
- Likely to have limited manufacturing experience at commercial scale, which presents the opportunity to leverage life cycle validation principles
- May need to consider launch with initial commercial supplies from a clinical manufacturing facility with clinical fit-for-purpose formulations and then convert over to a commercial formulation and plant immediately post-approval.
- The formulation and process could be ready for transfer, but the commercial facility is unavailable or not ready.
- Limited data sets from which to derive specification acceptance criteria

Using hypothetical case studies based on actual CMC development programs, a series of potential scenarios are given which could lead to discussions with the FDA. These case studies highlight from the overall development program the origins of the potential CMC challenges listed above. Discussions with the Agency should balance the risk of having less traditional CMC data at the time of filing with the potential benefit of a speedy delivery of critical product to patients. Regulatory approaches are proposed to address the lack of some "traditional" CMC data at the time of filing by:

- Employing more flexible filing processes; such as leveraging developmental data and risk assessments in lieu of some commercial scale experience.
- Using post-approval life-cycle management plans
- Including more comparability protocols in NDA submissions
- Employing more interaction opportunities with the Agency

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Considerations are also given regarding facilitating interactions between a sponsor and FDA during a breakthrough therapy CMC development.

Introduction

On 9 July 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted in the US, which created the breakthrough therapy designation for promising new drugs that demonstrate substantial improvement over existing therapies for a serious or life-threatening disease in early clinical studies. The Breakthrough Therapy (BT) designation created an additional regulatory process for the FDA to expedite the development and commercial approval of drugs intended to treat a "serious disease or condition." Other existing regulatory processes available to the FDA include accelerated approval, fast track and priority review. Table A is provided below to identify the primary criteria for each category and its impact on pharmaceutical development and regulatory review.[2]

The FDA's breakthrough therapies pathway focuses on accelerating the existing approval process by having sponsors work closely with the Agency to develop trial designs that shorten or combine traditional phases of drug development. Other regulatory authorities are also considering programs for speeding access of promising new drugs to patients. In March 2014, the European Medicines Agency (EMA) announced an adaptive licensing pilot program[3] which will use regulatory processes within the existing EU legal framework. In April 2014, the UK Agency, the Medicines and Healthcare products Regulatory Agency (MHRA) announced an early access to medicines scheme[4] to support access to unlicensed medicines in areas of unmet medical need; and the Japanese regulatory agency, Ministry of Health, Labor and Welfare (MHLW) is considering introducing an accelerated regulatory processes to make promising new drugs available as quickly as possible to patients.

This article focuses on the US FDA Breakthrough Therapy Program and considers the impact of receiving a breakthrough designation early in clinical development and the challenges for accelerating CMC development activities to meet the expedited clinical development timelines.

Accelerated clinical and safety programs under the BT designation could lead to marketing applications up to two years or more earlier than a more conventional clinical development program. Review of potential CMC development programs required developing a formulation and manufacturing process capable of providing a sufficient reliable supply of product to patients at the time of approval on an indication designated as BT is likely to occur before all "traditional" CMC studies and data sets can be completed. This will require risk-based prioritization of time, resources and materials to accelerate certain activities and provide sufficient data and information to ensure an adequate supply of quality product for patients at the time of approval.

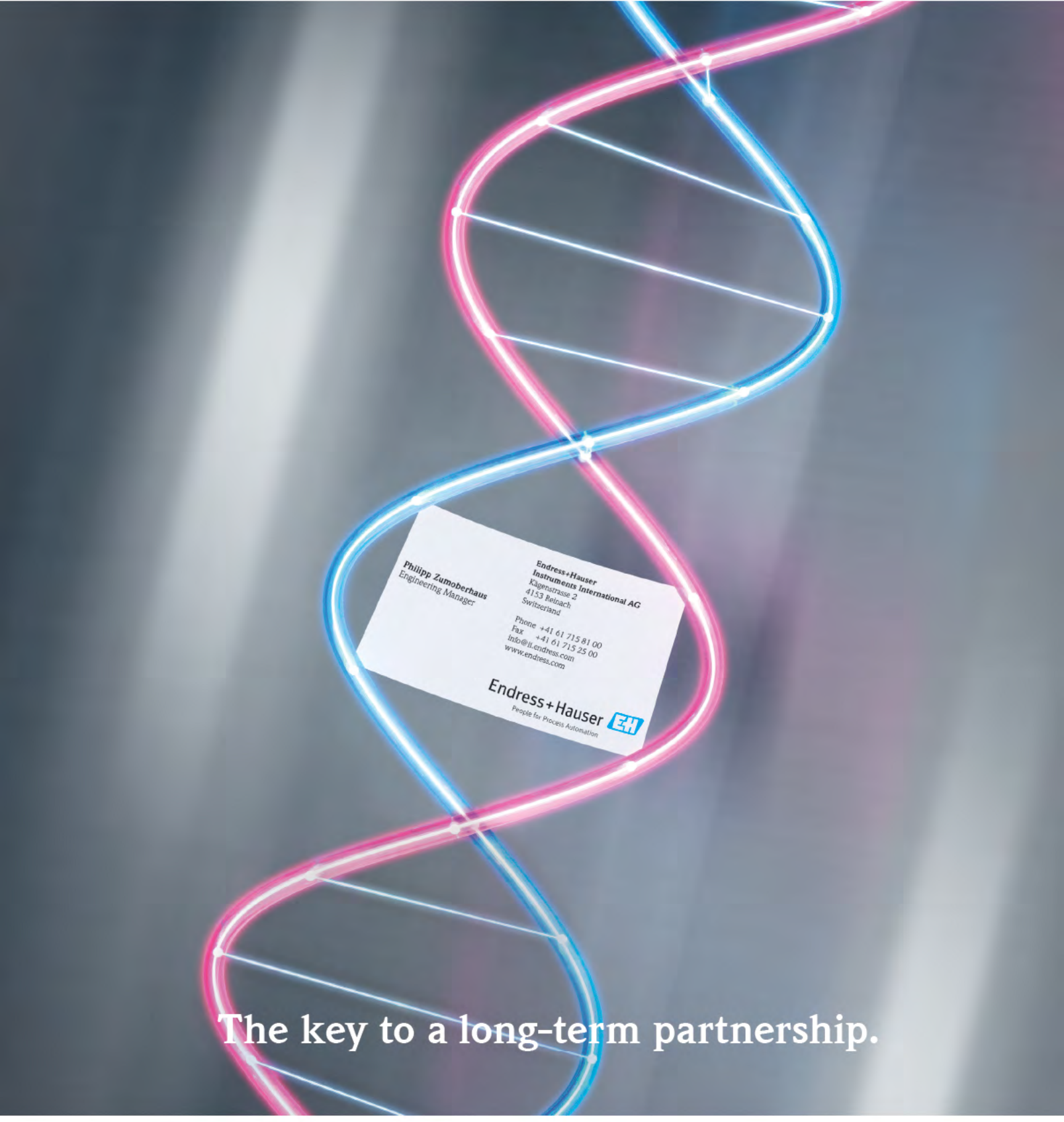
This article uses four case studies to exemplify how two different BT clinical development program scenarios could each impact a small molecule and a large molecule CMC development program. Using these scenarios, a range of CMC challenges are identified and proposals for progression discussed.

Category	Applies to	Impact to Pharmaceutical Development and Regulatory Approval
Accelerated Approval Pathway	Allowance to use a surrogate endpoint in clinical trials for initial approval in disease states with a substantial unmet need.	Completion of confirmatory Phase III studies is still required.
Fast-Track Designation	Granted to drugs intended to treat serious conditions and fill an unmet medical need.	Completion of Phase III studies is still required although rolling submission is allowed, enabling portions of the NDA and data (clinical and non-clinical) to be submitted as it becomes available.
Breakthrough Therapy Designation	Granted to drugs that may demonstrate substantial improvement over existing therapies in early clinical trials.	Commercial application may be submitted based on early clinical evidence (completion of Phase III may not be required at time of initial submission). All benefits of the fast-track designation (i.e., rolling submission) are automatically built in. A single cross disciplinary project manager is assigned at the FDA and commitment is made to frequent the FDA/sponsor meetings throughout the development and review periods.
Priority Review Designation	May be granted at the time of NDA submission to drugs which have achieved any of the above three criteria.	Shortens the statutory review period from 10 months to six months for new chemical entities. Can also apply for a priority review in the case of supplemental applications in which case the review timeline is shortened from 10 months to six months.

Table A. Existing process for accelerated approval.

Introduction to Case Studies – Development Project Background

In this section, high-level development project plans are discussed examining the impact on CMC development of outcomes from clinical programs. From a drug development perspective and review within industry of current projects designated as breakthrough therapies, there are many scenarios. To simplify the



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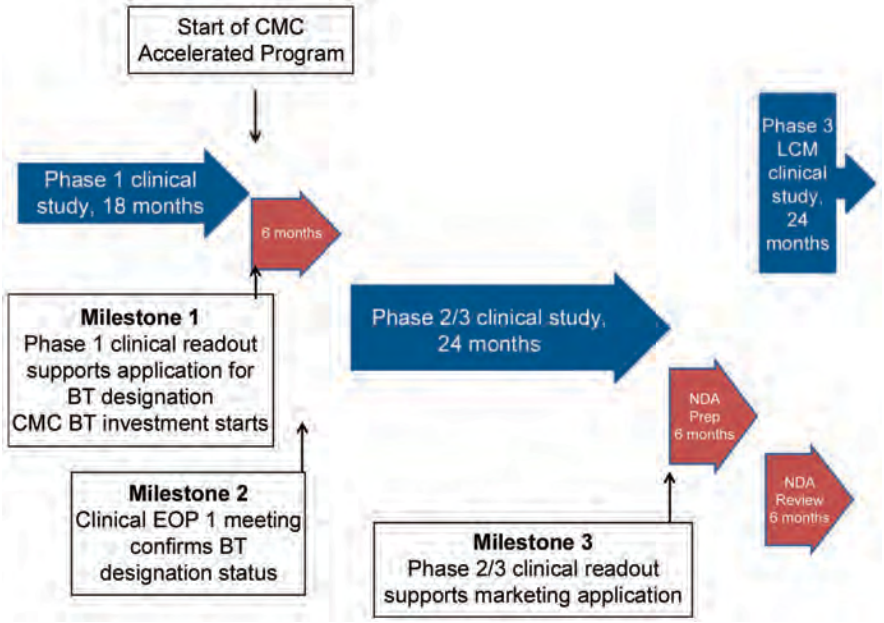

Figure 1. Breakthrough therapy designation based on Phase 1 data.

discussion, two potential clinical development scenarios for the timing of receiving BT designation are discussed. These have been chosen when BT designation is given relatively early in the clinical program leading to greatest challenges for CMC development, where CMC is on the critical path. These two scenarios result when outstanding clinical findings for a serious disease or condition are observed from:

- Phase 1 studies in patients
- Phase 2 studies

In Figure 1, a well-controlled study for a serious disease or condition leads to application for breakthrough therapy designation based on outstanding Phase 1 data. These studies would be conducted in patients, e.g., in oncology indications rather than volunteers and are unlikely to be comparative as required ideally by FDA guidance. At Milestone 1, outstanding clinical data are obtained leading to application for BT designation. It is possible that in the clinical End of Phase (EOP) 1 meeting, designation of BT status could be granted and a comparative Phase 2/3 clinical study agreed. Assuming good outcomes from the Phase 2/3 study, a marketing application could be filed. It is likely that clinical lifecycle expansion program (s) could commence at approximately the time of marketing application filing, which will be another challenge for the CMC development team in terms of product choice and supply.

For this development scenario, it is assumed that there is approximately 36 months from receipt of outstanding **Phase 1 clinical data** (Milestone 1) and filing for a marketing application. For comparison, it could be expected that a "traditional" development program would be approximately 36 months from receipt of good **Phase 2 clinical data** to NDA filing.

In Figure 2, outstanding clinical data for a serious disease or condition emerge from an interim readout of a well-controlled Phase 2 study, which supports a company considering application for breakthrough therapy designation (Milestone 1). In this case, confirmation of outstanding clinical data would lead to a formal BT designation (Milestone 2) and this could lead to a marketing application filing six to nine months later based on these Phase 2 data. It is also likely that a confirmatory Phase 3 clinical study as well as clinical lifecycle studies could commence about the time of BT NDA filing. In this case, a Milestone 3 is given where the CMC team review CMC challenges with FDA.

In this case, there would be approximately 18 months from receipt of a good

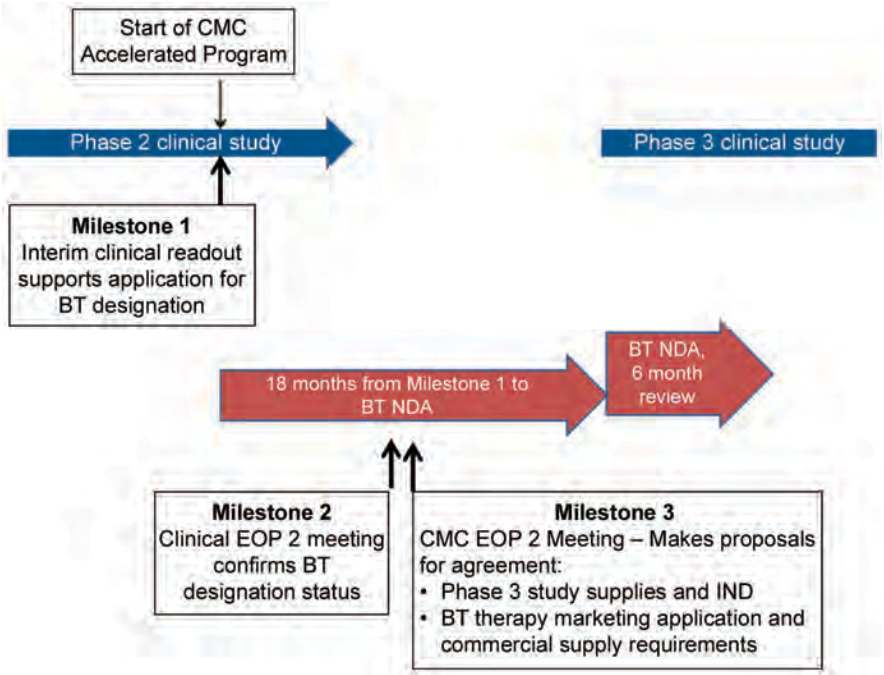

Figure 2. Breakthrough therapy designation based on Phase 2 data.

clinical signal to a marketing application filing.

CMC Case Studies and Topics for Discussion with FDA relating to Potential Flexibility

Four case studies are presented to highlight the variety of CMC issues that could be faced when clinical programs are accelerated and these are given as follows:

Case Study 1 – accelerated development of small molecule commercial formulation, non-ICH. stability data at time of marketing application and approval, and non-standard bioequivalence study.

Case Study 2 – accelerated development of a large molecule leading to non-ICH stability package and absence of PPQ data for drug substance and drug product in the marketing application.

Case Study 3 – accelerated development of a small molecule, which requires launch of clinical formulation from clinical manufacturing site and rapid change for patients to commercial formulation sourced from a commercial manufacturing site.

Case Study 4 – accelerated development of a large molecule, which for patients requires launch from clinical manufacturing site and rapid change to manufacture at a commercial site.

In all cases, proposals are made to optimize availability of patient-acceptable drug product to patients.

Common to all scenarios is the request to provide regulatory flexibility. Topics of interest are discussed with suggestions provided with justifications regarding approaches, which could be taken. In all discussions, it should be clear how the risks of different levels of information compared with a "traditional" application and the risks of supply of quality product to patients are mitigated. This risk mitigation strategy should be thoroughly explained and justified to the Agency.

There are other CMC issues, which could arise, for example setting of specification acceptance criteria from limited data, and changes of route of drug substance synthesis, which will allow facile provision of materials. These have not been exemplified in these case studies

It should be noted that the working estimate for time saved in an accelerated clinical program is approximate 18 to 24 months. This translates to 18 to 24 months less time not only to complete all the activities necessary for CMC approval, but also to complete the activities necessary to launch and maintain commercial supply directly after approval.

To simplify the examples and focus on the main CMC is-

sues, the following general assumptions are made regarding CMC development:

- There is no "front loading" of CMC development activities in the Phase 1 case studies. While "front loading" may be considered an expected business risk given the goal is the pursuit of unmet medical needs, there are large uncertainties regarding clinical outcome, which arises much later in the program. Large companies have multiple projects to fund, resource and hence prioritize, and small companies are unlikely to have the investor support.
- Some front loading is assumed for the Phase 2 case studies since it is assumed that a company will support its own judgment that it has a BT drug candidate, prior to FDA granting BT designation, i.e., between Milestones 1 and 2 in Figure 2.
- Small molecule drug substance synthesis is relatively straightforward.
- For small molecule, drug product is a tablet.
- For large molecules, a platform of monoclonal technology is used.
- Drug substance and drug product are stable.

Case Study 1 – Small Molecule, Phase 1 Entry

Assumptions for this case study in addition to the general assumptions given above are:

- "Simple" formulation used for Phase 1 studies – e.g., powder blend filled into a capsule
- BCS Class 1 drug substance (high solubility, high permeability)
- Limited time and availability of drug substance before Phase 2/3 study start to develop commercial formulation using QbD approach. A QbD approach will be used, however.
- Availability of sufficient drug substance for manufacture of clinical supplies is rate limiting and amount restricts commercial formulation development studies to small scale.

An outline CMC development plan is given in Figure 3 for a small molecule, which enters BT designation after Phase 1 clinical studies.

In the following CMC development plans, clinical programs are given in the top activity row, timescales and activities being taken from Figures 1 and 2. Drug substance development activities are given in orange, drug product activities in green and stability studies in yellow. CMC issues, which arise from this plan, are:

- Non robust formulation used to supply Phase 2/3 study due to lack of time and drug substance.
- Formulation change required for commercial supply. Bioavailability study conducted using commercial formulation manufactured at pilot scale.
- Reduced data set on commercial formulation, e.g., stability data.
- Process Performance Qualification (PPQ) of drug product conducted in a phased manner and completed post approval.

These challenges would be identified for discussion with the FDA early in the accelerated CMC development program, approximately in the range months three to six in Figure 3, when submitting the IND for the Phase 2/3 study.

Topics for Discussion with FDA relating to Potential Flexibility

Topic of Interest – Formulation Development and Bioequivalence

A robust formulation is required to supply patients bioequivalent to the formulation used in the pivotal Phase 2/3 clinical studies.

Proposal for Consideration

Present approach to formulation development, particularly the QbD approach to development of the commercial formulation as part of the IND Phase 2/3 submission along with the clinical strategy. Propose to demonstrate bioequivalence in two steps:

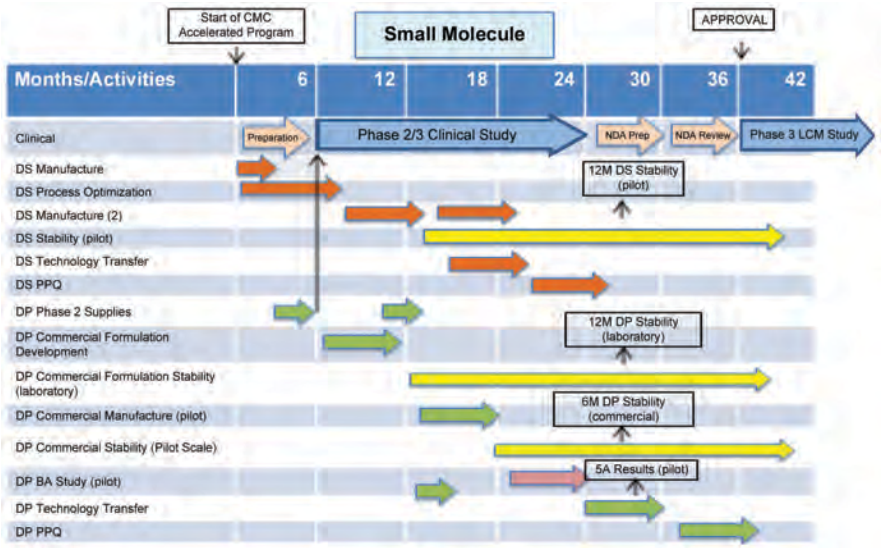

Figure 3. Small molecule, Phase 1 entry.

1. First demonstrating bioequivalent of commercial formulation at a 1/10th scale with Phase 2/3 formulation data in submission.
2. Followed by in vitro dissolution comparison of PPQ batches as given in FDA Guidance, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System5 and SUPAC IR Guidance.6 Submit the results of the scale-up and characterization of the initial PQ batches in support of the CMC section with a commitment to complete PQ post approval in alignment with the FDA Guidance on the Process Validation Lifecycle.

Supporting Information

There is good assurance that the commercial scale drug product of this BCS Class 1 drug will be bioequivalent to the formulation used in Phase 2/3 studies. Bioequivalence data are provided in the NDA comparing pilot scale commercial formulation and Phase 2/3 formulation, and additional data are provided during review showing in vitro equivalence of commercial scale and pilot scale batches of commercial formulation. Given the benefit of providing product to patients at the time of BT approval, this approach is considered low risk.

Topic of Interest – Shelf Life, Drug Product

A shelf life of at least 18 months of shelf life is needed to maintain small molecule drug product in the supply chain for patient availability given the long lead-time for production and potentially low demand, at least initially.

Proposal for Consideration

Initiate the CMC section submission with 12 months data from three laboratory scale batches and six months data from three pilot scale batches of the commercial product packaged in the commercial pack assuming with a commitment to provide additional data during review and normal post approval commitments.

Supporting Data

Stress and accelerated studies during development demonstrate that the product is not prone to significant degradation or changes, confirmed by 12 months laboratory scale date. There are also data from stress and accelerated studies showing that there is no impact of scale on drug product chemical, physical and subjective stability. Assuming a rolling submission as proposed, further data could be provided during review, e.g., 18 month laboratory scale and nine and/or 12 month pilot scale data. Commercial scale stability data

would commence about the time of or shortly after projected approval to confirm this approach as low risk, even though it is different from ICH Q1A(R2) Stability Testing of New Drug Substances and Products.[7]

Topic of Interest – Phased Process Performance Qualification

At the time of anticipated clinical approval, the traditional process performance qualification of the large a molecule drug product will not be completed.

Proposal for Consideration

Supply product to patients immediately after approval with material from the first performance qualification batch.

Supporting Data

This approach is supported by the opportunity to use the concurrent release of PPQ btches approach given in FDA Process Validation guidance.[8] Given the benefit to patients and the assurance that this batch and subsequent batches comply with the PPQ protocol there is good assurance that quality product will be provided to patients. Additionally, it could be suggested that the PPQ protocol is provided to reviewers during review. Overall, this approach is considered low risk.

Case Study 2 – Large Molecule, Phase 1 Entry

Assumptions for this case study in addition to the general assumptions given above are:

- Solution formulation for Phase 1.
- Limited time to develop and scale-up drug substance process prior to start of Phase 2/3 clinical studies.
- Studies to optimize and scale-up the drug substance process focus on process reliability over yield and cost of goods.

An outline CMC development plan is given in Figure 4 for a large molecule, which enters BT designation after Phase 1 clinical studies. CMC issues, which arise from this plan, are:

- Stability data for drug substance and drug product do not comply with ICH Q5C, Stability Testing of Biotechnological/Biological Products9 at time of proposed filing of marketing application.
- Process Performance Qualification (PPQ) of drug substance and drug product are not complete at time of proposed filing of the marketing application. It is conducted in a phased manner and completed post approval.
- Patients are proposed to be supplied from PPQ batches.

These challenges would be identified for discussion with FDA early in the accelerated CMC development program, approximately in the range months three to six in Figure 4, when submitting the IND for the Phase 2/3 study.

Topics for Discussion with FDA relating to Potential Flexibility

Topic of Interest – Storage Period, Drug Substance

A storage period of at least 12 months is required for the large molecule drug substance to provide sufficient time to allow compounding into multiple batches of drug product without waste. Shorter storage periods would lead to unacceptable levels of waste from the batch size of drug substance justified and proposed in the NDA, or increased resources conducting re-testing.

Proposal for Consideration

A storage period for commercial scale drug substance of 12 months is proposed based on provision of three month data from one batch of commercial scale biologic drug substance provided in BLA with a commitment to provide six months during review and to supply further commercial scale data to a pre-agreed protocol.

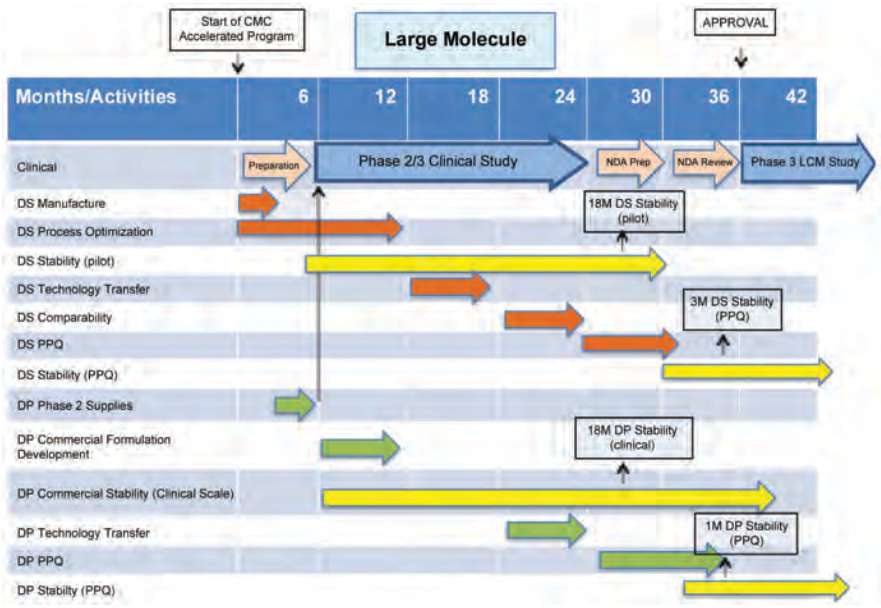

Figure 4. Large molecule, Phase 1 entry.

Supporting Data

This proposal is supported by 18 months good data on pilot/clinical batches with the option to provide additional data (e.g., 24 months) during review. There is additional assurance regarding absence of stability differences due to scale from other earlier studies with similar monoclonal antibodies manufactured using the same platform technology, and evidence supports that it is a stable drug substance. Given the good stability performance of this drug substance, this is considered a low risk approach even though it is different from ICH Q5C, Stability Testing of Biotechnological/Biological Products.[9]

Topic of Interest – Shelf Life, Drug Product

A shelf life of at least 18 months is needed to maintain product in the supply chain for patient availability given the long lead-time for production and potentially low demand, at least initially.

Proposal for Consideration

An initial expiry 18 months is proposed based on 18 months real time data provided in the commercial pack from two pilot (clinical) scale batches for a stable drug product with the option to provide 24 months data during review. Commercial scale stability studies are performed to a pre-agreed protocol. One month data from a PPQ batch could be available late during the review period. The protocol for commercial stability studies is proposed to be a matrix of time period, test and size of container.

Supporting Data

This is supported by results from extensive development studies (e.g., accelerated and stress studies examining as independent variables, scale of manufacture and volume size of the commercial pack) showing that scale (essentially time of filling) of an aseptically-filled solution drug product and volume size of commercial pack do not impact stability. Stability data from at least one technology transfer batch (three months) at commercial scale could be available at time of filing of BLA. Given the good stability performance of drug product and the sponsor's commitment to comply with the protocol this is considered a low risk approach even though it is different from ICH Q5C, Stability Testing of Biotechnological/Biological Products.[9]

Additional note: ISPE sees an opportunity to provide guidance/best practices related to designing and documenting early stability programs to support expiration dating for product launch.

Topic of Interest – Process Performance Qualification

Clinical approval overlaps with the execution of the process performance qualification studies for drug substance and drug product, which for a large molecule marketing application results are required in BLA submission. The product has a long lead-time in production. The production timing is such that to have material available for launch supplies as soon as possible following clinical approval, it will be necessary to utilize the PPQ batches for commercial supply.

Proposals for Consideration

Two proposals related to provision of process performance qualification information are:

1. Submit the available scale-up, comparability and characterization data along with the PPQ protocol with a commitment to provide the data as it becomes available during review and, depending on timing, concurrent with product release. This assumes data meet all requirements under the protocol.
2. Submit drug substance comparability protocol and data, and PPQ protocols for drug substance and drug product in the BLA. Provide all data for drug substance, which should be completed, during review. For drug product, provide all available data during review.

Drug product is proposed for supply to patients using material from PPQ batches complying with PPP protocol criteria

Supporting Information

Considering the compatibility has already been established, providing PPQ data in a phased manner as suggested above provides maximum information for review prior to approval. Process performance qualification contains many repeat studies conducted as part of the comparability program and hence the risk of failure to comply with PPQ protocol criteria is low.

Given that platform technology is being used, that comparability studies are completed and acceptable comparing commercial scale batches with clinical batches and a good package of drug substance and drug product information is included in the BLA to support presentation of the drug product process performance qualification protocol, it is proposed that drug product from process performance qualification batches complying with the protocol is used to supply patients. This suggestion is in line with the concurrent release of PPQ batch approach given in FDA Process Validation Guidance.4 It is proposed that PPQ qualification report is provided to the Agency on completion, post approval if required. This is considered a low risk approach.

Case Study 3 – Small Molecule, Phase 2 Entry

Assumptions for this case study in addition to the general assumptions given above are:

- Phase 2 formulation is fit-for-purpose, however, not optimized in terms of robustness or commercial presentation (Phase 2 studies are blinded).
- Strong need for patients to introduce "improved" formulation as soon as possible.
- Drug substance route is adequate for Phase 3 clinical and toxicology study supply.
- BCS Class 1, high solubility, high permeability.

An outline CMC development plan is given in Figure 5 for a small molecule, which enters BT designation after Phase 2 clinical studies. CMC issues, which arise from this plan, are:

- Propose launch of "fit-for-purpose" Phase 2 formulation from pilot/clinical manufacturing site.
- Reduced stability dataset for Phase 2 formulation from pilot/clinical site at time of marketing application.
- File for change of formulation and site of manufacture approval before approval of Phase 2 formulation.
- Reduced stability dataset for commercial formulation from commercial manufacturing site at time of marketing application.

These CMC issues would be evident at the start of an accelerated program and hence could be discussed with FDA at or shortly after Milestone 2 in Figure 2 when there is agreement to BT designation.

Topics for Discussion with FDA relating to Potential Flexibility

Topic for Discussion – Formulation and Site of Manufacture Change

The clinical formulation and site of manufacture are not suitable for long term supply to patients.

Proposal for Consideration

The clinical formulation is fit-for-purpose for Phase 2 clinical studies, which are blinded. It is not viable for long term commercial supply to patients. In order to meet patient needs at the time of proposed clinical approval it is proposed to supply Phase 2 clinical formulation sourced from the clinical manufacturing site. Change to an "improved" formulation to meet patient needs better and to source from a commercial manufacturing site is proposed with the marketing application submitted before approval of the Phase 2 formulation.

Supporting Information

Feedback from patients and medical practitioners during the Phase 2 is that the tablet dosage form is too large. Given the patient population intended to be treated there is a strong requirement to re-formulate to a smaller dosage form more acceptable to patients.

At the time of anticipated clinical approval the commercial formulation cannot be developed and shown bioequivalent to the Phase 2 to allow initial launch of the commercial formulation.

Topic for Discussion – Non-Standard Stability Package for Phase 2 Formulation Marketing Application

A shelf life of at least 18 months is needed to maintain product in the supply chain for patient availability given the long lead-time for production and potentially low demand, at least initially.

A retest date of at least 12 months is required to support smooth progression of drug substance into drug product.

At the time of marketing application for the Phase 2 formulation manufactured at the clinical manufacturing site the stability package does not comply with ICH Q1A(R2).

Proposal for Consideration

Stability data at time of filing of Phase 2 formulation marketing application:

- 3 month of 3 batches of drug substance manufactured at

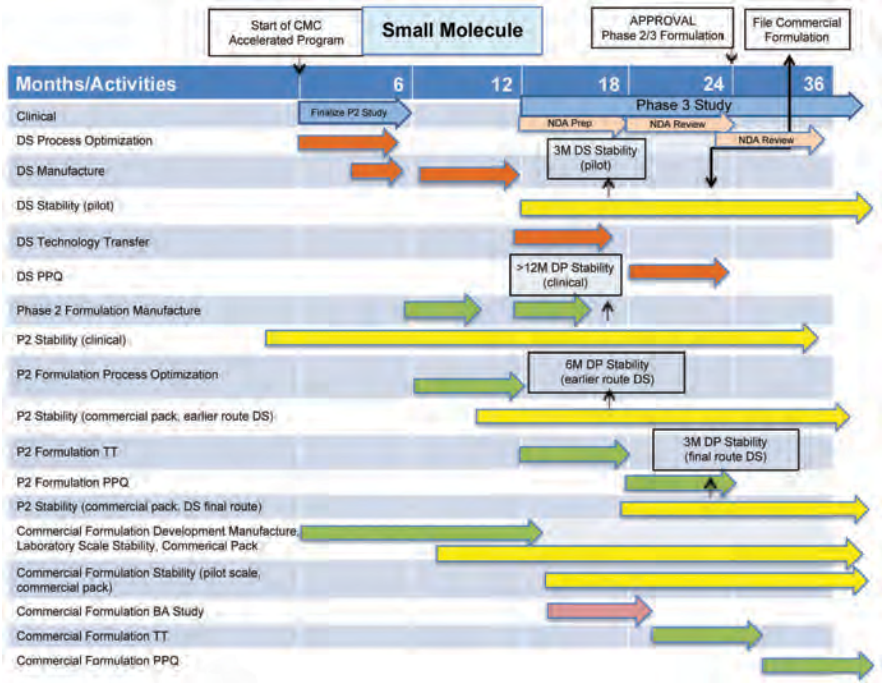

Figure 5. Small molecule, Phase 2 entry.

pilot scale using commercial synthetic route supported by 12 months from >1 batch manufactured by an earlier synthetic route

- >12 month from 1 batch of drug product packaged in the clinical pack
- 6 months from 3 batches of drug product manufactured from an earlier synthetic route packaged in commercial pack
- 3 months from 3 batches of drug product manufactured using final route synthesis drug substance and packaged in commercial packs available during review

Supporting Information

A shelf life of 18 months is proposed for the Phase 2 formulation packaged in the commercial pack based on greater than 12 months data for this formulation packed in the clinical pack plus three months data using final synthetic route drug substance and six months data from the previous route. Accelerated data on both drug product and drug substance show no difference in stability due to route of synthesis of drug substance. Development studies also show no difference in stability between drug product assembled into clinical and commercial packs. The Agency will be informed immediately if data are generated outside an agreed protocol. Given the substantial amount of data for this stable drug product the proposed shelf life and overall approach is considered low risk even though it is different from ICH Q1A(R2) Stability Testing of New Drug Substances and Products.[8]

A retest date of 12 months is proposed for drug substance supported by at least 12 months satisfactory data from an earlier synthetic route and three months of accelerated data for a stable drug substance showing good stability from three batches of drug substance manufactured at pilot scale. For a stable drug substance, the proposed retest date is considered low risk even though it is different from ICH Q1A(R2) Stability Testing of New Drug Substances and Products.[8]

Topic for Discussion – File Marketing Application for New Formulation Before Phase 2 Formulation Approved

It is proposed to file the new formulation and site based on the information given above during review of Phase 2 formulation (for example about one month before expected approval) with the proposal that review of this application is also subject to BT timelines. The benefit would be a more reliable supply of quality product to patients.

Proposal for Consideration

This non-standard regulatory process would require much discussion and prior agreement from the agency.

There are many points of discussion, however, to take stability and bioavailability of drug product as an example,

the following data should be available at time of filing for commercial formulation marketing application:

- BA study comparing new formulation using material from pilot scale manufacture vs Phase 2 formulation
- 3 month stability data from pilot scale batches of drug product with 6 month data available during review of new formulation

Supporting Information

It is proposed to demonstrate bioequivalence in two steps:

1. First demonstrating bioequivalent of commercial formulation at a 1/10th scale with Phase 3 formulation with data in submission.
2. Followed by acceptable in vitro dissolution comparison of PPQ batches as given in FDA Guidance, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System5 and SUPAC IR Guidance.[6]

An 18 month shelf life for drug product would be justified by:

- Extensive development data from pre-formulation studies
- Stress and accelerated data comparing the commercial formulation and the Phase 2 formulation
- Stress and accelerated data comparing different scales of manufacture of the commercial formulation
- Real time data on pilot scale formulation

For a stable drug substance, the proposed retest date is considered low risk even though it is different from ICH Q1A(R2) Stability Testing of New Drug Substances And Products.[7] It is a stability package which is similar to an ANDA application particularly if one or three months stability from at least one commercial scale batch of drug product were provided during review.

Case Study 4 – Large Molecule, Phase 2 Entry

Assumptions for this case study in addition to the general assumptions given above are:

- Phase 2 solution formula proposed as commercial dosage for filing
- Focus time available to filing on process optimization studies
- Immediate scale up required to supply anticipated commercial demand

An outline CMC development plan is given in Figure 6 for a large molecule, which enters BT designation after Phase 2 clinical studies. To meet anticipated clinical approval timelines it is proposed to launch from pilot scale drug substance and drug product sites, which obviously assume that projected initial market demand can be met; however, projected demand requires scale up as soon as possible. Delay of approval of the commercial manufacturing site may result in stock outs and rationing of supplies to patients.

Given the patient need and availability of expertise and resource to support drug substance process development and scale-up, there needs to be a balance of resource applied to qualification studies for pilot scale manufacture and scale-up studies and qualification of production scale manufacture.

These CMC issues would be evident at the start of an accelerated program and hence could be discussed with the FDA at or shortly after Milestone 2 in Figure 2 when there is agreement to BT designation

Topics for Discussion with the FDA Relating to Potential Flexibility

Topic for Discussion – Site of Manufacture Change, Balance of Pilot Scale PPQ Studies, and Commercial Scale-Up and PPQ Studies

This CMC scenario is considerably different from a "traditional" submission for a BLA and would require substantial

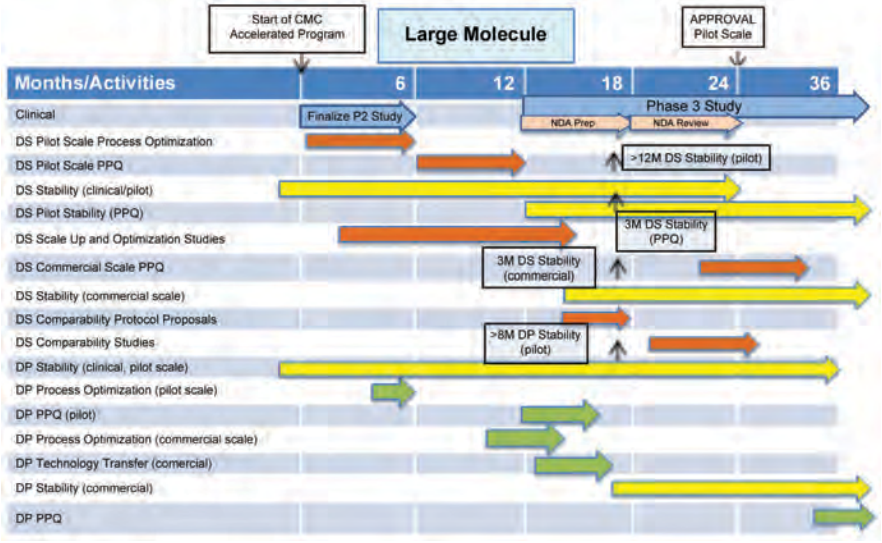

Figure 6. Large molecule, Phase 2 entry.

discussion with the Agency, an example of major differences from the 'traditional' approach being:

- Filing with limited qualification data from pilot scale.

Proposal for Consideration

Protocol and study design for PPQ studies to support a BLA application for pilot scale manufacture requires discussion and agreement with the Agency, potentially on more than one occasion.

During these discussions, it would be appropriate to agree studies to support PPQ of commercial scale manufacture and the timing of the proposed marketing application for commercial scale manufacture. The date of filing for commercial scale manufacturing is not given in Figure 6; however, from a patient viewpoint, this should be as early as possible.

Supporting Information

Information for the discussion would be developed using a risk-based approach utilizing prior knowledge from the platform technology, and development studies performed for this drug substance. Studies for PPQ at commercial scale would be informed by parallel studies conducting PPQ of pilot scale manufacture

Topic for Discussion – Shelf Life Request

The amount of drug substance stability data at pilot scale should be sufficient, for example greater than 12 months on an early batch, and six months from three batches from proposed initial scale of supply.

The amount of stability data for pilot scale drug product should also be sufficient given that there will be at least six months data on three batches from the intended initial scale of supply. A shelf life of greater than six months would be requested to maintain supplies to patients, for example 18 months (re-labeling after approval of shelf life extensions is not practical).

Conclusion

If a development project generates outstanding clinical data for a serious disease or condition, it is likely that a company or the FDA will request that formal application is made for BT designation. If the development project team considers this a good possibility, the implications on CMC development are significant. For example:

- BT nomination could give insufficient time to complete all 'traditional' CMC studies.
- BT CMC work for filing should use a risk-based approach to prioritize time, resources and materials to provide data and information to support a BT NDA filing, and to ensure supply of quality product to patients.
- Given the assumption that CMC is not complete, there is likely to be more post approval activity, for example:
  - More stability data
  - Additional confirmatory validation (process robustness) studies
  - Changes of site, scale of manufacture, raw material supplier
  - Changes of drug substance synthetic route
  - Change of formulation with supporting bioavailability studies

In conclusion, there is sufficient justification in all the above cases studies to discuss with the Agency filing using more flexible regulatory approaches to provide patients with an exciting new drug based on providing assurance of quality.

Dialogue with the FDA should be early, fast and effective to provide the CMC development team with answers to which they can respond in the limited time available to ensure that, given approval, patients can be supplied with quality drug product. It is submitted that the current process of providing a briefing document about three months before a meeting with the FDA and receiving formal answers about a month following the meeting is an insufficient level of assurance that answers can be addressed so that there is a positive impact on a NDA/BLA filing strategy. Better interactions with the FDA are being employed to facilitate accelerated approvals, for example use of:

- "Informal" telephone conversations. There still the responsibility of the sponsor to record the conclusions of the conversation.
- IND amendments

BT designation produces many CMC challenges which a sponsor and the FDA need to address using a risk-based approach to assure sufficient information available to support approval and supply of quality product for serious disease or condition' demonstrating "substantial improvement over existing therapies to patients.

References

1. Food and Drug Administration Safety and Innovation Act (FDASIA), (Pub. L. 112-144), 9 July 2012, www.fda.gov.

2. *FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics,* June 2013, U.S. Food and Drug Administration (FDA), www.fda.gov.

3. EMA/254350/2012, *Pilot Project on Adaptive Licensing,* 19 March 2014, European Medicines Agency (EMA), www.ema.europa.eu.

4. Early Access to Medicines Scheme, http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON404193, 7 April 2014.

5. *FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System,* August 2000, U.S. Food and Drug Administration (FDA), www.fda.gov.

6. Immediate Release Solid Oral Dosage Forms: Scale Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (1995) and SUPAC-IR Questions and Answers about SUPAC-IR Guidance, 1997.

7. *ICH Q1A(R2) – Stability Testing of New Drug Substances and Products,* Step 4, 6 February 2003, www.ich.org.

8. *FDA Guidance for Industry: Process Validation – General Principles and Practices,* January 2011, U.S. Food and Drug Administration (FDA), www.fda.gov.

9. *ICH Q5C – Stability Testing of Biotechnological/Biological Products,* Step 4, 30 November 1995, www.ich.org.

About the Authors

Earl S. Dye, PhD, Director, Technical Regulatory Policy, Genentech Inc.

John Groskoph, Senior Director, Global CMC, Pfizer, Inc.

Brian Kelley, Vice President, Bioprocess Development, Genentech Inc.

George Millili, PhD, Senior Principal Technical Advisor, Genentech Inc.

Moheb Nasr, PhD, VP, CMC Regulatory Strategy, RD Chief Regulatory Office, GlaxoSmithKline

Christopher J. Potter, PhD, ISPE Advisor and CMC Pharmaceutical Consultant

Eric Thostesen, Sr. Director, Regulatory Compliance, Johnson & Johnson

Hans Vermeersch, Senior Technical Director, Janssen Pharmaceuticals

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Science-Based Quality Risk Management

This article describes Quality Risk Management as it relates to ISPE Guidance Documents and was developed collaboratively by the leaders of the Guidance Documents Committee.

Risk management is a systematic application of management policies, procedures and practices to the task of identifying, assessing, controlling and monitoring risks. It is typically an iterative process.

Risk management should be based on good science and product and process understanding – for example, an understanding of Critical Quality Attributes (CQAs) – which is based upon and ultimately traceable back to the relevant regulatory submission.

Qualitative or quantitative techniques may be used. The focus should be on the risk posed to patient safety and product quality. Risk management should reduce risks to an acceptable level. Complete elimination of risk is neither practical nor necessary.

For a given organization, a framework for making risk management decisions should be defined to ensure consistency of application across functions. Such a framework is most effectively implemented when it is incorporated into the overall quality management system.

ICH Q9 Quality Risk Management Approach

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline (ICH Q9) describes a systematic approach to quality risk management. ICH Q9 is used as the basis of the quality risk management approach described in the guideline.

ICH Q9 defines two primary principles of quality risk management:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

ICH Q9 is intended for general application within the pharmaceutical industry.

ISPE Guides use the following key terms taken from ICH Q9:

- **Harm:** damage to health, including the damage that can occur from loss of product quality or availability.
- **Hazard:** the potential source of harm.
- **Risk:** the combination of the probability of occurrence of harm and the severity of that harm.
- **Severity:** a measure of the possible consequences of a hazard.

ISPE Guides apply the principles of ICH Q9 to describe a general process for quality risk management consisting of the following elements:

- Risk Assessment
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation
- Risk Control
  - Risk Reduction
  - Risk Acceptance

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- Risk Communication
- Risk Review

The process is described in more detail in the following sections.

Overview of the Quality Risk Management Process

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in Figure 1, which is taken from ICH Q9.

The emphasis on each component of the framework might differ from case to case, but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Initiating Quality Risk Management

Quality risk management should include systematic processes designed to coordinate, facilitate, and improve science-based decision making with respect to risk.

The following steps should be considered when initiating and planning a quality risk management process:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk
- Assemble background information and/or data on the potential hazard, harm, or human health impact relevant to the risk assessment
- Identify a leader and necessary resources
- Specify a timeline, deliverables, and appropriate level of decision making for the risk management process

Determining the risks associated with a particular topic area requires a common and shared understanding of relevant product and process factors.

Example factors to consider, which are related to oral solid dosage, may include:

- Is the facility multi-product? If so, which vectors (e.g., people, clothing, air currents, rodents, raw materials, or equipment) might bring contaminants in contact with the product?
- Will the facility need to accommodate highly hazardous compounds or compounds requiring isolation?
- Are the products microbiologically sensitive?
- Are processing conditions necessary to meet quality standards and to ensure patient safety, documented?

Example factors to consider, which are related to GxP regulated computer systems, may include:

- Impact of the computerized system on patient safety and product quality
- Supported business processes including consideration of any affected CQAs
- System user requirements
- Regulatory requirements
- Project approach (contracts, methods, timelines)
- System components and architecture
- System functions
- Supplier capability

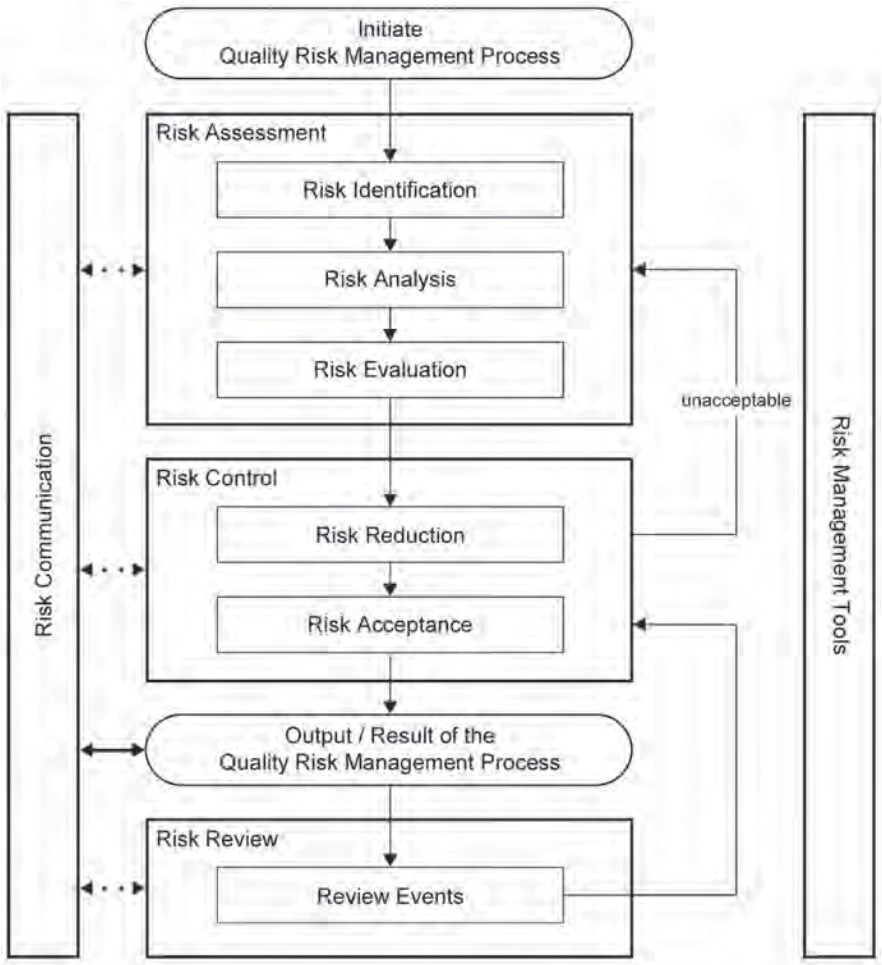

Figure 1. Overview of a typical quality risk management process taken from ICH Q9.

Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards, and consists of *identification, analysis,* and *evaluation* activities.

Risk assessment addresses the following fundamental questions:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses "What might go wrong?" including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Example hazards to consider, which are related to oral solid dosage, may include:

- Cross-contamination or microbiologic contamination from, e.g., clothing, people, rodents, or air currents)
- Non-compliance with regulatory expectations regarding zoning
- Processing conditions – how can they go out of specification – e.g., Critical Process Parameters (CPPs)
- Mixing or commingling as a result of material flow
- Processing conditions, residence time, etc.
- HVAC or processing equipment cross-contamination potential

Example hazards to consider, which are related to computerized systems, may include:

- Human error (includes errors of judgment and errors in carrying out required actions)
  - Change error
  - Unauthorized change
  - Undetectable change
  - Wrong access rights

- Computer-related
  - Hardware undersized
  - Hardware loss (e.g., disk crash)
  - Data loss (e.g., backup failure)
  - Wrong version of software
  - Multiple versions of software
  - Software lost or deleted
  - Software failure
  - Printer error or failure

- Physical/Environmental
  - Power surge
  - Power failure
  - Fire and/or smoke
  - Environment problem

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. The ability to detect the harm also should be considered in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

Often the outcome of the risk assessment will be expressed using qualitative descriptors, such as "high," "medium," or "low." These terms and how they are used should be defined in as much detail as possible.

Risk Control

Risk control includes decision making either to *reduce* risks or *accept* them, or both. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort applied to risk control should be proportional to the significance of the risk.

Risk control addresses the following questions:

1. Is the risk above an acceptable level?
2. What can be done to reduce or eliminate risks?
3. What is the appropriate balance among benefits, risks, and resources?
4. Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detect-ability of hazards and quality risks might also be used as part of a risk control strategy.

The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence the results of risk assessment should be revisited to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified.

For some types of harm, even the best quality risk management practices might not entirely eliminate risk. In

these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

Example controls for risks/hazards that exceed the acceptable level of risk, which are related to oral solid dosage, may include:

- Process design and PAT
- Use of HEPA filters to prevent cross-contamination
- Cleaning validation (including microbiological considerations if products support microbial growth)
- Change control procedures which ensure update of critical process documentation (e.g., P&IDs)
- Use of minimal contact between people and materials through building design
- Develop procedural controls to prevent cross-contamination/commingling
- Rodent controls
- Zoning requirements (people and HVAC)
- Differential air-pressure between zones

For computerized systems, procedural and technical controls available to reduce risks to an acceptable level may include:

- Security management
- Backup and restore
- Disaster recovery and business continuity
- Change control
- Validation
- Audit trail
- Record copying controls
- Record retention controls
- Software controls
- Hardware controls
- Policies, procedure, and training

Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process.

The output and result of the quality risk management process should be appropriately documented, and communicated, e.g., to regulators, to the patient, within a company.

Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

> *"Risk management should be based on good science and product and process understanding – based upon, and ultimately traceable back to, the relevant regulatory submission.*

The output and results of the risk management process should be reviewed to take account of new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall).

The data gathered by the quality system should be used to find opportunities to further minimize the GMP risks.

Quality Risk Management Tools

No one tool or set of tools is applicable to every situation in which a quality risk management process (as described) is applied. ICH Q9 provides a general overview of, and references for, some of the primary tools used in quality risk management by industry and regulators.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.

Conclusions

Risk management is a systematic application of management policies, procedures, and practices to the task of identifying, assessing, controlling, and monitoring risks. Risk management should be based on good science and product and process understanding – based upon, and ultimately traceable back to, the relevant regulatory submission.

As noted in ICH Q9, the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

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Risk Analysis and Annual Training Program Definition

by Luca Falce

This article presents an example of risk analysis.

Risk analysis is a technique used in all areas of the pharmaceutical industry; however, its major use is associated within the field of validation (equipment, machinery, utilities, cleaning), program inspections definition (audits) and design/maintenance.

This article presents an example of risk analysis associated with quality assurance and an annual training program conducted by an Italian pharmaceutical company with the objective of reducing deviations linked to human error.

Introduction

According to regulatory authorities,[1-2] risk analysis is a technique which could be applied in the pharmaceutical industry; however, examples where this methodology is used in areas other than technical ones are not easily found. This in part lies with the origins of the instruments used, and equally with the difficulty in the application of these concepts to situations related to factors of human behavior.

In the following case, the risk analysis technique has been applied to a variety of human behaviors. The application of this technique is related to the desire of the company's Board to follow authority expectation in order to solve a recurrent problem and to both update and increase the knowledge of company personnel. In concert with the approval of the 2010 Final Quality Report (January 2011), it was decided to create a study group to analyze deviations and to try to reverse the already present trends that indicate that the human factors are a frequent cause for deviations).

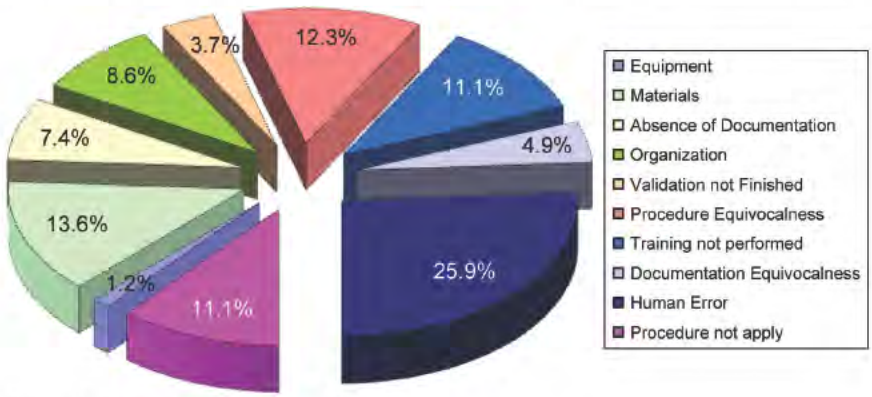

Figure 1. Deviations 2009.

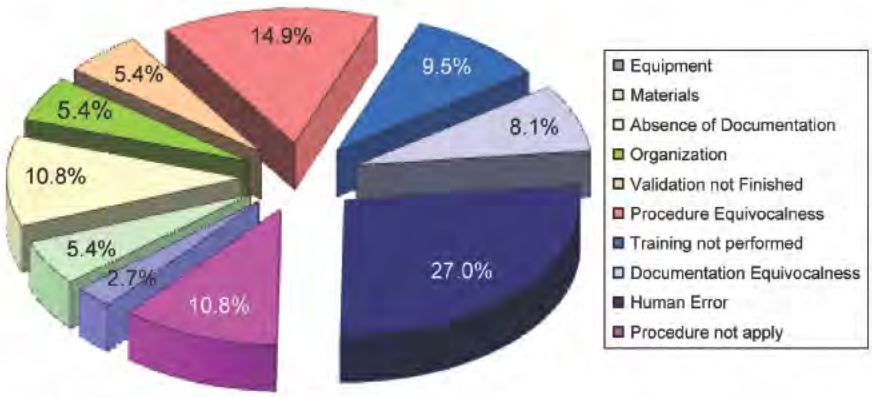

Figure 2. Deviations 2010.

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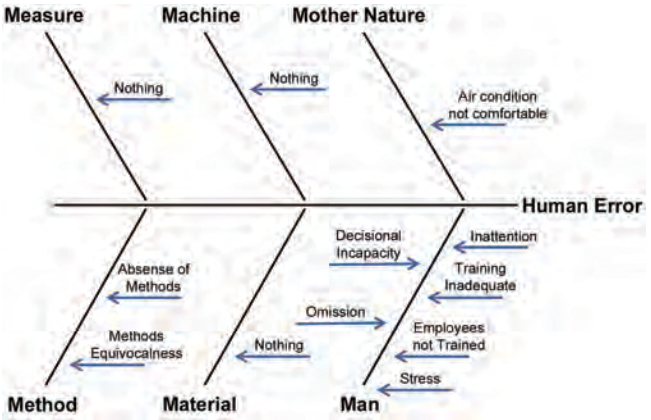

Figure 3. Ishikawa diagram.

Performed Activities

Preliminary Analysis

The working group was comprised of quality assurance personnel who ran the deviations and training and occasionally, depending on the needs/issues) by staff from various departments. The first activity was to re-check deviations identified as resulting from human errors.

It was decided to use an Ishikawa diagram as seen in Figure 3 to highlight the possible causes for deviations. The results were analyzed with respect to the applicability of a logic tool similar to Fault Tree Analysis (FTA), i.e., the same concept but no reference to the actual technique. At the end of this analysis, some cases were considered by the group as significant with the situation as seen in Table A.

This analysis showed the need to review the documentation by including:

- Photos
- Symbols
- Diagrams of processes
- Flow charts
- Checklists

In order to improve memory skills, learning and decision capability of the operator, the changes led to the addition of some organizational devices to make the work easier, i.e., coding/identification by color of parts and formats, dedicated equipment or similar but used for different products, etc. Examples are:

- Color identification of piping depending on the type of product (diluents – white color, analgesic – yellow color) and position identification depending on the technical parameters (diameter/length; tube 1, tube 2, etc.) as seen in Figure 4.

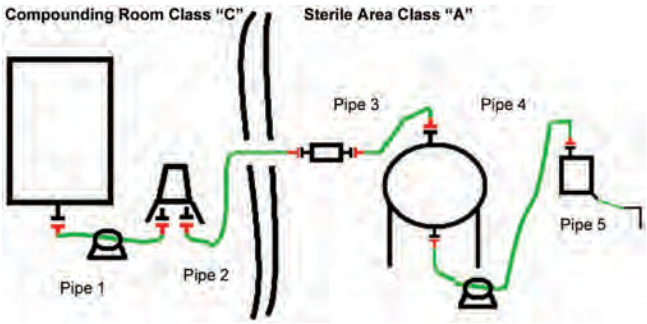

Figure 4. Tube set-up flow diagram.

Cause	Applicability	Explanation/Reason	Action
Air condition not comfortable	No	Air condition system works with the following set point: • 40 % < RH% < 60% • 19 < T < 23 °C	Nothing
Absence of methods/Manuals	Yes	In some case documents are missing because at the beginning they were considered not necessary	Issuing of documentation
Methods equivocalness	Yes	Some manuals are too specific or written by technician people so that not all steps are described.	Revision of manuals by addition of pictures, flow charts and check lists to help understanding and memorization. Training after issuing of new versions.
Stress	No	Type of work and working rate cannot considered like an alienating job	Nothing
Employees not trained	Yes	Due to increased work some people were put on the line without an adequate training.	Revision of training procedure to clarify minimum request for each department
Training inadequate	Yes	Job rotation without appropriate know-how to cover unplanned absences	Revision of training procedure to clarify minimum request for each department
Omission	Yes	People know the procedures but are not able to put in practice their knowledge and so operate by guess.	Revision of internal manuals by addition of pictures, flow charts and check lists to help understanding and memorization. Training after issuing of new versions.
Decisional Incapacity	Yes	People know the procedures but are not able to put in place their knowledge and so when necessary don't decide how to manage the situation.	Revision of manuals by addition of pictures, flow charts and check lists to help understanding and memorization. Training after issuing of new versions.
Inattention	Yes	In some situation people are not concentrated in their work and so they are not able to understand what happens or how to manage the situation.	Emphasize the value of the work. Modify the plant by adding, where possible, acoustics and visible signals to highlight dangerous situations. Revision of manuals by addition of pictures, flow charts and check lists to help understanding and memorization. Training after issuing of new versions.

Table A. Cause analysis/applicability/action.

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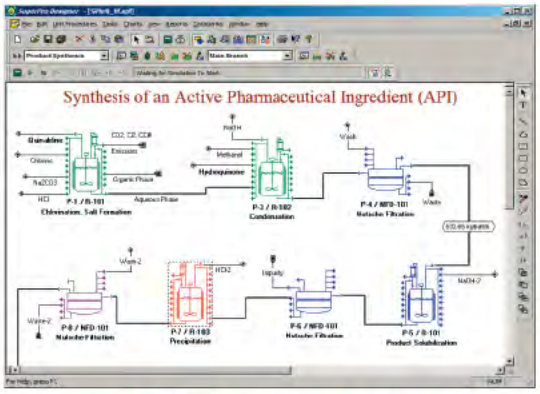

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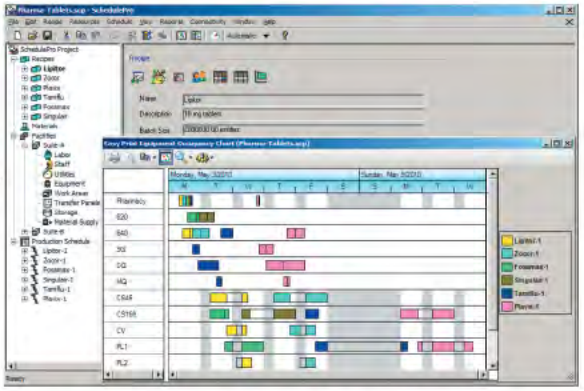
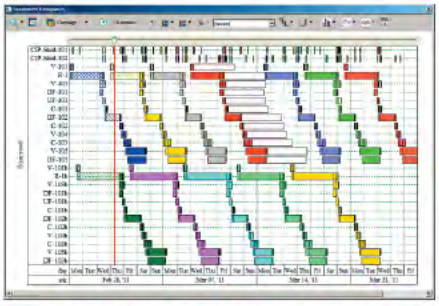


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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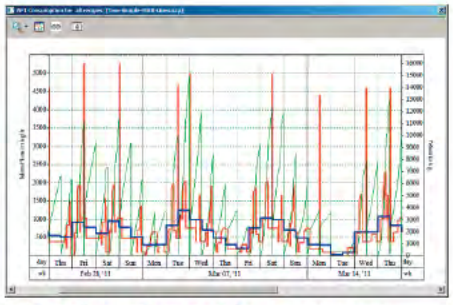
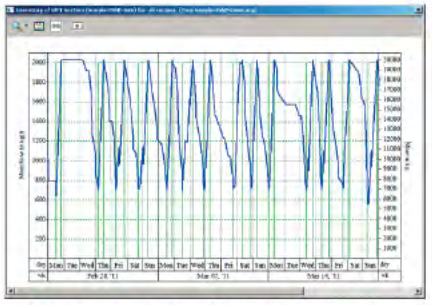


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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- Changing operational description of sequences with added details and graphics/images:
  - Before – Press the start button and follow the instructions that appear from time to time on the display.
  - After – Hold for at least 3" the start button (the green button) as seen in Figure 5.

Figure 5. Start button.

After the system has completed its initial tests, "cycle ready" will appear on the display, press again the green button until you hear the gasket lock after the pumping up with compressed air.

Failure Modes, Effects, and Criticality Analysis (FMECA) and Classification of Training Chapters

In addition to these activities, it was necessary to change the theoretical and practical training plan by customizing it to be common for all functions.

Through the use of the FMECA technique,[3] for all the different functions, each chapter constituting the annual training plan was analyzed using:

A. GMP standards (such as general SOP training – change controls – deviations)

B. Dressing and behavior in the pharmaceutical plant

C. Dressing and behavior in the class "D" and "C"

D. Dressing in class "A" and "B"

E. Behavior in class "A" and "B"

F. Drawing up and correction of documentation

G. Use of equipment/machineries/tools

H. Cleaning of equipment/machineries/tools

I. Activity execution

Among these, some were selected to perform and other to postpone until the next evaluation.

Before starting the assessment, Severity (S), Detection (D), Activity Impact (A) and Probability/frequency (P) scales were defined - *Tables B, C, and D.*

The definition of scale led to several compromises between group but in the end customized scales specifically created for the work were chosen as customization became necessary to make the judgments as objectively as possible.

Probability/frequency (P)

With the availability of the list of deviations that occurred over several years, it was decided to consider each working day (220 days/year) as an opportunity for a "deviation possibility" and basing on the average of the last two years. The score percentage was determined by rounding to the next higher number in case of decimal.

Example – Human error deviations injectable department:

- four deviations in 2009 (1 for dressing and behavior in the Class "D" and "C", 1 for dressing in Class "A" and "B", 1 for behavior in Class "A" and "B" and 1 in the execution of the activity)
- three deviations in 2010 (1 for dressing and behavior in Class "D" and "C", 1 for dressing in Class "A" and "B" and 1 for behavior in Class "A" and "B")

Score	Evaluation	Description
1	Nothing	Only bureaucratic activity is necessary to solve the deviation.
2	Low	Operational activity is necessary to solve the deviation
3	Moderate	Material rejection could happen due to the deviation
4	High	Reworking could happen due to the deviation
5	Maximum	Drug product rejection could happen due to the deviation

Table B. Severity (S).

Score	Evaluation	Description
1	Sure	Simultaneous double checks and IPC in stop are in force
2	High	Simultaneous double checks are in force
3	Average	Check list is present at the end of the activity
4	Low	Double checks are present at the end of activity
5	Nothing	No double checks, no check lists and no IPCs

Table C. Detection (D).

Score	Evaluation	Description
1	Nothing	Activity without impact on final product, intermediate, manufacturing materials (API, excipient, packaging)
2	Low	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow
3	Moderate	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow
4	High	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step
5	Maxim	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step

Table D. Activity Impact (A).

Frequency deviation for dressing and behavior in the local Class "D" and "C":

$1/220 \times 100 = 0.45\%$

After defining the scale of magnitudes, the Risk Priority Number (RPN) has been fixed with a conservative approach as seen in Table F.

After the set of the scale of FMECA and RPN value were used to determine the priority in training, the various departments were analyzed with respect to the chapters of the annual training plan. In order to do this, quality assurance personnel, managers and supervisors of the departments who have analyzed department participated in order to formalize the rules to be followed in allocating scores:

- Microbiology Quality Control (Micro QC) performs in process controls during production in sterile areas
- Chemistry Quality Control (CH QC) follows sampling in non-sterile area
- Warehouse performs the dispensing

Score	Evaluation	Description
1	Nothing	$0 \leq \% \leq 0.2$
2	Low	$0.2 < \% \leq 0.5$
3	Moderate	$0.5 < \% \leq 2.0$
4	High	$2.0 < \% \leq 10.0$
5	Maxim	$> 10.0\ \%$

Table E. Probability/frequency (P).

RPN	Color	Action
≤ 54		Training can be postponed to the next evaluation waiting for SOP expiry.
54 <		Training has to be performed.

Table F. RPN table decision.

- Technical Services (TS) performs the maintenance, calibration and validation
- The calculations of the analysis are to be performed manually on notebook (there is no management information system)

Training Chapters	Impact of Deviation	S	P	Check	R	Activity Impact	A	RPN
GMP standards (such as general SOP Training – Change Controls – Deviations)	Nothing; operator doesn't perform directly the activity object of these chapters	1	1	Activities are always performed by a supervisor	2	No impact on final product, intermediate, manufacturing materials (API, excipient, packaging)	1	2
Dressing and behavior in the pharmaceutical plant	Nothing; operator has to change his dressing before getting in contact with any object used for manufacturing	1	1	Colleague check	4	No impact on final product, intermediate, manufacturing materials (API, excipient, packaging)	1	4
Dressing and behavior in the class "D" and "C"	If the operator doesn't follow the procedures, it could be necessary to repeat some Operational activities	2	2	Before going inside the rooms a picture to show the correct dressing and a mirror to perform a self-check are present	3	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	3	36
Dressing in class "A" and "B"	Drug product rejection could happen if the operator doesn't follow the procedures	5	2	Before going inside the rooms a picture to show the correct dressing and a mirror to perform a self-check are present	3	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	4	120
Behavior in class "A" and "B"	Drug product rejection could happen if the operator doesn't follow the procedures	5	2	Colleague check	4	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	200
Documentation design and correction	If the operator doesn't follow the procedures, it could be necessary to repeat some Operational activities	2	1	Activities are checked by another operator	4	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	2	16
Use equipment/machinery/ tools	Drug product rejection could happen if the operator doesn't follow the procedures	5	1	Simultaneous double check are in force	2	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	50
Cleaning equipment/ machinery/tools	Drug product rejection could happen if the operator doesn't follow the procedures	5	1	Cleaning Batch Record/ cleaning modules are in force	3	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	75
Activity Execution	Drug product rejection could happen if the operator doesn't follow the procedures	5	2	Simultaneous double check are in force	2	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	100

Table G. Injectable department.

- Cleaning batch record/cleaning modules are in force
- If not applicable, should be scored as a minimum
- All production activities are performed by a team of at least two people

Training Chapters	Impact of Deviation	S	P	Check	R	Activity Impact	A	RPN
GMP standards (such as general SOP Training - Change Control - Deviations)	Nothing; operator doesn't perform directly the activity object of these chapters	1	1	Activities are always performed by a supervisor	2	No impact on final product, intermediate, manufacturing materials (API, excipient, packaging)	1	2
Dressing and behavior in the pharmaceutical plant	Nothing; operator has to change his dressing before getting in touch with any object needed for manufacturing	1	1	Colleague check	4	No impact on final product, intermediate,manufacturing materials (API, excipient, packaging)	1	4
Dressing and behavior in the class "D" and "C"	Reworking activity could happen due to the deviation	4	2	Before going inside the rooms a picture to show the correct dressing and a mirror to perform a self-check are present	3	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	3	72
Dressing in class "A" and "B"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Behavior in class "A" and "B"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Documentation drawing up and correction	If the operator doesn't follow the procedures, it could be necessary to repeat some Operational activities	2	1	Activities are checked by another operator	4	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	2	16
Use equipment/machinery/ tools	Drug product rejection could happen if the operator doesn't follow the procedures	5	1	No other checks are in force	5	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	5	125
Cleaning equipment/ machinery/tools	Drug product rejection could happen if the operator doesn't follow the procedures	5	3	Cleaning Batch Record/ cleaning modules are in force	3	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) but cleaning or decontamination step are still present in the flow	3	135
Activity Execution	Drug product rejection could happen if the operator doesn't follow the procedures	5	1	No other checks are in force	5	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	4	100

Table H. Warehouse department.

Training Chapters	Impact of Deviation	S	P	Check	R	Activity Impact	A	RPN
GMP standards (such as general SOP Training - Change Control - Deviations)	Drug product rejection could happen if the operator doesn't follow the procedures	5	2	Activities are checked by another operator	4	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	4	160
Dressing and behavior in the pharmaceutical plant	Only bureaucratic activity is necessary to solve the deviation	1	1	Colleague check	4	Activity without impact on final product, intermediate, manufacturing materials (API, excipient, packaging)	1	4
Dressing and behavior in the class "D" and "C"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Dressing in class "A" and "B"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Behavior in class "A" and "B"	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Documentation drawing up and correction	If the operator doesn't follow the procedures, it could be necessary to repeat some Operational activities	2	2	Activities are checked by another operator	4	Activity with direct impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	5	80
Use equipment/machinery/ tools	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Cleaning equipment/ machinery/tools	Not pertinent	1	1	Not pertinent	1	Not pertinent	1	1
Activity Execution	Only bureaucratic activity is necessary to solve the deviation	1	1	Activity are checked by another operator	4	Activity with indirect impact on final product, intermediate, manufacturing materials (API, excipient, packaging) without any cleaning or decontamination step	4	16

Table I. Quality Assurance department.

Training Chapters	Injectables	Orals	Packaging	Warehouse	QA	CH CQ	CQ Micro	TS
GMP standards (such as general SOP Training – Change Control – Deviations)	NO	NO	NO	NO	NO*	NO	NO	NO
Dressing and pharmaceutical behavior in the plant	NO	NO	NO	NO	NO	NO	NO	NO
Dressing and behavior in the class "D" and "C"	NO	YES	NO	YES	NO	NO*	NO	NO
Dressing in class "A" and "B"	YES	NO	NO	NO	NO	NO	YES	YES
Behavior in class "A" and "B"	YES	NO	NO	NO	NO	NO	YES	YES
Documentation drawing up and correction	NO	NO	NO	NO	YES	NO	NO	NO
Use equipment/machinery/tools	NO	YES	NO*	YES	NO	NO*	NO	NO
Cleaning equipment/machinery/tools	YES	YES	YES	YES	NO	NO*	NO	NO
Activity Execution	YES	YES	NO*	YES	NO*	YES	YES	NO*
*Training Chapter chosen even if its score was inferior to limit score, in order to reach minimum number.								

Table J. Training plan for 2011.

Examples of the assessments for three different departments, made during the meetings, are reported in Tables G, H, and I.

The activities started in January, 2011 and finished in March, 2011. The activities were completed in time to prepare the annual training program and to put into force all the corrective actions linked to the lack of documentation, an raised during the work.

The annual training program was prepared by choosing all the chapters with a score higher than the fixed limit score (54) with no regard to the final number of chapters. If "red zone" chapters were less than 3, green zone chapters with decreasing scores were considered in order to assure that at least three chapters were considered for training purposes.

If training was linked to a document that according to the outcome of the analysis was to be re-issued, the training was postponed until the new version was issued.

It is possible to see the final action plan for all plant departments. "Yes" or "No" has been indicated as to which training chapters had to be considered and for which department - *Table J.*

	2009	2010	2011
Equipment	1	2	5
Materials	11	4	4
Absence of Documentation	6	8	5
Organization	7	4	11
Validation not Finished	3	4	5
Procedure Equivocalness	10	11	5
Training not Performed	9	7	8
Documentation Equivocalness	4	6	2
Human Error	21	20	12
Procedure not apply	9	8	6
Total	81	74	63

Table K. Trend deviations for 2009 – 2011.

	2009	2010	2011
Equipment	1.2%	2.7%	7.9%
Materials	13.6%	5.4%	6.3%
Absence of Documentation	7.4%	10.8%	7.9%
Organization	8.6%	5.4%	17.5%
Validation not Finished	3.7%	5.4%	7.9%
Procedure Equivocalness	12.3%	14.9%	7.9%
Training not performed	11.1%	9.5%	12.7%
Documentation Equivocalness	4.9%	8.1%	3.2%
Human Error	25.9%	27.0%	19.0%
Procedure not apply	11.1%	10.8%	9.5%

Table L. Trend deviations % for 2009 – 2011.

Results

At the end of 2011, the deviation report showed an improvement in not only in the "human error" field, but also in all the usual deviations areas. The improvement derived from the analysis, which led to a more customized training plan and a different type of internal documentation (manual and procedure user oriented) with direct impact onto working activities as seen in Tables K, L, and Figure 6.

> *"The improvement derived from the analysis, which led to a more customized training plan and a different type of internal documentation with direct impact onto working activities...*

Conclusion

The activities were aimed at increasing the know-how of the risk analysis tools and achieved significant results not only in the main sector (human error – percentage of human error decrease for more than 25% at less than 20%), but also in all of the fields involved in the work.

Together with the reduction of training hours (from minimum of 10 hours to minimum of 4 hours of training for each operator), this shows how it is possible to increase the efficacy and the efficiency of the activities, while preserving the quality by means of tools present in normal working life. At the same time shows, it also demonstrates how it is possible to improve the know-how of the people and improve their efficiency.

References

1. EudraLex Volume 4, Annex 20 "Quality Risk Management."
2. ICH Q9 Quality Risk Management.
3. CEI IEC 812 Analysis Techniques for System Reliability – Procedure for Failure Mode and Effects Analysis.

About the Authors

Luca Falce obtained his engineering degree from the Milan Polytechnic in1997; in the same year, he received his professional diploma. He has been in the pharmaceutical field since 1997 with varying technical experience, including validation, quality assurance and production, for both pharmaceutical and engineering companies. He is currently the Production Site Manager in Laboratori Farmaceutici SIT. Speaker in technical courses (QRM – Validation – Water); author of technical articles. He can be reached by email: l.falce@sit-farmaceutici.com.

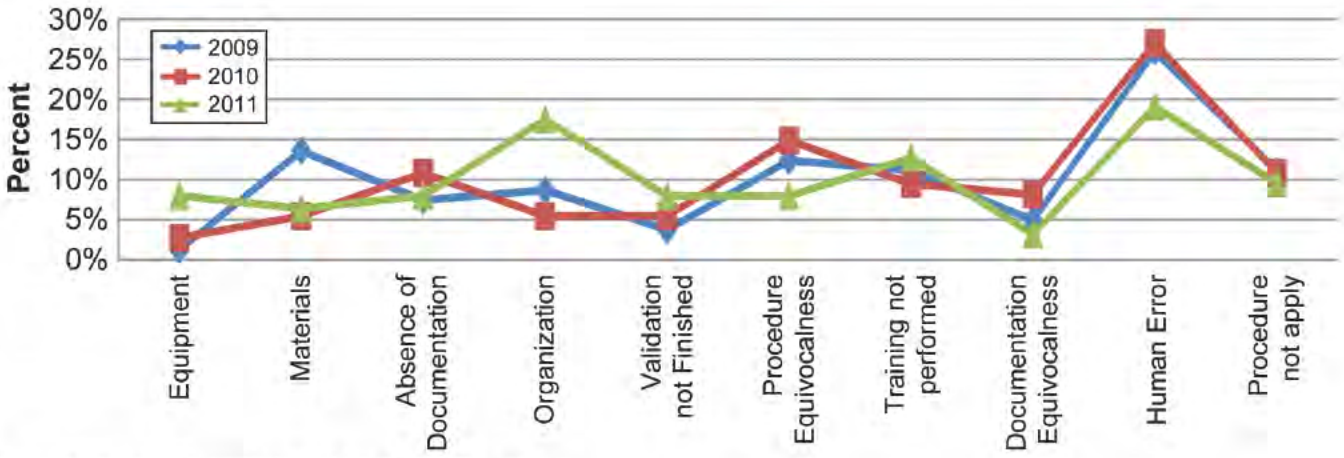

Figure 6. Deviation comparison and trend for 2009 – 2011.

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How Type I Error Impacts Quality System Effectiveness

by Jeff Gardner

This article presents how Type I errors when using statistical process controls can negatively impact quality systems and what steps can be taken to reduce this impact.

Most are familiar with the story of the boy who cried "Wolf!" How he was assigned by some in his town to watch a flock of sheep and call out "Wolf!" whenever a wolf threatened the sheep, how on two occasions he called out "Wolf!" when in fact no wolf was in sight, and finally how because of his previous false alarms no one heeded his cries when a real wolf actually came along.

It may be that many modern pharmaceutical and biotech manufacturers are setting themselves up for a similar fate when it comes to watching out for real threats to product quality via Continued Process Verification (CPV). CPV constitutes Stage 3 of the lifecycle approach to process validation per FDA's 2011 process validation guidance document;1 at its core, it features the use of univariate Statistical Process Control (SPC) charts for monitoring process or product performance. In most instances, the SPC charts used are Shewhart control charts. A seldom-discussed aspect of using Shewhart charts is the propagation of Type I error (also known as alpha error) when multiple charts are being used to monitor different process or product characteristics. Many manufacturers have unwittingly incorporated this Type I error into their quality systems and as a result have experienced serious consequences that will be discussed in this article.

Stated simply, within the context of SPC, Type I error is the probability of concluding that the process is out of control when in fact it is in control. In Shewhart SPC charts, the limits are usually selected so that this probability is very low. For situations where the results for a monitored characteristic follow a normal probability distribution, a popular choice of limits is $\bar{x} \pm 3s$, where $\bar{x}$ is the estimated process mean and s is a standard deviation estimate for the process. This choice is popular because the associated Type I error is 0.27% (based on the normal probability assumption). Upon seeing a result that is outside the $\bar{x} \pm 3s$ range, one can be reasonably confident that there is some assignable cause or event that has impacted the process in such a way as to produce the result.

No matter how confident one might be; however, there is still a chance that this conclusion is wrong, i.e., there is no assignable cause and the observed result is truly just a random occurrence. This chance is quantified via Type I error, and it increases as more process characteristics are monitored via Shewhart methodology. Consider the most simplistic theoretical scenario: a manufacturing process where batches are tested for 10 statistically independent and normally distributed quality attributes has an overall Type I error rate of $1 - (1 - 0.0027)^{10} = 1 - 0.9973^{10} = 2.67\%$, which translates into an average run length of one every 37 tests. Since every batch is tested 10 times, this means that on average an out-of-control signal will be generated every three to four batches. This process is not likely to be considered "in control" if every third or fourth batch has some suspicious result associated with it.

The above scenario does not take into account correlation between quality attributes or analytical methods, nor does it consider autocorrelation within certain quality attributes where one batch's results are in some way linked to results obtained for the previous batch (or batches). These factors plus the use of multiple criteria for identifying out-of-control

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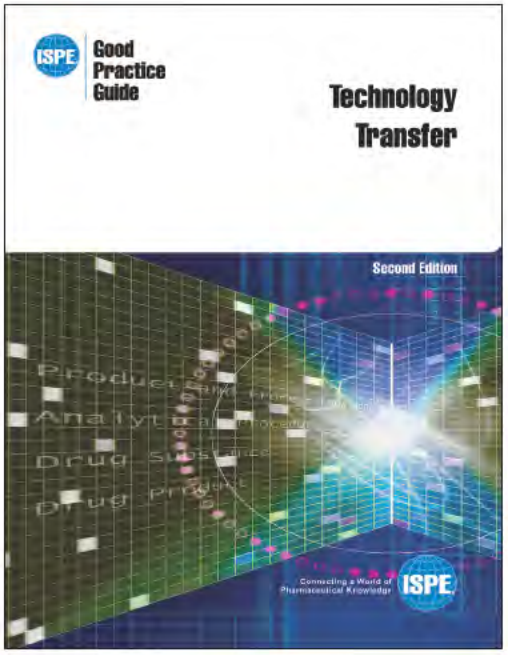

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signals ("run rules") significantly inflate the Type I error probability so that even more false alarms are generated. And all of these reflect the manner in which many manufacturers monitor their processes: by using multiple charts, each using multiple rules for detecting out-of-control signals, each tracking a separate process or product characteristic, and with some characteristics exhibiting variability that does not completely satisfy the required underlying assumption of statistical independence between results. Yet despite the increased risk of false signals, manufacturers integrate the use of univariate Shewhart charts into their quality systems in such a way as to initiate the quality investigation process whenever an out-of-control signal is observed for a batch. By doing so, companies inherently link the effectiveness of their quality systems to the overall Type I error rate for their monitoring programs and suffer significant consequences as a result.

The first consequence is that a much higher volume of investigations is produced purely due to Type I error; this inherently discourages the acquisition of process knowledge. As more investigations are opened, the producer's investigation resources are spread thin. Additional pressure to close investigations in a timely manner results in less effort to truly understand the underlying causes of "real" out-of-control signals. It must be pointed out here that not all assignable causes are easily identifiable "smoking guns;" some issues require sustained effort over a protracted period of time to gain sufficient insight into the interconnectedness of facts that make up the total picture. This phenomenon can therefore be best described as an "interference" effect: a large amount of resources devoted to investigating random, non-substantive process noise interferes with the ability to detect and thoroughly address real process issues.

A second related consequence is what might be characterized as a "low morale" effect. The high volume of quality investigations due to Type I error can contribute to other aspects of poor quality system performance. Investigations are often either open for longer periods of time (as people try to leave no stone unturned in finding an assignable cause), closed as inconclusive because there is no assignable cause to be found, or both. This leads to the effectiveness of the investigation process being questioned by both internal and external reviewers, and erodes personnel's confidence in the statistical methods being used until they are seen to be of little to no value at all. Metaphorically speaking, there can be only two outcomes: either the townspeople exhaust themselves to no avail running back and forth, while responding to the boy's cries of "Wolf!" or the boys' cries eventually go unheeded. Neither is a desirable outcome.

To avoid these crippling effects, there are four actions producers can take to reduce the impact of Type I error and thereby maximize quality system effectiveness:

1. Establish an Overall Type I Error for the Monitoring Program

Although the choice of a nominal Type I error is somewhat arbitrary, selecting a sufficiently low value greatly increases a practitioner's confidence that an observed signal on any individual chart will lead to an assignable cause. Values that might be considered include 0.1% or 0.27%. For example, using the earlier case of a process with 10 statistically independent and normally distributed characteristics, declaring an overall Type I error of 0.27% results in an individual chart's Type I error of 0.027% and corresponds to control limits set at $\bar{x} \pm 3.64s$.

Of course, establishing an overall Type I error also means increasing the probability that an individual chart will indicate the process is in control when in fact it is not (i.e., Type II error). Therefore, when choosing this option, organizations must consider for themselves what might be the optimal balance between overall Type I error and individual Type II errors.

2. Consider Alternative Univariate Control Charts for Process Monitoring

As stated earlier, many manufacturers use multiple criteria for identifying out-of-control process conditions on Shewhart control charts (e.g., "run rules" such as nine consecutive results on one side of the empirical process average or six consecutive increasing or decreasing results). The basic underlying rationale is that there may be shifts in process mean or subtle changes in variability that occur within the $\bar{x} \pm 3s$ range that escape detection.

Where small process shifts are a concern, manufacturers should consider SPC charts other than Shewhart charts as part of CPV. Cumulative sum (cusum) charts and Exponentially Weighted Moving Average (EWMA) charts are two examples; both are specifically designed for close monitoring of process means to ensure process consistency. These univariate charts also can be easily set up to have lower Type I error rates than conventional Shewhart charts using multiple "run rules" for flagging out-of-control results or trends.

3. Incorporate Multivariate SPC into the Monitoring Program

Previous discussion highlighted that, even when characteristics are independent and uncorrelated, Type I error increases as more characteristics are monitored via Shewhart charts. This effect is amplified when characteristics are correlated. As many manufacturing processes have multiple characteristics which share some kind of relationship or correlation with each other, producers should seriously consider the impact this increased Type I error has on their quality investigation processes.

Another limitation of using Shewhart control charts is the inability to detect changes in the relationship between two

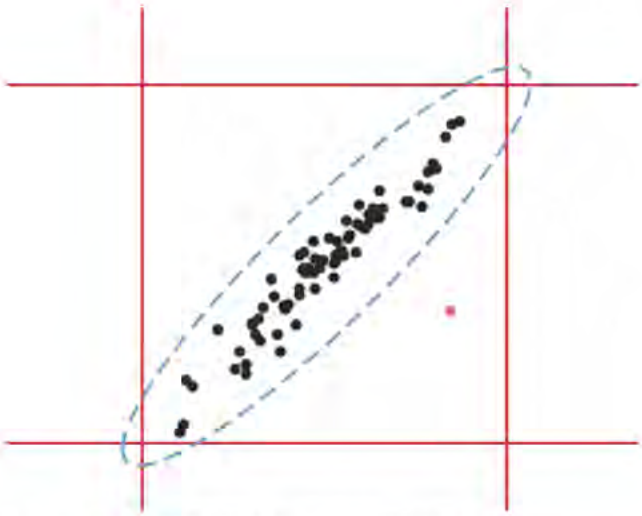

Figure 1. Shewhart limits vs. correlated variables.

or more characteristics. Consider Figure 1 which shows a correlation between two variables. The solid red lines reflect the Shewhart SPC limits for each characteristic. The dashed blue line defines a 99% predictive ellipse which characterizes the relationship between the two characteristics. Note the solitary point in pink; it is clearly within the control limits for both characteristics yet is inconsistent with the observed relationship. This is a manifestation of Type II error in that a producer using Shewhart methodology would conclude that the process is in control when in fact it clearly is not.

The occurrence of Type I and Type II errors for correlated characteristics can be reduced by using a multivariate SPC method such as the T^2 chart. The T^2 chart is specifically designed to detect instances where a set of differing yet correlated characteristics for a batch reflects a different relationship between these characteristics than that which has been observed historically. Since regulatory agencies have made it abundantly clear that manufacturers are expected to demonstrate process understanding and how process changes impact product quality, failures to detect such departures from typical process behavior represent lost opportunities to better understand the process and meet regulatory expectations.

4. Separate the Quality Investigation Process from SPC Chart Signals

This is not to say that out-of-control signals on SPC charts should be ignored. It does mean, however, that not every SPC chart signal necessitates a quality investigation. Organizations should have a system in place for triaging signals and deciding what the most appropriate course of action will be based on the weight of evidence each signal provides. The quality investigation process should be invoked when an out-of-control signal is truly indicative of an adverse risk to the patient, a reduction in the product's fitness for use, or a clear contravention of established procedures or operating parameters. Signals that lack such evidence should be treated differently; they provide potential gateways into expanded process knowledge which may culminate in process improvements.

Most organizations have clear delineations separating business processes which are responsible for "correcting and preventing" from those responsible for "improving." The status quo use of SPC tends to channel everything into the former; alternatively, organizations should use SPC as a trigger for determining which of these two paths should be followed.

Mainly due to their ease of implementation and interpretation, univariate Shewhart control charts are widely used by manufacturers as the tool of choice for maintaining consistent processes. Unfortunately, many may not fully recognize the implications of Type I error as it is propagated through the use of multiple charts for monitoring different process characteristics. Upon further consideration producers may find that stresses on their quality systems may largely be attributed to the overall Type I error for their respective monitoring programs. Such organizations should evaluate their existing monitoring programs by examining the prevalence of investigations related to trending signals, i.e., individual out-of-control results or "run rule" violations. In turn, they should further consider any combination of the four recommendations discussed above as part of a comprehensive strategy to make their investigation processes more focused and more effective.

References

1. FDA (CDER, CBER, and CVM), *Process Validation: General Principles and Practices,* Guidance for Industry, January 2011, www.fda.gov.

About the Author

Jeff Gardner is President and Principal Consultant at DataPharm Statistical and Data Management Services, where he provides statistical analysis, data management, and analytics talent recruiting services to pharmaceutical and biotech manufacturers in the US. He is an ASQ Certifed Quality Engineer with over a dozen years of expertise in applying statistical methods to maintaining and improving product quality, and has worked in this capacity for multiple companies including Abbott, Amgen, and Boehringer Ingelheim. An avid SAS programmer, Gardner also has developed and validated GxP-compliant applications for automating data collection, analysis, and reporting. He holds a BS in mathematics from Marquette University in Milwaukee, Wisconsin. He can be reached by email: jgardner@data-pharm.com.

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Implementation of QbD using MES

by Michael Choi, Mehron Mirian, Pamela Bruen Docherty, and Gregory Ruklic

This article explores the use of Manufacturing Execution System (MES) software as an enabling tool for the Product Lifecycle Management (PLM) aspect of Quality by Design (QbD).

As life sciences industries endeavor to bring the concept of Quality by Design (QbD) from opportunity to implementation, companies can either develop new tools in software and data management or apply existing tools to facilitate a more cost effective path. One such opportunity is to utilize Manufacturing Execution System (MES) software and related systems to enable the knowledge and risk management aspects of QbD. A major obstacle to this approach is mainly perceptual, in that MES technology was originally developed and is viewed as a manufacturing tool set only, even though the technology can be used in various portions of the product development phases in the product lifecycle. Product Lifecycle Management (PLM), improvement of process performance and product quality as in ICH Q10, Section 3 typically utilizes a series of gate processes to require examination of the state of lifecycle requirements at each phase, allowing a decision to pause/correct issues and requirements or release to the next phase. MES capabilities, such as recipe creation, as well as data presentation can create knowledge while providing a consistent tool set and user interface throughout the lifecycle across departmental functions.

There are a number of activities within the QbD paradigm to which MES tools can provide an engine for implementation:

- Configuring MES as a knowledge repository. MES technology presents industry with a great opportunity to utilize existing and proven technology to create and manage a knowledge repository.
- Utilizing MES as a continual improvement tool for manufacturing. MES software can be used to interpret the flow of process data into practical and useful information for continual improvement.
- Using MES as a tool to allow knowledge gained from manufacturing to be transported back into R&D for assimilation as "prior knowledge." New knowledge learned in manufacturing is systematically collected in MES and made available through the system to R&D to improve process design and development of a control strategy. This, in turn, results in systematic incremental improvement to the robustness of the manufacturing process and reduction in time and effort for new product launches, completing the circle of knowledge movement within the lifecycle.

This article will introduce these concepts and explore the opportunities in application to QbD.

QbD Concept

The concept of QbD incorporates the paradigm that quality can be *designed* instead of tested, as defined in ICH Q8(R2) and outlined in the FDA guideline *Pharmaceutical Quality for the 21st Century: A Risk-Based Approach*. The focus of QbD is building quality into a product, which involves a thorough scientific understanding of the product and processes by which it is developed and manufactured, and

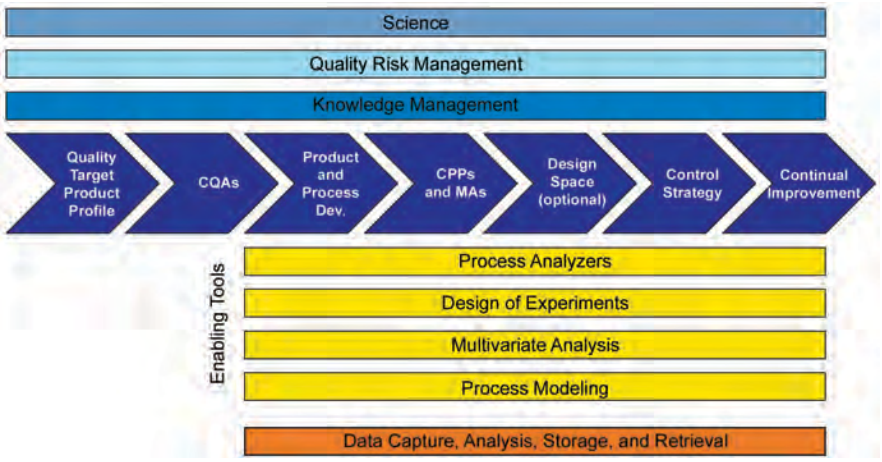

Figure 1. QbD approach showing overarching principles and some enabling tools (source: ISPE PQLI® Guide Series: Part 1 – Product Realization using Quality by Design (QbD): Concepts and Principles, including Overview, Criticality, Design Space, and Control Strategy).

knowledge of the manufacturing risks at product realization and throughout the lifecycle of the product. The conceptual application of QbD through a product's lifecycle is shown in Figure 1. A product lifecycle approach makes use of product formulation and process characterization in the forms of statistical, mechanistic, and first-principle model information to be in a format that facilitates Knowledge Management (KM). Similarly, the risk-based approach to QbD requires the same disciplined approach to identify, analyze, control, and communicate quality risks throughout the life of the product.

Manufacturing execution systems are an integral part of a complete automation solution especially in processes that interface with other applications.

Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) focus on establishing the relationship between quality attributes of the product and their impact on safety and efficacy. The subsequent parts in Figure 1 greatly benefit by application of the enabling tools and data management. For further information, refer to the International Society for Pharmaceutical Engineering (ISPE) Product Quality Lifecycle Implementation (PQLI) Guide Series. Also, more detailed examples of knowledge needs for QbD can be found in the concept paper by the ISPE PAT COP.[1]

MES Concept

MES is considered to be the complete interactive system of human, electronic, and mechanized functionality to execute manufacturing operations. Manufacturing execution systems are an integral part of a complete automation solution especially in processes that interface with other applications. The MES domain as shown in Figure 2 includes recipe management and weigh and dispense with integration to Laboratory Information Management System (LIMS), control systems, Enterprise Resource Planning (ERP), document management and other systems or applications. Common MES functionality includes process management, data collection and acquisition, product tracking, and parts traceability (genealogy of raw materials, product, equipment calibration, etc.) Note that this is a functional model and does not restrict a function to any particular software application.

MES as Lifecycle Knowledge Repository

MES is largely a data management system. Data is verified and transported from MES into downstream system to facilitate human interaction and automated execution. Newly created data from these activities are transported back to MES for distribution, storage and further activities. To realize MES as a lifecycle knowledge repository, data must

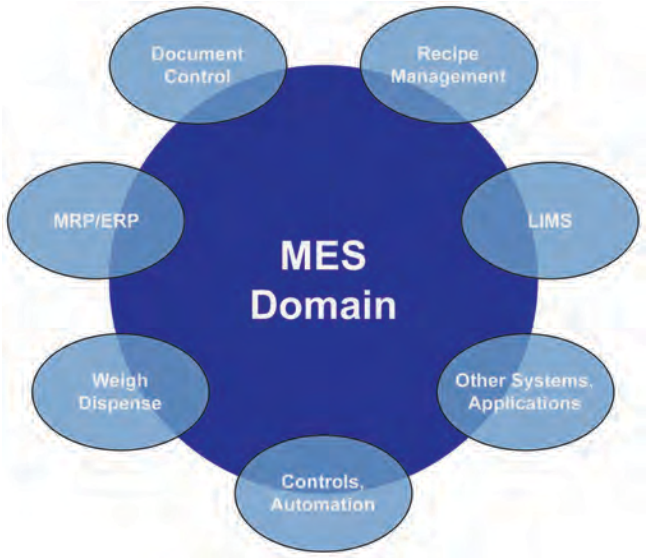

Figure 2. MES domain (source: GAMP® Good Practice Guide: Manufacturing Execution Systems – A Strategic and Program Management Approach).

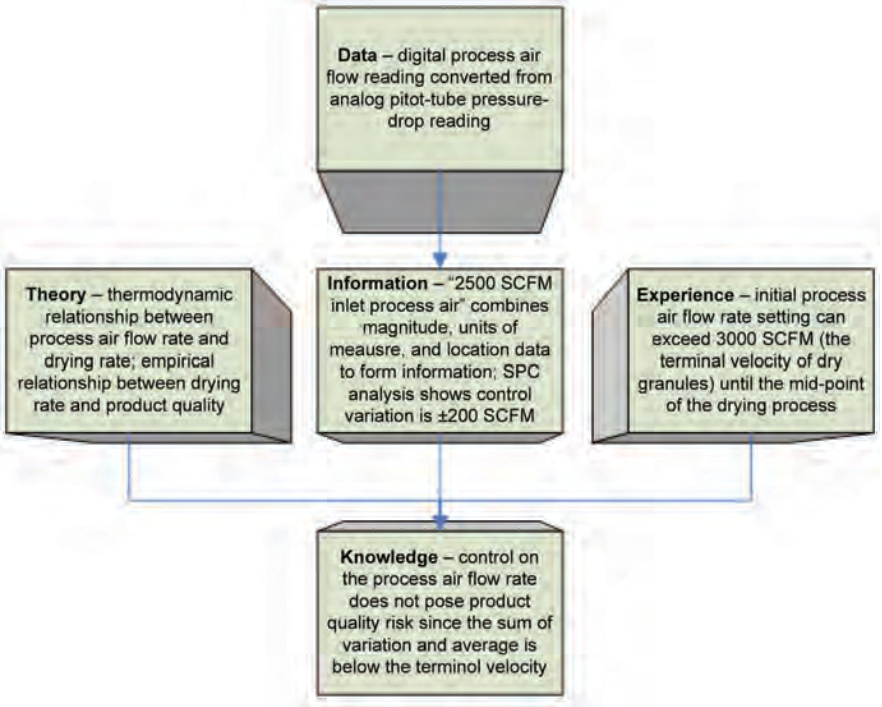

Figure 3. Example illustration of data to knowledge (SCFM = Standard Cubic Feet per Minute; SPC = Statistical Process Control).

be transformed into knowledge (Figure 3). Data management systems collect values of qualitative and quantitative (factual) information. Typically, data by itself represents pieces of information and not necessarily *whole information*, e.g., reporting process parameter data without units of measure or other contextual information has no physical meaning until these data are combined. Similarly, a set of information is combined into *knowledge* through establishing information relationships, performing analysis and making judgments,e.g., *whole information* about one parameter is not considered useful *knowledge* until its relationship to process and product performance is established. Therefore, to address the knowledge management needs of QbD, MES capabilities would include means of organizing data into information, and further organizing information into knowledge.

Another component of QbD is risk management. Quality Risk Management (QRM) as in ICH Q9, consists of risk assessment (identification, analysis and evaluation), risk control, risk review and communication of risks. Within each part of QRM, risk information is captured and tracked on top of the factual information. For example, the relationship between a CQA and a process parameter is established and captured as a relational knowledge in KM. If this relationship is such that the variability of this parameter impacts the CQA, this parameter is identified as a Critical Process Parameter (CPP) and a potential risk is identified. Analysis of development information and manufacturing capability information in KM allows estimation of the probability and detectability of potential hazards that are used in risk assessment, such as in Failure Mode Effects Analysis (FMEA). If the risk is high, changes are implemented in the process to reduce this risk. The changed process is then monitored and communicated via real-time alerts, alarms, and reports of Out-of-Trend (OOT) and Out-of-Specification (OOS) conditions. Changed process monitoring and communications are available in current MES technology to accommodate the risk knowledge (via automated and manual observation and information capture, and risk-based controls and communication.)

In addition to the factual and risk information captured as knowledge, the scope of KM in MES should also encompass description and experiences. Risk-based justifications are often made in consideration of internal quality policies and procedures, agency guidances (e.g., SUPAC), and agency responses to regulatory compliance concerns such as documented 483 inadequacies). KM at the minimum should capture these descriptions and experiences, which also would allow improved estimation of the probability or detectability of potential hazards.

MES, as primary or as an integrated system, may be a repository of :

- API characterization
- Finished-product characterization
- Process characterization
- Manufacturing capability

The contents may include:

- Data from clinical, development, validation to manufacturing
- Correlations between parameters and quality attributes
- Risk rankings – justifications for and means of correlating values of uncertainty, severity, probability, and detectability in risk management
- Justifications (e.g., risk priority/threshold value) for critical parameters and internal limits
- Quality and regulatory limits, policies, standards, and procedures

The interfaces to the repository should include all relevant data sources, e.g., LIMS, ERP, change-management system,

and Process Analytical Technology (PAT) and historian data.

MES as Continual Improvement Tool

Continual improvement tool requires continual flow of information translated into useful knowledge and applied to improve the process. As an example, assume a CPP-CQA correlation model created at the R&D stage from first principles, mechanistically, or statistically through Design of Experiments (DOE). The model coefficients are progressively improved by the continuous circulation of new information back to developmental phases for testing, confirmation, and update of process specifications concurrent with commercial manufacturing. Of course, these changes are managed by proper configuration management and change control gate processes coordinated with lifecycle management gating processes. The new information may be from online (real-time), offline, and at-line data. As the model improves with new information, the specified control limits will be adjusted accordingly. Variability in manufacturing can be used to correlate the effect of process, operations, and raw material properties on quality attributes, which results in continuous enhancement of process knowledge and in turn leads to an improved process. Either the continual improvement or variability approach can systematically address the need for continued process verification.[2]

Additionally, a model in combination with PAT can optimize the process in real time, and ultimately be used for real-time release. For example, PAT may include a control system with an NIR sensor that detects the dryness endpoint of fluid bed dryer. Combined with a drying model, this system can be made to control multiple variables (e.g., the process air flow rate and inlet air temperature) simultaneously within the predefined Design Space (DS) to speed up the drying process while maintaining the same quality endpoint. The outputs from the new control setting are transmitted to MES and verified against the acceptable range. The correlation between acceptable range and product performance can be used as an enabler to real time batch release The new control settings and process outputs feed back into MES to further enhance the process knowledge by refining the model coefficients for future application.
Enhanced features of MES, as the continual improvement tool, may include:

- Real-time monitor of process capability of univariate and multivariate (assuming the multidimensional QbD design space is implemented) systems using statistical and multivariate analysis capability.
- Continuous tracking and updating of empirical models describing the CPP-CQA relationship.
- Adjustment of recipe parameters/set points based on the changes to current product knowledge.
- Update of risk ranking and tolerance values for alerts and alarms based on process feedback.

Considering the above, MES technology can be a tool to improve design space by facilitating analysis of risks in multidimensional combination of CQA and CPP and improve the criteria for release of batches per improved process specification limits based on the updated understanding of CQA-CPP relationship. These enhanced features may be integrated directly into MES or be a separate software linked dynamically to MES. Since new type of analysis may be needed with new knowledge, modular add-on software design may be used to accommodate new improved models for the design-space characterization.

MES as Prior Knowledge Provider for R&D

MES as prior knowledge provider is a natural extension of the knowledge repository and continual improvement tool in R&D. MES as knowledge repository provides development history and knowledge of prior studies done during development. If scientific principles were applied in prior studies such that mathematical and statistical models explain manufacturing process models or drug-delivery mechanisms, fewer experiments should be needed to confirm the prior findings and not repeat the same exploratory studies that are costly and time-consuming. MES as continual improvement tool provides process knowledge gained from manufacturing back into R&D. This knowledge, in the form of CPP-CQA relationships, contributes to reducing process development efforts and time to market while strengthening the robustness of the manufacturing process design for a new product. This knowledge is directly applicable to setting the control strategy and understanding the risks associated with the control strategy.

MES, as the prior-knowledge provider, may require:

- First-principle models (e.g., thermodynamics)
- Empirical and semi-empirical model coefficient data to be generated, stored, and recalculated
- Multivariate statistical modeling from manufacturing data
- Statistical design of experiment set up and modeling using experimental results
- Non-dimensional parameters that are scale independent
- Deterministic or Monte-Carlo simulation tools to assess risks associated with control strategy

For example, to determine the initial control strategy of a coating process for a new product, process performance information from coating processes of existing commercial products from the same coating equipment can be correlated by analyzing the operating conditions and process responses (e.g., using a process thermodynamics relationship).[3] Process variability information also can be obtained in the same

regression analysis that is used to build the correlation. This variability information can be used to estimate the risk probability information for an FMEA-type risk assessment. This process correlation and risk information can be used as prior knowledge for setting and understanding the risks of the initial control strategy.

MES enables an integrated smooth tech transfer from R&D to commercial manufacturing by managing process controls.”

Note that control strategy is a key element of QbD and risk-based manufacturing approach, and the main deliverable of Stage 1: Design Qualification in FDA Guidance for Industry.[2] MES plays a key role in managing the continuous process quality verification of CQAs and controlling CPPs. This also includes the management of the process models. The control strategy must be developed and managed along the product quality lifecycle. MES enables an integrated smooth tech transfer from R&D to commercial manufacturing by managing process controls. This in total builds the overall process performance and product quality monitoring system.

For Further Information

For more detail and related information, the following ISPE resource is available:

MES Special Interest Group (SIG)

The MES-SIG is comprised of volunteer professionals who identify, analyze, and propose solutions to specific MES problems faced by life science companies.

This article has been developed by the Manufacturing Execution Systems Special Interest Group (MES SIG) of the GAMP Community of Practice (COP), a technical subcommittee of ISPE

Acronyms

API	Active Pharmaceutical Ingredient
CQA	Critical Quality Attribute
CPP	Critical Process Parameter (in this article, CPP, for practical purposes, is defined as “all critical independent controls” that impact CQA including raw material attributes)
DOE	Design of Experiment
DS	Design Space
ERP	Enterprise Resource Planning
FDA	Federal Drug Administration
FMEA	Failure Mode Effects Analysis
KM	Knowledge Management
ISPE	International Society for Pharmaceutical Engineering
LIMS	Lab Information Management System
MA	Material Attribute
MES	Manufacturing Execution System
NIR	Near Infrared
PAT	Process Analytical Technology
PLM	Product Lifecycle Management
PQLI	Product Quality Lifecycle Implementation
QbD	Quality by Design
QTPP	Quality Target Product Profile
R&D	Research and Design
SCFM	Standard Cubic Feet per Minute
SPC	Statistical Process Control

References

1. ISPE Process Analytic Technology (PAT) COP Data Management Task Team, “Implementing Knowledge Management in Bioprocesses: A QbD Driven Approach Turning Data into Knowledge in Reference to the CMC A-Mab Case Study,” Concept Paper, March 2012, www.ispe.org.

2. Section IV.D Stage 3 – Continued Process Verification in “Guidance for Industry, Process Validation: General Principles and Practices” (FDA, 2011), www.fda.gov.

3. Choi, M., “Applications of Process Thermodynamics in Pharmaceutical Coating,” *Tablets and Capsules Magazine*, April 2007, www.tabletscapsules.com.

About the Authors

Michael Choi, PhD is General Manager for Johnson & Johnson HyangNam Pharmaceutical plant in the Janssen Supply Chain. Previously, he served as Head of Process Robustness for Americas Technical Operations at Teva, Senior Principal

Scientist for Consumer Healthcare R&D at Schering Plough, and Senior Process Engineer for Pharmaceutical Technology and Engineering at Merck & Co., Inc.

Johnson & Johnson HyangNam Pharmaceutical Plant, 45 Jeyakgongdan 2-gil Hyangnam-Eup, Hwasung-si, Gyeonggi-do, 445-937, Korea.

Mehron Mirian has more than 14 years of experience as a quality professional in the medical device, pharmaceutical and diagnostic industries. Mirian holds a BS in biology and has worked for several companies, including B. Braun, Bio-Rad, and Cardinal Health in the United States. He currently manages a commissioning and qualification of automation project at B. Braun Medical, Inc. as the Senior Computer System Validation in Quality Assurance Department.

Pamela Bruen Docherty has more than 15 years' experience in batch automation and spent 12 years focusing on pharmaceutical production. She began her career at Siemens Energy and Automation where she worked five years as a batch product specialist. She then worked at Merck & Co. in West Point, Pennsylvania as an automation engineer supporting their biologics pilot plant. After Merck, Bruen Docherty joined Honeywell POMS where she provided Manufacturing Execution System (MES) technical demonstrations. She recently returned to Siemens Industry as the Life Sciences Industry Manager for the United States.

Gregory Ruklic, independent senior computer systems compliance and technology specialist, formerly Pfizer Global Engineering and Wyeth Central Engineering, has an extensive background with more than 25 years in the biopharmaceuticals industry in automation and integrated MES-related systems design, validation and quality/compliance oversight. Working for engineering and quality unit organizations, Ruklic has successfully implemented validated manufacturing-related systems internationally, and has held leadership positions in the development and implementation of site, operating unit and corporate level systems standards and guidance. He is the USA co-chair of the GAMP MES Special Interest Group and contributing author to GAMP publications including GAMP® 5. He has presented at US and international forums on topics ranging from MES design in support of flex-team based manufacturing, to systemic (built-in) risk management.

Expanded Bed Adsorption – Challenges and Advances in Column and Process Design

by Zuwei Jin, PhD

The article presents a comparison of different column designs for Expanded Bed Adsorption (EBA).

The concept of chromatography in Expanded Bed Adsorption (EBA) was first proposed in early 90s.[1] The initial advantage of the idea was to be able to directly process particulate containing biological feedstocks for target products, while still maintaining sufficiently high separation efficiency that is usually enjoyed only by the traditional chromatography columns.

EBA could potentially replace several traditional unit operations combined, namely centrifugation, filtration, and capture chromatography. EBA can significantly shorten the overall processing time, increase the overall yield, and save both capital investment and operating cost for many biological purification processes - *Figure 1.*

EBA is different from the fluidized bed used in the traditional chemical industry.[2] The media beads are only intended to be fluidized in their local area, instead of a full mixing stage as in a fluidized bed, to provide reasonably high separation efficiency (plate count).

A typical EBA operation involves the following steps: bed stabilization/equilibration, sample loading, washing, elution, regeneration and cleaning, and re-equilibration as shown in Figure 2. The settled EBA bed is first expanded by applying upward flow that is sufficiently fast to fluidize the media beads. Particulate containing feedstock will be directly applied into the column after equilibration. The target proteins or smaller molecules will be binded to the EBA absorbent while other contaminants such as Nucleotide and lipids pass through. A wash will be applied using fresh buffer to remove the loosely bound contaminant molecules after the sample loading. Elution step is usually run as a packed bed by lowering the top adaptor and applying downward flow. The target proteins or molecules that were binding on the adsorbent will be eluted from the column and collected. The column will then be cleaned/regenerated using stronger agents such as sodium hydroxide and re-equilibrated using the starting buffer for the next loading cycle.

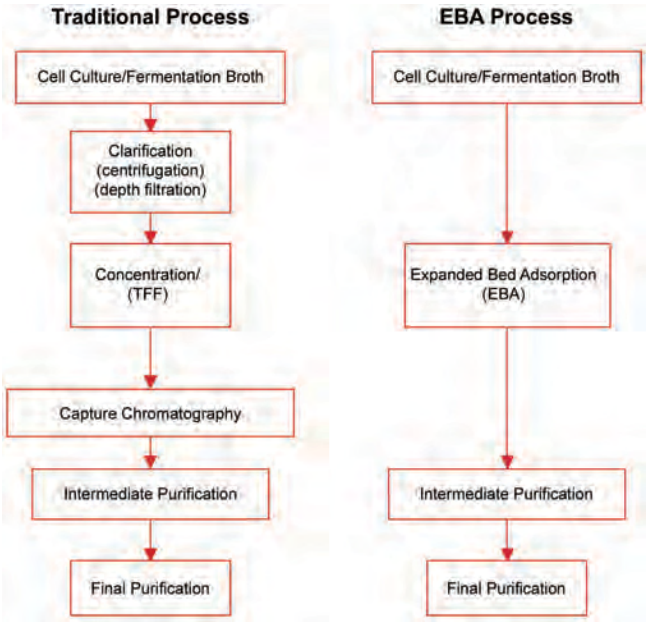

Figure 1. Comparison of traditional downstream purification process with one applying EBA.

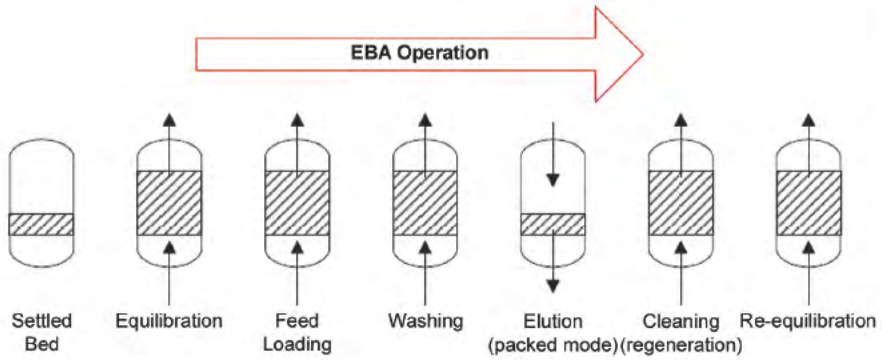

Figure 2. Concept of EBA operation.

The early EBA columns are susceptible to fouling and clogging in its distributor. The main drawbacks in EBA process were hygienic issue and bed stability. The issues were associated with the distributor, which is a critical component in providing even flow distribution in EBA technology. As some kind of high flow resistant components were necessary for distributing the flow, it turned out that it is difficult to clean the aggregates formed upstream of the high resistance component inside the distributor, which could happen as a result of aggregation of cells and biomass over time.[3] Aggregations of biomass and interactions between media and cell debris sometimes also causes bed stability and channeling problem. The first generation EBA column did not see wide application mostly owing to the hygienic issue involved with the distributor and bed stability with difficult feedstock from cell lysis.

The EBA technology was further developed into its second generation that features a patented distributor with moving arms to distribute the flow toward the bottom of the column. The distribution concept is illustrated in Figure 4. The second generation EBA column has an open flow design in the distributor and a bypass on the top adaptor and therefore has no cleaning issues. The distributor leads to significant back mixing in the lower part of the column. There are concerns regarding media grinding, operation reliability, and maintenance cost. In addition, elution can only be done in expanded bed mode. The concentration factor of the process is therefore much lower than the traditional EBA.

The second generation EBA column only had a dismal launch in the industry. In fact, some major players decided

to stop manufacturing and marketing the product shortly after the second generation design was introduced to the market.

While EBA has obvious advantages, the challenges in developing EBA process are the hygienic design of the flow paths, stability of the expanded bed, and maintaining even flow distribution (to achieve sufficient separation efficiency).

A bed independent flow distributor with open cleanable flow paths is considered the critical challenge to make EBA a robust technology. A traditional distributor relying on high resistance components (such as the perforated plate or a thick mesh in the first generation of design) does not meet the hygienic requirement as the upstream of the high resistance component will be subjected to fouling and clogging and will not be cleanable by the flow itself. Aggregation formed in the bed and inside the distributor during the usually long time loading step cannot be effectively and reliably cleaned which is imperatively needed before elution starts.

On the other side most of the open channel distributors will not be able to distribute the flow without making significant disturbance to the EBA bed. It is therefore technically challenging to find a way to distribute even flow without high flow resistance components.

However, recent developments in improving distributor, column, and process have made it necessary to reevaluate the technology. A tangent flow pattern with feed recirculation was suggested to be used in the distributor. The concept was first seen in a poster in Prep in 2004. A similar concept was disclosed in a US patent application.[4] A 2010 patent revealed a design with radial tangent flow and more sophisticated flow paths of varying channel heights.[5-7] It was claimed that bed independent even flow distribution was achieved and flow paths are completely open and self cleanable.

Modern biological applications tend to be cell culture based and the target products are secreted from the cell. The feed stocks are relatively clean and not subjected to biomass aggregation and interaction between biomass and absorbents. Hygienic issue with the distributor and the mesh that existed in the old EBA design may be addressed by newly proposed ones that feature completely open and self cleanable flow paths and bed independent flow distribution.

The objective of this article is to analyze the technical challenges in EBA technology and evaluate the EBA design ideas for industrial applications. Bed independent flow distributor with open channels addresses the main technical challenge in EBA and may possibly make the key benefit of EBA technology realistic. The future of EBA looks promising and most of the modern biological applications are well fitted to it. In addition to possible applications in traditional biotech and biopharmaceutical industries, a particular exciting future for EBA could be the cell separation, which will be the next biggest separation challenge as biotechnology moves from proteins to cells.

EBA Technology Review

Operation Concept

Like fixed bed chromatography EBA operation involves equilibration, loading, washing, elution, cleaning and regeneration as shown in Figure 2.

The settled EBA bed is first be expanded by applying upward flow that is sufficiently fast to fluidize the media beads. The beads are dynamically balancing by the gravity force and the dragging force of the upflow so that the beads will be fluidized in a local vicinity. The expanded bed is dynamically stabilized and chemically equilibrated after enough buffer passing through. The column is then ready for the next step, sample loading.

Particulate containing feedstock will be directly applied into the column. The cells, debris, and solid particulates will pass the bed though the void space in the bed. The target proteins or smaller molecules will be binded to the EBA absorbent while other contaminants such as Nucleotide and lipids should not.

A wash starts by applying fresh buffer after the sample loading is completed. During wash, the loosely bound contaminant molecules on the EBA absorbent will be eluted and any contaminants in the bulk flow will be washed away as well. The column is then ready for elution.

Elution is usually being performed using down flow in fixed bed mode. The up flow will first be stopped and the movable top adaptor is lowered to form a loosely packed fixed bed. The elution buffer will then be applied from the top down. The target proteins or molecules that were binding on the adsorbent will be eluted from the EBA column and collected. The column will then be cleaned/regenerated using stronger agents such as sodium hydroxide and re-equilibrated using the starting buffer for the next loading cycle.

EBA can replace several traditional processing steps by one simple unit operation and greatly reduce the overall processing time. In addition to the possibility of processing feedstock directly, EBA process allows much higher throughput without sacrificing much on binding capacity. The productivity, which is binding capacity times throughput, can be significantly increased. The usual long time loading step in chromatography process will not be the capacity bottleneck anymore, which also eliminates concerns associated with proteases during sample holding.

Evaluation of Separation Efficiency: Plate Count and HETP

A commonly used criterion for evaluating a chromatography column is total plate count and Height Equivalent To Plate (HETP), which are sometimes collectively called separation efficiency. Total plate count is a concept based on the theory of Residence Time Distribution (RTD).[8] According to RTD theory, a complete mixing stage such as a fully fluidized bed or fully stirred tank has total plate count of one while a plug

flow with no back mixing would have a total plate count of infinitive. RTD theory was specifically built on the model of a series of Continuous Stirred Tanks (CSTR) and the number of tanks that allow the series of tanks to have the same kind of RTD as the actual flow system is theoretically the total plate count. Total plate counts in practice can be calculated from the actual RTD data of inert tracers using a pulse or step responding tests.

Figure 3 shows how a pulse injection is used to determine the total plate count of a flow system. A pulse injection of the tracer goes into the flow system from the inlet and the concentration of the tracer and the time elapsed at the outlet of the flow system are monitored.

According to RTD theory, N the total plate count, can be calculated based on the responding behavior of the trace material (pulse testing) going through the flow system.

$$N = \frac{\tau^2}{\sigma^2} \quad (1)$$

where

$$\tau = \int_0^\infty tE(t)dt \quad (2)$$

$$\sigma^2 = \int_0^\infty (t-\tau)^2 E(t)dt \quad (3)$$

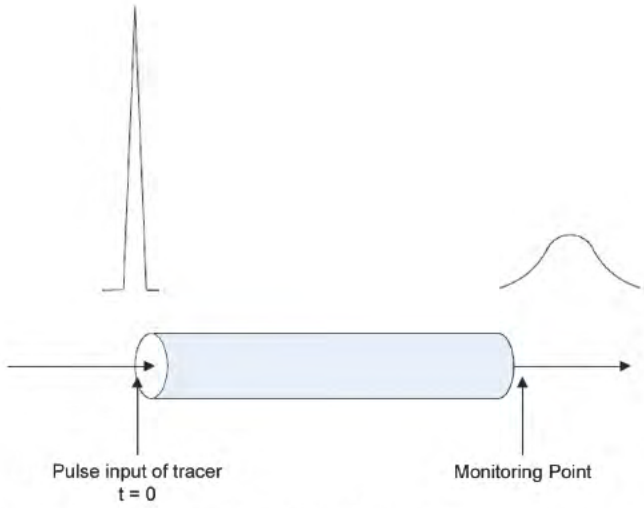

Figure 3. Residence Time Distribution (RTD) measurement using tracer material.

$$E(t) = \frac{c(t)}{\int_0^\infty c(t)dt} \quad (4)$$

In other words, t is the mean residence time of the tracer and σ is the standard deviation of the residence time.

HETP is defined as the bed height of the column divided by the total plate count.

$$HETP = \frac{H}{N} \quad (5)$$

where H is the height of the bed and N is the total plate count.

Total plate count is one of the most important factors to separation performances in both adsorptive and distributive chromatography. Plug flow is desired in chromatography to achieve best performance. Increase of total plate count in EBA can dramatically increase the media binding capacity when the total plate count increases from one to several hundred. Total plate count however does not contribute much to separation performance in most adsorptive chromatography when the total plate count is greater than 1000 or the adsorption isotherm is ideal where the adsorption is independent of the target concentration in the bulk solution.

Alternatively, the non-ideal behavior of the flow system can be described using the axial dispersion model.[8] The governing equation in a dispersion model has the following form:

$$\frac{\partial C}{\partial t} + U\frac{\partial C}{\partial z} = D_a\frac{\partial^2 C}{\partial z^2} \quad (6)$$

where is concentration averaged over the radius, U is the superficial velocity.

In a close-close system, D_a is the characterizing parameter of the axial dispersion model. Sometimes Peclet number Pe_r is used instead.

$$Pe_r = \frac{Ul}{D_a} \quad (7)$$

where U is the superficial velocity in the column and l is the column length.

Pe_r can be calculated using RTD data of tracer material according to dispersion model

$$\frac{\sigma^2}{\tau^2} = \frac{2}{Pe_r} - \frac{2}{Pe_r^2}\left(1 - e^{-Pe_r}\right) \quad (8)$$

Total plate count is significantly reduced with increasing back mixing which could be caused by either undesired flow pattern or dilution. Column structure, operating condition, and bed condition have direct impact on total plate count and it is usually described by Van Deemter equation.[9]

$$HETP = A + \frac{B}{u} + Cu \quad (9)$$

where u is the superficial velocity of the fluid and A, B, and C are constants.

Although Van Deemter equation is an empirical equation, there is an analytical solution in similar form, which helps to give the physical meaning of A, B, and C in the Van Deemter equation.

The three terms in the equation, in short terms, A stands for the contributions from the basic bed structure, B/u, where B is proportional to tracer diffusivity, stands for diffusive mixing among different molecules, and C, where C is proportional to the sectional area of the beads, stands for back-mixing from convective flow. u is the linear velocity (superficial velocity) of the flow in the column.

The non-ideal behavior (anything between one and infinitive) can be described using total plate count or Peclet number. Total plate count N and $HETP$ are most popular in evaluating chromatography column performance for its simplicity and straightforward physical meaning.

One of the key benefits that the original idea of EBA was pursuing at was the relatively high plate count in comparison to a single stage of adsorption (such as in a fluidized bed). However, this has proven extremely difficult to achieve when aggregation happens in the feed and cleanability has to be taken into consideration.

EBA Column and Process Design

The flow distributor in the column is critically important to support EBA operation as the expanded bed lacks the kind of flow resistance required to help with evening the flow velocities along the radius. There has been recent progress both in the column design and the process configuration in achieving the appropriate flow distribution and cleanability.

Several early designs of EBA columns are shown in Figure 4. The first type uses a perforated plate underneath a mesh. There are usually vortex at where the perforated holes are and therefore the back mixing in the lower part of the column is still significant. The space between the mesh and the plate is considered non-hygienic and is problematic for pharmaceutical production. The second type uses a gradual opening shape with a ball check valve at the bottom of the column. The flow path is completely open and cleanable, but the flow distribution is not ideal at all as shown in the diagram. The third type is called large bead distributor which provides a good even flow distribution, but hygienic aspect inside the beads bed is still a concern. The fourth type is thick porous plate. The problem is clogging and cleaning as well. The fifth type is the rotating arms with perforated holes. It is a cleanable design, but back mixing at the lower part of the column is significant.

The perforated plate and mesh went commercial and became the first generation EBA design. The other types never went to commercial except the rotating arms which is the second generation and showed up on the market only briefly.

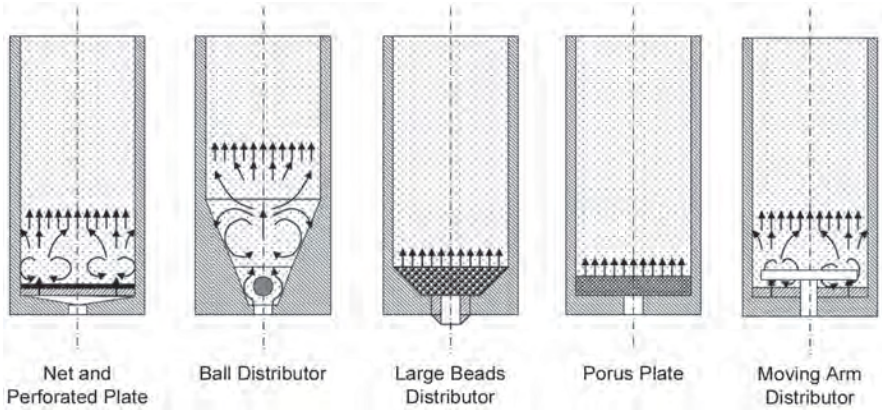

Figure 4. Comparison of different EBA distributors.

Perforated Plates – First Generation Streamline

As shown in Figure 5 with more details, the first generation design of EBA column was introduced as an improved version of the traditional mesh support in fixed bed columns. Underneath the mesh, there is a flat or bowl shaped plate facing the mesh. On the bottom of the bowl, there are several symmetrically made holes to lead the flow to the mesh and the bed.

The earlier researchers realized that special distributor is required to pre-distribute the flow to provide the desired plug-like flow to the expanded bed. Extensive research was done to investigate different types of distributors.[10,11] Multiple outlets from four to eight and sophisticated channel shapes were explored in experiments. Bed stability and total plate count have been the main challenge. Until 2005, the only commercially available EBA column was the perforated plate design. The perforated plate distributor was chosen and researchers tend to agree that most of the open channel distributors did not even perform as well as the perforated plate in terms of the separation efficiency and bed stability.

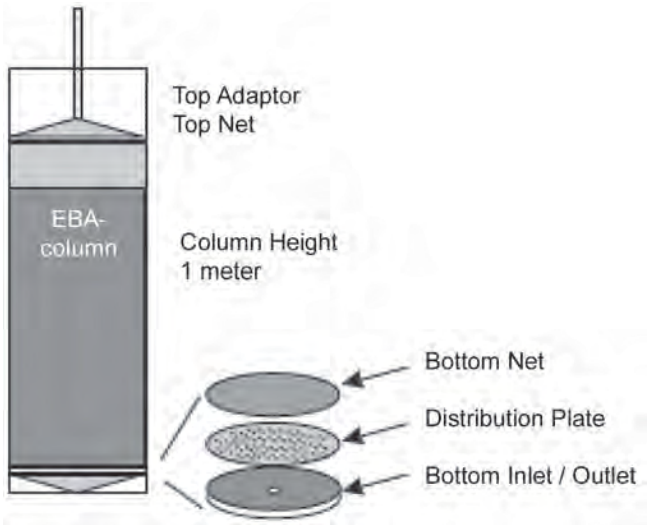

Figure 5. First generation EBA column design.[10]

A perforated plate inside the distributor however causes a largely enclosed space in the flow path. This space is not self-cleanable by flow in case aggregation happens inside it. Such aggregation is very likely during the long time loading step. The aggregation thus formed cannot be reliably cleaned before the elution and would therefore contaminate the product during the elution. Figure 6 shows the accumulated impact of aggregation inside a first generation distributor.[12] It was a challenge to clean such aggregates inside this enclosed space even during the CIP cycle where much stronger chemicals are used.

This drawback on the first generation distributor has significantly limited the possible applications of the EBA technology.

Movable Distributing Arms – Second Generation Distributor

The second generation of EBA was necessary as the first generation EBA columns suffered from serious cleanability issues. Cleanability became a top priority for EBA to be able to find realistic applications in the pharmaceutical industry.

As shown in Figure 7, the second generation EBA column does not have a bottom net.[13] Instead there is a movable device with multiple arms with perforated holes, placed at the center of the column bottom. Feed comes in from a tube at the center and flows into the perforated arms radially. The feed will then be distributed into the column through the perforated holes, which usually are pointing downward to the bottom of the column. These tubes will rotate

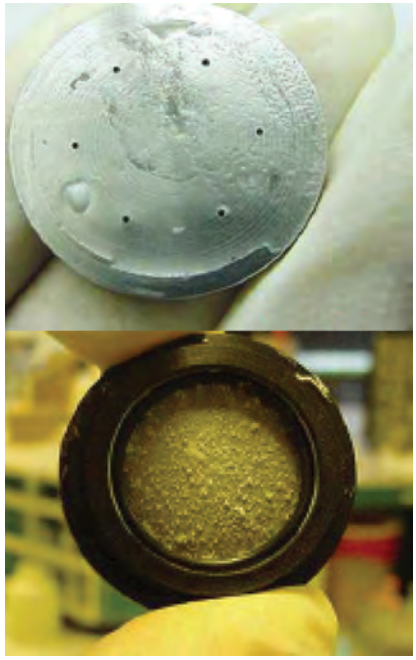

Figure 6. Fouling and aggregation in first generation distributor.[12]

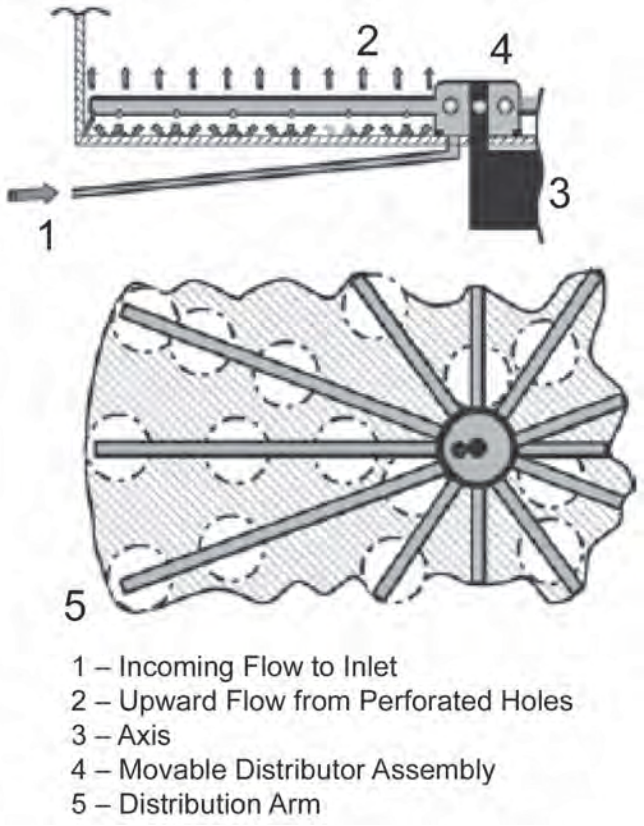

Figure 7. Second generation distributor: rotating/oscillating distribution arms.[13]

or oscillate during operation to provide more even distribution performance. There is no net or porous media inside the entire flow path.

As the flow needs to turn from downward to upward and the moving arms keep disturbing the bed at the bottom portion of the bed, the back-mixing is particular an issue with the second generation designs as shown in Figure 4.

Elution in fixed bed using downward flow cannot be done in the second generation column because there is no bottom net. The concentration factor of the process is therefore reduced because of its less plate count compared to fixed bed as a result of having to do elution in expanded bed mode. The drawback of the design also may be the moving/oscillating arms that accidentally grind the absorbents. The moving and wearing parts in the column raise concerns on the reliability of the operation and increases maintenance requirement.

Distributor with Recirculation – Third Generation

The third generation of EBA column introduced a mechanism of flow recirculation under the mesh inside the distributor.[13] The initial idea was to have feed flow coming from one side of the distributor tangential to the mesh and out on the other side to avoid fouling and clean aggregates inside the distributor.[13] The original idea did not take into account of flow distribution and obviously does not apply to large diameter columns.

A radial flow pattern with sophisticated multi-layer of flow channels of varied channel height was proposed for a recirculation distributor as shown in Figure 8.[5] There is a nozzle with many holes pointing tangential to the net, placed at the center of the bottom adaptor right underneath the distributor mesh. Inside the distributor, there is a distributor core which separates the space inside the distributor into upper channels and lower channels. The feed flow goes into the distributor through the inlet at the center and injects into the upper distribution channels through the nozzle, and comes back out from the lower returning channels for recirculation.

The distributor core is particularly important as it is shaped in such a way that it helps to even out pressure along the radius and assure cleanability in the channel. The even pressure will lead to an evenly distributed flow across radius into the bed.

In addition to the above external loop for recirculation, which is supposed to be driven by an external pump, an internal recirculation loop is also introduced between the upper channel and the lower channel to improve the homogeneity as shown in Figure 8. Such an internal recirculation loop could further improve the even flow distribution along the radius and reduce the recirculation flow rate required to achieve the even flow distribution.

Column Efficiency and Processing Capacity

Most of the fixed bed chromatography columns have plate count greater than 3000/m. High resolution columns may

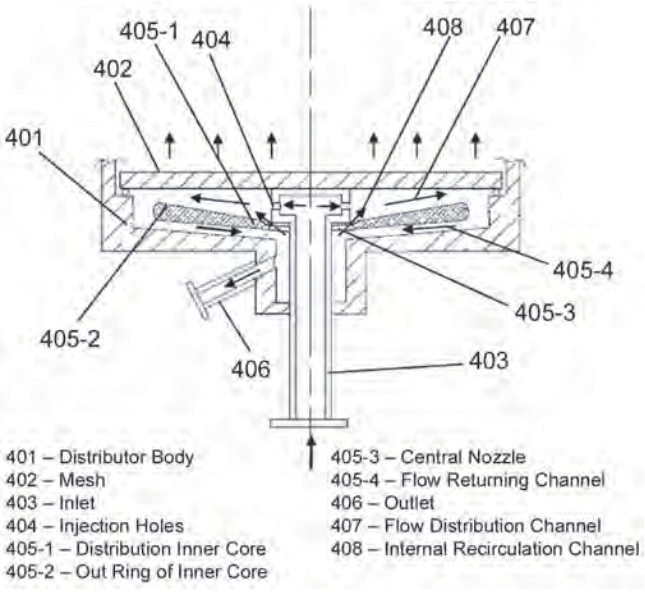

Figure 8. Third generation distributor: recirculation.[5]

have 10,000 to 20,000/m plate counts. Performance of adsorption chromatography improves significantly when the column total plate count increases from one to several hundred, but becomes non-controlling factor when it is above 1000 for most of applications.

A traditional EBA column with perforated plate has a total plate count around 30 or 150/m.[11] Increasing the plate count in the EBA column will therefore significantly bring up the dynamic binding capacity of the column.

Distributor Design

Deviation from ideal plug flow is the main reason the plate count goes down. In an EBA column, back mixing happens in both the distributor and the column. In a traditional perforated distributor, while the distributor was an improved version of a fixed bed, the distributor however causes significant back mixing in the lower part of the column.

The second generation of the EBA column with moving arms did not improve the plate count in the column as the result of the significant back mixing at the lower part of the column. The plate count was reported in the range of 5 to 20.[14] The downflow from the distributing arms need to turn around to back up and the moving arms cause constant disturbance to the bed. The highest was at the condition of moderate linear flow rate and medium oscillating frequency.

Dilution, either caused by convective flow or molecular diffusion, is another form of deviation from ideal plug flow. Over expanded bed and inappropriately designed distributor with large dead space could cause unnecessary dilution in sample concentration which in turn reduces total plate count and separation efficiency.

Traditional EBA columns, both the first generation and the second generation, need to have an expansion ratio (expanded bed height over sedimented bed height) of 2.5 to 3.0 to achieve the most total plate count.[14] One example of bed expansion in a second generation column is shown in Figure 9. The undesirable dilution in the bed is therefore quite significant.

It is important to note that such high expansion of bed is not required for cells, cell debris and particulates to pass through, but for flow to even out radially to overcome the back mixing unavoidably happening in the lower part to the column.

Bed expansion is characterized using expansion ratio which is defined as:

$$\frac{H}{H_0} = \frac{(1-\varepsilon_o)}{(1-\varepsilon)} \quad (10)$$

where H is expanded bed height, H_0 is settled bed height, ε is expanded bed voidage, ε_o is settled bed voidage.

The third generation of the EBA column introduced a mechanism of flow recirculation under the mesh inside the distributor.[7] The idea was originally to address the clogging issue on the adaptor mesh, but it was later realized that the recirculation flow can greatly help with even flow distribution over the radius.

As described in the previous section, the distributor has a radial flow pattern and multi-layer of flow channels with sophisticated varied channel height. There is a distributor core inside the distributor which separates the space inside the distributor into the upper distribution channels and bottom returning channel. The shape of the distributor core allows additional possibility of achieving even pressure and cleanable path along the radius. An internal recirculation loop is also introduced between the upper channel and the lower channel to improve the pressure homogeneity. As the pressure underneath the mesh is mostly homogeneous the feed will flow through the mesh and into the bed in a uniform fashion similar to a plug flow.[7]

The third generation design is expected to have much higher total plate count and completely self-cleanable flow path as the result of the open recirculation paths. It was reported that impressive plug like flow has been demonstrated in experiments using tracer materials.[5] CFD modeling also supported the assumption that the radial flow pattern will lead to even flow distribution along the radius.[5] It was reported that the higher the recirculation flow, the more even the flow distribution will be and the bigger the column diameter is the more significant the improvement on even flow performance will be.

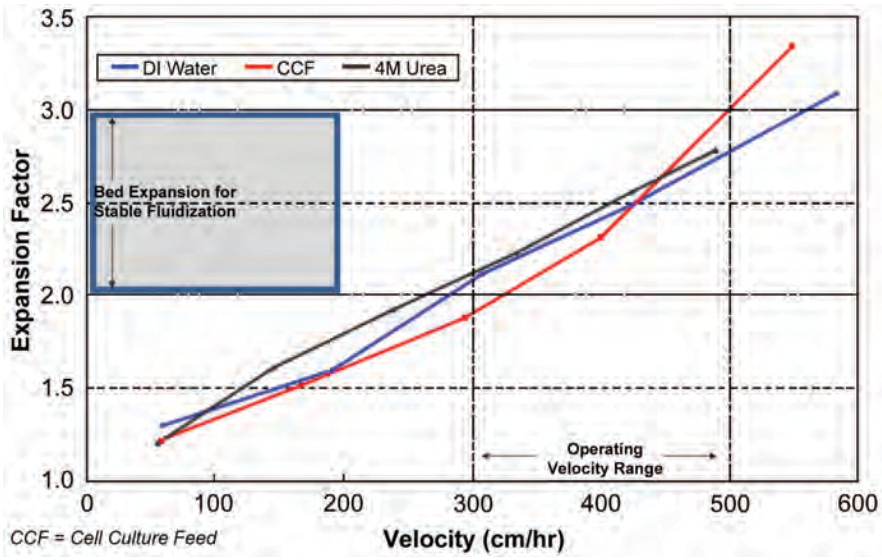

Figure 9. Operating range in a second generation EBA column.[14]

While the first and second generation columns require 2.5 to 3.0 expansion to achieve the most plate count, the third generation column expects to achieve much higher plate count (>50) at much smaller bed expansion (~1.5).

Absorbent Development

EBA absorbents need to have higher density than the media beads for normal fixed bed chromatography. As the beads are balanced by gravity and dragging force by the flow in expanded beds, higher density of the beads will allow bigger throughput without the bed being over expanded or washed away.

Most of the EBA absorbents are made by porous matrix coated around a high density core. The most commonly used cores are made of quartz, Zirconium, Tungsten, and stainless steel.[15-18] See Table A for some of the commercially available EBA media and their physical properties.

The non-absorbing core does not take away the functional space of the beads. It has been long realized that the core of the media beads is barely accessible for effective binding because of the diffusional limitation for target molecules to reach there. Putting an inert core inside the media beads will therefore not reduce the beads' effective binding capacity. On the other side, heavier beads allow much higher processing throughput. As a result, the productivity of EBA process could be much higher than a traditional fixed bed chromatographic process. The additional advantage is that it also reduces holding time of samples during loading step, which is critical in avoiding target molecule deterioration and keeping up good yield. The development of heavier EBA adsorbents however had limited impact in improving column efficiency and bed stability.

It is worthwhile to note that improvement on the density of the absorbent does not have significant impact on the flow distribution or column efficiency. The main advantage is that the process would allow much higher throughput. As can be seen from Table A, the operating velocity was initially only 300 cm/hr when the agarose/quartz media was first developed by GE Healthcare, but the highest mean density of EBA media commercially available is now about 3.5 mg/ml (from UpFront) or 900 cm/hr. On the other side, the higher density does not help improve the expansion profile to achieve the best plate count. As evidenced by the work in Biogen Idec,[14] the column (e.g., a second generation column) with more dense media would need the same kind of expansion (2.5 to 3.0) to achieve the best total plate count as with less dense media.

Open Flow Path and Self-Cleanability

Flow distribution, the challenge of even flow in traditional chromatography column design, was mitigated by the relatively high flow resistance from the fixed bed itself. In expanded bed mode, the flow needs to be distributed into the bed almost independent of the flow resistance from the bed since the bed provides no resistance at all.

EBA bed does not provide much flow resistance and the open channel distributors (such as the second generation design) failed to provide the desired flow pattern and led to low separation efficiency. The lower part of the EBA bed in general has significant back mixing and is the main reason why the EBA column plate count is low.

A traditional EBA distributor relying on high resistance components (such as the perforated plate or a thick mesh in first generation) does not meet the hygienic requirement as the upstream of the high resistance component will be susceptible to fouling and clogging and is not cleanable by the flow itself.

On the other side most of the open channel distributors will not be able to distribute the flow without making significant disturbance to the EBA bed. In other words, most open channel distributors tested so far are not bed independent distributors as they have to perform with the bed in existence.

Both the first and the second generation of EBA columns provide very low total plate count. The second generation does improve the cleanability by using the moving distributing arms.

The third generation design as described in previous section may be on the verge of achieving both higher total plate count and complete cleanability. While it provides even flow

Company	Product	Functionality	Base Matrix/ Core	Particle Size (µm)	Mean Density (g/ml)	Operating Velocity (cm/hr)
GE Healthcare	Streamline	rProtein A, Q, SP, DEAE, Phenyl, IMAC	Agarose/ Quartz	100-300	1.2	200-400
GE Healthcare	Streamline Direct	Q, DEAE, MMC	Agarose/ Stainless Steel	80-165	1.8	400-800
Pall BioSepra	HyperZ	Q, CM	Zirconium Oxide (hydrogel filled)	45-101	3.2	300-450
UpFront	FastLine	rProtein A, MMC, PEI	Agarose/ Tungsten Carbide	20-200	2.5-3.5	600-900

Table A. Commercially available EBA media and their physical properties (company websites and product data sheets).

distribution to the EBA bed, the aggregates underneath the mesh, in case it does happen, will be swept away from the mesh during the recirculation. It was suggested that coarse in-line filter be used to remove the aggregates before the feed returns to the recirculation tank.[5] The third generation design provides bed independent even flow distribution and have flow paths that are completely open and self-cleanable.

To assure cleanability inside the column, in addition to distributor, both the second generation and third generation columns have a bypass opening on the top mesh to allow aggregates formed in the EBA bed to be removed. A more carefully designed version was disclosed using back flush instead of bypass for the third generation design.[5]

Recirculation Flow

The recirculation was initially proposed as a means to sweep away the aggregation underneath the mesh inside the distributor. The high recirculation flow will prevent fouling underneath the mesh from happening. It was later suggested that such recirculation could be a powerful instrument in helping with even flow distribution as well.

The ratio of recirculation flow to column operation flow could have desirable impact on the flow distribution into the bed. As mentioned previously, it was demonstrated in experiments using tracer material that the even flow distribution can be improved with increasing ratio of recirculation flow to column flow. The principle was proven in a CFD study as well.

In most of the cases, a radial flow with no recirculation has already shown satisfactory even flow distribution.[5] The larger the column diameter; the more significant the improvement. However, shear stress, which most of animal cells are sensitive to, may possibly be a concern.

Most animal cells are shear sensitive. CHO cells are relatively high shear tolerant. Shear stress was not considered as a problem in the previous designs of EBA column and distributor. Shear sensitive feedstocks such as animal cells has proven to be able to stand the perforated plates, the meshes, and the perforated holes in rotating arms. However, shear stress may need to be carefully considered in the recirculation design of the distributor.

High recirculation ratio will lead to unnecessary shear stress on the cells and cause cells to break, which will in turn deteriorate the adsorption performance because of the competitive binding from intracellular and cell membrane components.

Since cell lysis is a problem for EBA, it is a problem for all the chromatographic processes. Cell lysis also happens during centrifugation and TFF filtration. Such upper limits are usually controlled by the nature of different feedstocks. There have not been many reports about the impact of recirculation flow on cell lysis.

From the design point of view, one way to mitigate the issue is to maintain the shear stress in the flow path at the same level as the feedstock would go through the pipes. It is possible to maintain the same level of shear stress in the new design as in the previous designs by carefully arranging the size of the flow paths.

The flow distribution without recirculation, in the third generation radial flow design, has already shown great improvement over the previous generations. This essentially means that a bed independent flow distributor does not need to rely much on the recirculation flow. Without using recirculation flow, the radial flow multi-layer distributor plus occasional back flush from above the mesh and sweeping flow underneath the mesh may well be sufficient to prevent aggregation and fouling from happening inside the distributor.

The ratio of recirculation to column flow is therefore more of a problem of engineering design for specific applications. This leaves the space for equipment vendors to continue the study before any commercial product can be available.

Process Control and Media Handling

The third generation column will require slightly different system setup to operate.[4-7] A modified operation scheme was proposed to use the third generation columns, as shown in Figure 10.

The buffer will first be pumped into the column from the center inlet on the bottom adaptor. Most of the buffer goes into the EBA bed and the rest circulates back into a recirculation tank to be fed to the pump again. Fresh buffer will

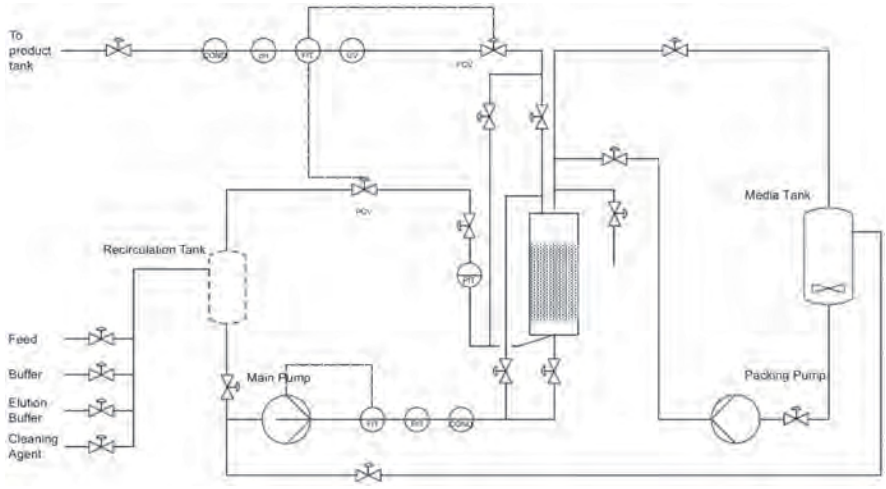

Figure 10. Process flowsheet of EBA with recirculation distributor.[6]

continue to be added to the recirculation tank. Plug-like flow goes through the EBA bed and prepares the bed physically and chemically as well.

After the EBA bed is stabilized and equilibrated with the equilibration buffer sample loading will start. Fresh feedstock is added to the recirculation tank instead of the buffer while the recirculation continues to run. The size of the tank is carefully chosen so that it is large enough to keep the recirculation, but not unnecessarily large to initially dilute the sample. Most of the feedstock will go into the bed in even flow fashion while the rest goes back to the recirculation pump. The recirculation ratio over column flow depends on specific applications. In many cases, only very small recirculation flow rate may need to be maintained. Occasional back flush from above the nets may be applied to remove any possible aggregates underneath the nets. Continue until all the feedstock is applied and washing will start.

Fresh buffer will again be added to the recirculation tank while the recirculation keeps running. Continue to wash until all loosely bound molecules and other contaminants in the bulk are washed out. The column is now ready for elution.

Elution buffer will either be added to the recirculation tank or be fed into the pump directly if recirculation is decided to be not needed. The elution can either be in downflow or upflow mode. Since the expansion is low, either up flow in expanded mode or down flow in packed mode could give satisfactory elution profiles. The movable top adaptor in down flow mode was not considered necessary for the same reason, which is another plus for the third generation design.

When product is collected and elution is finished, the column will be cleaned and regenerated. Cleaning reagent is added to the recirculation tank and recirculation keeps running for sufficient amount of chemicals and time. The column now needs to be rinsed and re-equilibrated.

Fresh buffer is added to the recirculation tank while maintaining the recirculation. Continue until sufficient buffer has gone through the EBA bed and the column is re-equilibrated and ready for the next cycle.

The size of the recirculation tank needs to be appropriately chosen. It should be as small as possible, but large enough to keep the recirculation running without cavitation. The liquid level in the tank can be controlled using level sensor or load cell.

A new fashion of handling EBA media in a more automated fashion was also proposed as shown in Figure 10.[7] In the design EBA, media are being packed or unpacked into or out of the column using flow itself with flow rate greater than the particle terminal velocity. This is a great advantage in terms of the automation of the process particularly at industrial scale.

Applications

EBA feedstock may contain cells, cell agglomerates, cell debris, and contaminants from cell membrane and intracellular materials such as lipids and nucleic acids, which poses a tough challenge to the media and the column. A secretion cell system or an intra-cellular system is the first factor that will impact how a EBA process can be effective or not. It is important that the cells will not be broken and release membrane components and intracellular contaminants such as DNA, lipids and other proteins.[11] It has been well known that the large molecules that are associated with outer membrane of a bacterial cell tend to foul the chromatographic adsorbent. Charged particulates can act as ion exchangers and adsorb proteins. Biomass, cells, and cell debris tend to aggregate at low pH and may lead to bed stability problem or clogging the flow path during feed application/loading in EBA.

While it is possible that EBA can be applied to cell lysis from troublesome intra-cellular systems, such as plant extract, chicken egg white, etc., it is critical to choose the appropriate solution system and absorbent to avoid the interaction between the biomass and the absorbent during process development. The effectiveness of EBA is therefore case by case depending on the specific feedstock and the solution chemistry. It impacts on bed stability which has more to do with the chemistry between the biomass and the media beads rather than the column and distributor design. Selection of different buffer systems with different pH and conductivity, selection of different EBA media should be the key variables that need to be carefully optimized during process development.

EBA had limited commercial success. Very few EBA applications to intracellular cell system, which will require cell lysis before processing, has been seen in the industry probably because the cost of pre-treating the feedstock may have outweighed the benefit of applying EBA.

Even with relatively clean secretion cell systems, hygienic issue and operation reliability tempering the

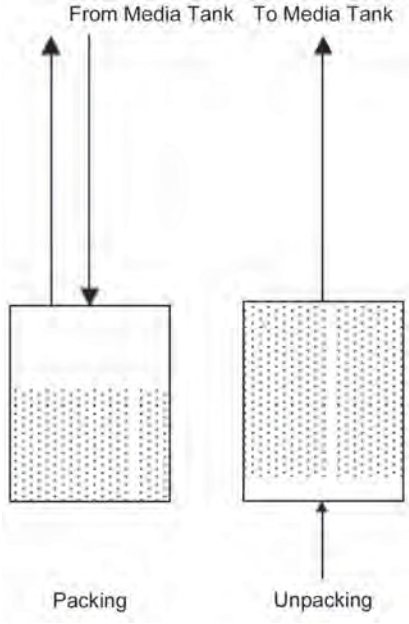

Figure 11. Media handling in EBA column.[6]

technology, EBA has never been widely accepted in biopharmaceutical industries. The road block was most likely the distributor and mesh fouling, the enclosed flow paths within the distributor and underneath the bottom and top meshes. Those issues may not be obvious in a short term operation, but could be a critical factor in repeated production operations.

Two exciting applications are with rHSA and Monoclonal antibodies. It has been reported that EBA was used in purification of rHSA from yeast fermentation media.[18,19] Monoclonal antibody (MAb) products from animal cell cultures were successfully captured using EBA at fairly large scale.[20-22]

Monoclonal antibodies (MAb) purification: MAb is becoming the biggest drivers in bio pharmaceuticals as the dosage usually leads to ton scale production. About 50% of top 15 blockbuster drugs are MAbs in 2012 and the percentage expects to further increase to 80% by year 2020. Few concerns regarding the interaction between the media and the cells or bed stability has been reported. MAbs are secreted from animal cells and cell culture is a great feed type that EBA can be effectively applied to.

Recombinant Human Serum Albumin (rHSA): rHSA estimated to have a global demand of 100 tons each year and is considered one of the strategically important pharmaceuticals. rHSA is secreted from yeast cells and EBA can be effectively applied for purification of the target rHSA.

Transgenic proteins from milk: transgenic drugs produced in animal such as cow may need to be purified from milk. As milk contains large amount of other proteins and lipids and is quite viscous fixed bed chromatography would often run into problems like bed clogging and over pressure. EBA could potentially be an ideal choice for processing such feedstock and simplify the entire process and reduce the cost.

Low value products are generally less incentives to drive this particular technology. One exception can be the purification of antibiotics from E.coli cells. Such process are usually at very large scale (greater than 10 tons a year) and downstream process capacity is critical in meeting its economical constraint. Many of the modern antibiotics require chromatography purification to bring up the purity of the drug to their specifications. Some of the processes were notoriously known for forming agglomerates even after microfiltration, which made it impossible for traditional fixed bed to be effective. EBA in such cases could be the perfect solution.

The last but not the least is the cell separation. As we all know that the next generation of biopharmaceuticals will evolve around cell products. Cell separation technology is becoming the most critical aspect in developing cell therapeutics.[23] Traditional chromatography using fixed bed will not be possible for cell separation because cells could easily clog the column and the cells would be stressed to break. EBA could however be very well adapted to cell separation.

Conclusion and Future Direction

EBA should not intend to be a universal solution for direct processing of all particulate containing stocks. Certain conditions such as heavy nuclei acid, lipids, and other biomass resulted from cell lysis for non-secreted protein products from cell lysis may be more economical to be pre-treated rather than being processed in EBA directly. However EBA is well fitted to most of the modern applications where the feed stocks are relatively clean and non-aggregating. Cleaning issue resulted from biomass or cell aggregation also may be effectively addressed by the new open path design for distributor and columns.

EBA brings in increased throughput without sacrificing binding capacity. As a result, the productivity of the process can be much higher than the traditional three steps. Particularly, there are technical advantages of reduced holding time of sample during the entire pre-capture stage.

It is not unreasonable to assume that the overall downstream process time using EBA may be 60% of the traditional three steps (A five day process may be done in three days). The overall yield also may increase by 6% as the result of combining three steps into one. If 80% of the production cost comes from time sensitive labor and overheads (as seen in most manufacturing process), it can be estimated that the Standard Production Cost (SPC) will roughly be reduced by 34% as far as the downstream SPC is concerned. This estimation does not even count the fact that there will be less consumables on operation cost and the initial capital investment may be one third of the traditional as there will be no expensive centrifugation and membrane filtration.

Depending on how expensive the raw materials are and the relative cost of the upstream process for the specific products this 35% could translate to significant cost reduction in the overall SPC.

EBA in technical sense may have been ready for industrial applications. However the drive for changing existing processes in pharmaceutical industry has been negligible because the risk involved with the regulatory control outweighs the economic benefit. Commercial driving force also ran out after GE Healthcare and Pall announced to pull out of the market. The main commercial activity about EBA has only been driven by UpFront at this moment. UpFront licensed its oscillating distributor technology to GE Healthcare, collaborated with DSM and Biogen Idec in commercializing its EBA technology.

Recirculation distributor has not seen any commercial activities probably because of the overall disappointing commercial environment around EBA. The main uncertainty regarding the recirculation distributor or the third generation EBA is around the shear sensitivity of the cells to the flow paths. Future researches need to focus on the application of the technology to real biological feedstocks and design details will be critical in bringing it to reality.

The economic benefit may still not be sufficient to drive a new wave of commercial efforts at this time, but considering the future of cell separation, which will be the next challenge for separation technology, the industry may start to see it differently.

References

1. Draeger, M.N., Chase, H.A., "Liquid Fluidized Bed Adsorption of Proteins in the Presence of Cells," *Bioseparations,* Volume 2, 1991, pp. 67-80.
2. Draeger, M.N., Chase, H.A., "Affinity Purification of Proteins Using Expanded Beds," *J. Chromatography,* Volume 597, 1992, pp. 129-145.
3. Feuser, J., et al., "Interaction of Mammalian Cell Culture Broth with Adsorbents in Expanded Bed Adsorption of Monoclonal Antibodies," *Process Biochemistry,* Volume 34, Issue 2, February 1999, pp.159-165.
4. Alaska, A., "Sweep-flow Methods and Clogging Disrupters, for Expanded Bed Chromatography of Liquids with Suspended Particulates," US2007199899A1 30, Aug 2007.
5. Gu, X., "Column Apparatus for Expanded Bed Adsorption (EBA) Chromatography for Bio-Separation" Chinese patent CN ZL201010564697.7. 30, Nov 2010.
6. Gu, X., "Column and Process for Expanded Bed Adsorption (EBA) Chromatography for Bio-Separation," Chinese Patent CN ZL201010565313.3. 30, Nov 2010.
7. Gu, X., "Expanded Bed Chromatographic Separation Column for Biochemical Separation Process and Technical Process Thereof," US20130248430, 29 May 2013.
8. Fogler, H.S., "Elements of Chemical Reaction Engineering," New Jersey; Prentice Hall, 2001, p. 871.
9. Deemter, Van, et al., "Longitudinal Diffusion and Resistance to Mass Transfer as Causes of Non Ideality in Chromatography," *Chem. Eng. Sc.*, Volume 5, (1952), pp. 271–289.
10. Feuser, J., et al., "EBA column at Technical Scale," EBA 2002, Florida, USA.
11. Amersham Pharmacia Biotech "Expanded Bed Adsorption – Principles and Methods," ISBN 91-630-5519-8.
12. Sonnenfeld, Alan and Thommas, Jorg, "A Methodology for the Efficient Development of a Protein aAffinity EBA Process," EBA 2002, Florida, USA.
13. Hobley, T., et al., "Scale-Flexible Fluid Distribution System for Expanded Bed Adsorption," EBA 2002, Florida, USA.
14. Ladiwala, A., et al., "Direct Capture of Monoclonal Antibodies," 2009 ACS meeting, Washington D.C. USA.
15. Hansson, K-A., et al., "Physical-chemical Properties of Streamline IOn Exchangers," Poster presented at 7th European Congress on Biotechnology, 1995, Nice, France.
16. Asghari, F., et al., "Preparation and Characterization of agrose-nickle nanoporos Composite Particles Customized for Liquid Expanded Bed Adsorption," *Journal of Chromatography A,* Vol. 1242, 15 June 2012, pp. 35-42.
17. Xia, Hai-Feng, et al., "Chromatographic Performance of macroporous cellulose-tungsten carbide Composite Beads as Anion-Exchanger for Expanded Bed Adsorption at High Fluid Velocity," *Journal of Chromatography A,* Vol. 1195, Issues 1–2, 27 June 2008, pp. 60-66.
18. Munehiro, N., et al., "Process for Purifying Recombinant Human Serum Albumin," US6617133 B1 09 Sep 2003.
19. Munehiro, N., et al., "Process for Purifying Recombinant Human Serum Albumin," EP0699687 B1 28 Jan 2004.
20. Batt, B.C., et al., "Expanded Bed Adsorption Process for Protein Recovery from Whole Mammalian Cell Culture Broth," *Bioseparations,* Vol. 5, 1995, pp. 41-52.
21. González, Y., et al., "Expanded Bed Adsorption Processing of Mammalian Cell Culture Fluid: Comparison with Packed Bed Affinity Chromatography," *Journal of Chromatography B,* Vol. 784, Issue 1, 25 January 2003, pp. 183-187.
22. Griffiths, B., et al., *Direct Capture of Recombinant Proteins From Animal Cell Culture Media Using a Fluidized Bed Adsorber, Animal Cell Technology: Products for Today, Prospect for Tomorrow,* Oxford, 1994, pp. 557-560.
23. Ujam, L., et al., "Cell Separations in Expanded Beds," EBA 2002, Florida, USA.

About the Author

Zuwei Jin is an experienced technical professional with a strong background in bioprocess solutions. He is adept at technical leadership in cross-functional and team settings. He has a PhD in chemical engineering with 16 years in the global life sciences industry, 10 years in the US, and six years in Asia/China as a US expatriate working for GE Healthcare Life Sciences. He is currently a Senior Consultant – Life Sciences Industry with Emerson Process Management. Jin is an ISPE Member and serves on the API Community of Practice Steering Committee.

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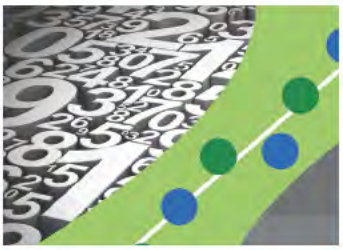

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Digital Image Processing for Bench Scale Cleanability Studies

by Kelly Scalva, Steve Buckingham and Keith Bader

This article is based on a presentation given at the ISPE 2013 Annual Meeting and presents an overview of a novel quantitative method utilizing imaging software combined with tightly controlled variables in lighting, angle, and distance, quantifies the amount of process residue on a surface using high-resolution photographs, to produce statistically significant data.

Problem Statement

Developmental cleaning studies are conducted on a bench scale level by evaluating the performance of a particular set of parameters; most commonly visual, gravimetric, and surface sampling assessment methods. Gravimetric and surface sampling experimental techniques can be stable and reliable, as long as there is enough process soil or residue available to accommodate the weight and need of the studies. In some cases, the limited supply and expense of residue for use in cleaning studies can lower the means of evaluating necessary treatment conditions. While visual assessment requires far less residue and is considered one of the most sensitive methods employed, the use of visual residue limits in cleaning studies can be unwieldy as the semi-quantitative nature of the testing requires developmental work for each residue of interest.

Considerable benefit is gained by conducting bench scale cleaning studies to determine the optimal cleaning chemistry, temperature, cleaning agent concentration, and cycle duration. Generally the first step in these studies is to determine the worst case residue(s), followed by an analysis of the interactions between the residue and different cleaning chemistries (acid, base, neutral, etc.) or cleaning agent selection. This is commonly followed by a design space exploration to assess the cleaning process response to a range of cleaning agent concentrations and temperatures. Finally, the most advantageous combination of parameters identified in the design space exploration can be used to estimate durations for the chemical wash phase in manufacturing-scale cleaning cycles. These bench scale cleaning studies are commonly completed using gravimetric means. The bench scale studies utilize small samples representative of the different Materials of Construction (MOC), found in manufacturing areas (316L stainless steel; 304 stainless steel, Hastalloy, Borosilicate glass, Polytetrafluoroethylene (PTFE), excreta) these small samples will be referred to as “coupons.”

Appropriate Representation of the Process Residues

Bench scale experimental testing is often completed by replicating residues in the laboratory, the production process

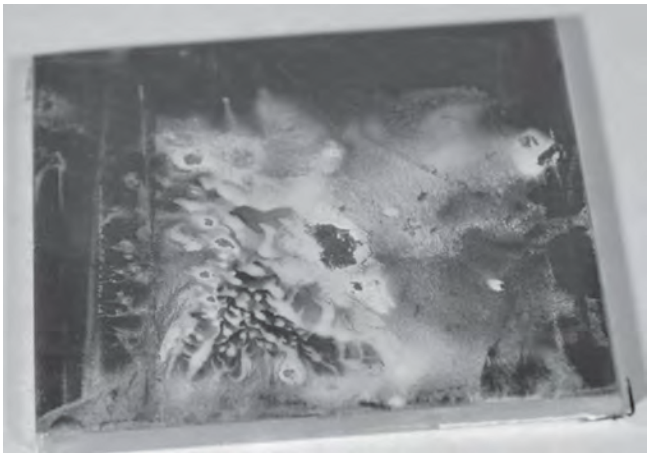

Figure 1. Process soil, deposited on coupons.

that created the white film could not be replicated in the laboratory without considerable knowledge of the process recipe, and thus coupons were physically incorporated into the process cycle in order to replicate the process soil present in the vessels. With the completion of the process run, the coupons were removed from the vessel coated with a non-uniform layer of the residue film as seen in Figure 1. This residue layer was not only unevenly coated onto both sides of the coupons, it also was present in too small an amount to capture with gravimetric means.

With the lack of process soils to gravimetrically assess the removal of the residue after the samples were subjected to different testing conditions, visual inspection was determined to be the only effective way to assess the removal of residue over time.

Visual inspection of manufacturing equipment is often utilized for cleaning validation and verification activities in pharmaceutical facilities operating according to Good Manufacturing Practices (GMPs). Often, cleaning processes for products that present minimal risk of carryover may be validated or verified using visual inspection alone. Additionally, the FDA Guide to Inspections Validation of Cleaning Processes (7/93) states that if the cleaning process is used only between batches of the same product (or for different lots of the same process intermediate), the firm need only meet a criteria of "visibly clean" for the process equipment.

...a quantitative method for visual inspection ... has enormous potential for use as a supplement or even a replacement for traditional visual inspection of process equipment.

Visual inspection is a powerful tool for cleaning validation and verification activities that allows for the detection of contamination concentrated in small areas that could otherwise go undetected by direct surface sampling or other types of analysis.[1] However, the accuracy and repeatability in the results from this visual inspection may depend significantly on the experience and level of training of the operator, as well as the quality of their vision. For example, operators requiring vision correction may experience glares on the lens of their eyeglasses that may impact the results, and wearing contact lenses may not be a viable option in certain manufacturing facilities. Additionally, the training of personnel for manual visual inspection of equipment is an ongoing requirement,[2] consuming valuable training resources. Therefore, a quantitative method for visual inspection that demonstrates low inter-operator variability and requires a minimal amount of training has enormous potential for use as a supplement or even a replacement for traditional visual inspection of process equipment.

Method Development

Through the use of an open source image processing software package combined with consistent, controlled photographic techniques, the amount of process residue was quantified by analyzing characteristics of the digital image; characteristics such as surface area coating, slight changes in color and the reflective intensity of the surface before and after testing can be transformed from the digital images into numerical data. This is performed by calculating the mean pixel intensity multiplied by the total number of pixels, hereafter referred to as the Pixel Mean X Area(PMXA) value. While this method parameter has no direct correlation to any physical parameter, it may be translated to the concentration of residue present through the generation of a calibration curve (similar to examining peak areas in HPLC

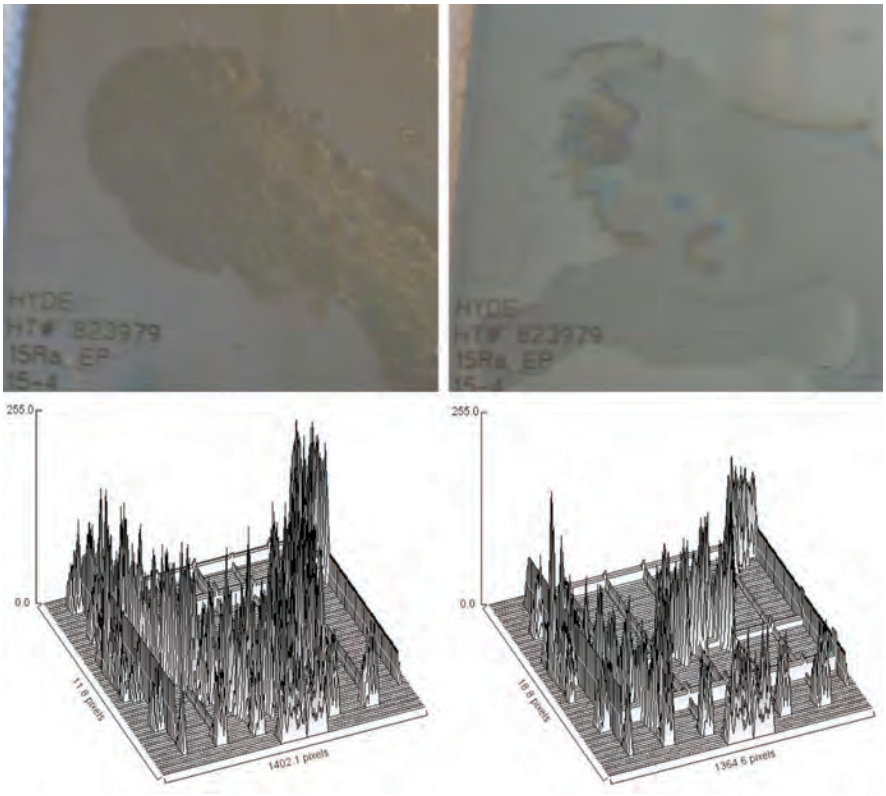

Figure 2. Surface plots of soiled (on the left) and partially cleaned coupons (right).

analysis).This data can in turn be used to contrast cleaning process performance under different conditions.

As an example, the 316L stainless steel coupons shown in Figure 2 are clearly different; though quantifying the differences through visual assessment would be somewhat problematic without a means of placing metrics on the light reflected from the coupon surface. Digital photos are typically 24 bit images, composed of overlaid red, green, and blue 8 bit images. The photos may be converted to a grayscale image in which the intensities or various shades of gray are converted to a value between 0 and 255. The result of this conversion expressed as a surface plot illustrates nicely how the relative intensities in the image can be correlated with relative surface concentrations of residual material on the coupon surface.

Gray scaling the photos can assist in the removal or filtration of the backgrounds to remove the shine brought on by the background light as well as any scratches or imperfections on the testing surface. It also allows the photo to be analyzed numerically based solely on the intensity of the reading and to change the different colors to a number. Additionally, humans have a bias to the color green[3] so filtering the photos to gray scale removes this initial visual bias.

Additionally, if the residues on coupon surfaces have a characteristic color, the image may be filtered to accentuate the residue of interest and therefore minimize the impact of surface effects or background color attributable to the coupon surface or material of construction. The metal coupon shown in Figure 3 is obviously soiled with a mineral residue; the residue appears to be multicolored or interspersed with corrosion. However, by looking at a histogram (Figure 4) of the image pixel intensity across the 0 and 255 range, it is obvious that the pixel intensity of the image changes over the range

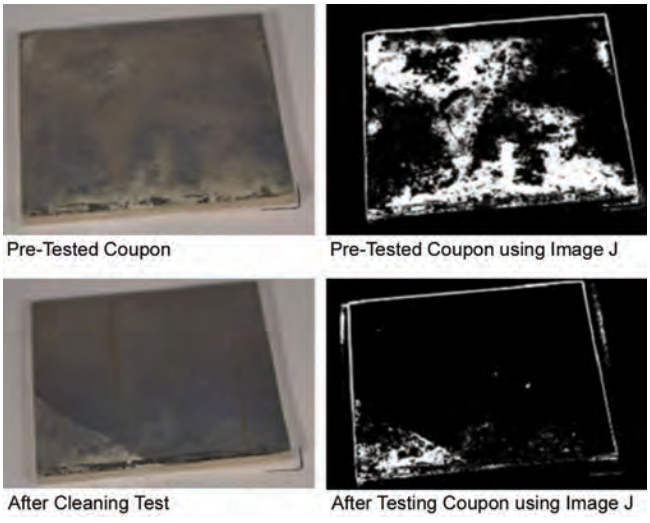

Figure 3. Soiled metal coupon.

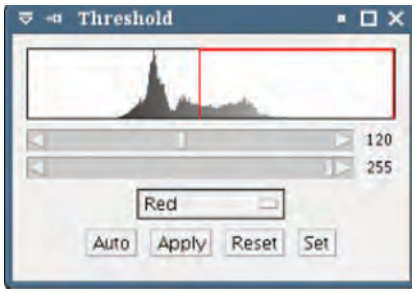

Figure 4. Histogram of image pixel intensities.

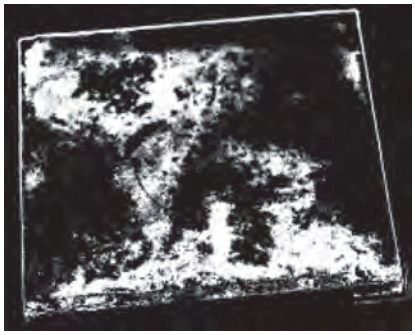

Figure 5. Binary image of residue on coupon.

between 0 and 255 and by isolating the pixels of interest, a much more distinct binary image is produced, as shown in Figure 5. Once this image has been generated, it can be processed through an image processing software platform in order to measure the intensity of the pixels in the selected region. The mean pixel depth returned from this operation is then used as a metric to quantify the amount of residue present on the coupon.

In order to properly simulate conditions for large cleaning processes at the bench scale, it is useful to address large scale conditions using parameters that translate well or that are insensitive to process scale. To properly simulate the cleaning conditions, four basic parameters that are of importance to cleaning must be maintained. Those conditions are the mechanical energy imparted to soils during cleaning, temperature of cleaning solutions, cleaning agent concentration, and the duration post production residues and equipment surfaces are exposed to cleaning solutions. For this study, Reynolds number, a dimensionless parameter quantifying turbulence, will be used as a means of characterizing mechanical energy. A Reynolds number of 4,000 simulates the mass transfer effect of a turbulent falling film in a vessel and will be used for all cleaning agent selection treatment conditions.

The duration for the cleaning tests is determined through initial range finding tests. Further, with all of the degrees of freedom for the system constrained (temperature, concentration, external energy, and duration); the bulk removal rate of the production residues then becomes a determinant for identifying the worst case residue.

The agitated immersion testing system allows for the control of each of the critical cleaning process parameters. Temperature is maintained through the PID controlled water bath. Cleaning solutions were prepared at the desired concentrations in a 1000 ml beaker and placed within the water bath. The stir rate was set by a stir plate and confirmed with the use of a digital laser tachometer. Coupons where then submerged into the 1000 ml beaker filled with a specified cleaning agent, concentration, temperature and stir rate.

To quickly conduct multiple iterations and replicates, an agitated immersion scheme was used, where each run allowed for the simultaneous testing of two coupons. In order to have enough data to calculate a standard deviation, four coupons were run for each treatment condition; the duration of each run was determined through range finding experiments and did not vary between treatment conditions of the same detergent. A second set of coupons was then run using the same conditions. The coupons were submerged in the solution, after removal from the solution the coupons were rinsed and dried in a low temperature gravity convection oven. The test was designed to leave approximately half of the spiked residue on the coupons, which was determined by analyzing pictures taken both before and after subjecting the coupon to the testing solutions.

The design space exploration was conducted using a Design of Experiments (DOE) methodology to allow multiple variables to be modified simultaneously in a prescribed manner such that more information regarding the individual variables may be extracted from experiments than an equal number of experiments in which variables are individually modified.

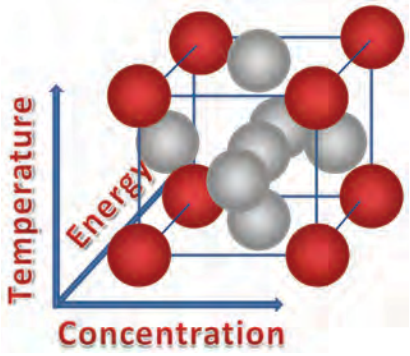

Figure 6. Composite experimental design with center points.

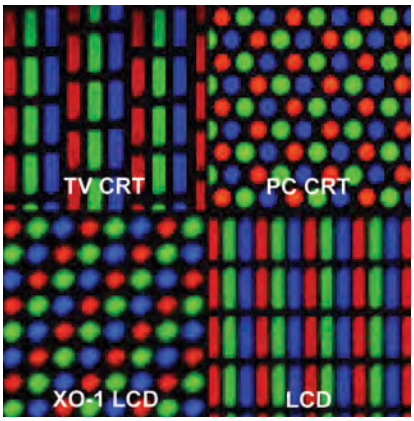

Figure 7. Various image display types.

For the design space exploration, a composite design in which turbulence, concentration and temperature were varied to produce a response surface that characterizes the removal rate over the defined design space, shown pictorially in Figure 6. This portion of the study consisted of 20 treatment conditions with four replicates for each treatment condition generating a total of 80 data points, all data points were determined via the pixel mean.

The pixel mean is the sum of the gray values of all the pixels in the selection divided by the number of pixels present in the picture, where the number of pixels that take up space in one photo is completely dependent on the type, make and model of the camera, illustrated in Figure 7. For best results, the same camera with the same lens were used for consistency in this study. The pixel mean was used to quantitatively assess the residue on the coupon before and after testing, and although this number does not directly correlate to any physical parameter; it could be used to analyze the best residue removal using statistical software. Extending this approach to images of both the front and back side of numerous coupons both before and after cleaning over a range of temperature and cleaning agent concentrations, the cleaning process response surface shown in Figure 8 was generated.

The cleaning rate results shown in the response surface in Figure 8 are expressed in terms of pixels mean change per second, and while not directly applicable to the cleaning process in mass units, this plot was used to determine which conditions produced the maximum bulk removal rates. These conditions could then be used in further experiments to ascertain the approximate durations necessary for effective removal of this post production residue from process equipment surfaces.

The response surface using the pixel means from both sides of each tested coupon gave statistically significant data. The tables in Figure 9 such as the Histogram of Residuals have a normal distribution as seen in the histogram to the bottom right. The Normal Probability Plot shows that the residuals are normally distributed if the points form a straight line, which in this case it does. The Residuals Versus Fit plot should show the residual values uniformly distributed on either side of the zero line running horizontally through the center of the plot. In addition, one also should look for a series of increasing or decreasing points, a predominance of positive or negative residuals, or patterns of increasing or decreasing residuals with changes in the fitted value. Such observations would indicate that the error was not random. Finally, the Residuals Versus Order plot in which the residuals are plotted in the order that the data was collected can be used to find non-random error related to time effects. A positive correlation is indicated by a clustering of residuals with the same sign. A negative correlation is indicated by rapid changes in the signs of consecutive residuals.

Results of the testing were captured for both cleaning temperature and cleaning agent concentration, represented in Figure 8 as a contour plot, where the darker shades of green indicates the higher rates of process soil removal. Using the digital image processing method, it was numerically ascertained that lower cleaning temperatures (25 to 40°C) in combination with the highest tested cleaning agent concentrations (10 to 15 wt% Acid) resulted in the fastest removal rates for the soiling material. Note that these results are specific to this particular soil, further corroborated by observations in which the residue was hard to remove at higher cleaning temperatures.

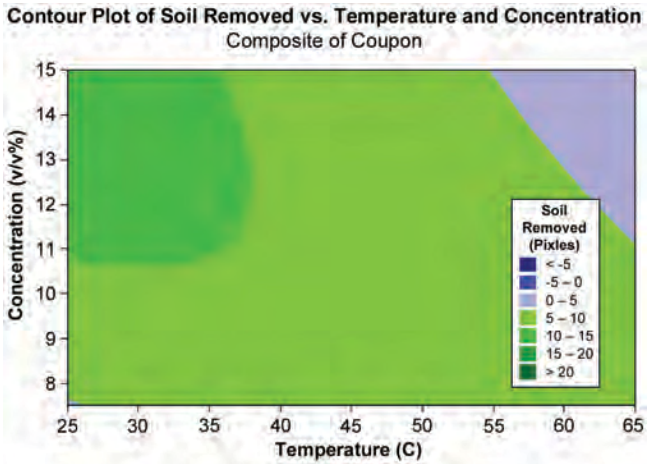

Figure 8. Contour plot of removal rate vs. cleaning test conditions.

Robustness of the Digital Image Processing

Method Sensitivity

When reviewing the coupon materials of construction and developing baseline data for the assessment of tested coupons, the laboratory team noted further evidence of the superiority of digital image processing to unaided visual inspection. The coupon in Figure 10 was provided as a representative of a "clean" baseline to compare pixel means of the tested coupons to determine a base. There was no visible residue on the control coupon; however, it was observed that the surface of the coupon displayed hydrophobic properties when rinsed with purified water; unusual for a clean 316L surface. Consequently, digital images of the coupon were analyzed and with the use of digital image processing, a faint residue deposition was revealed on the surface as Figure 10 (upper right software generated image). After cleaning the coupon via sonication with an alkaline cleaning agent, the hydrophobicity of the surface was no longer observed and the residue observed via digital image processing was no longer apparent Figure 10 (bottom right software generated image). It was theorized that the observed residue on the coupon was residual cutting oil from the manufacture of the coupons that was not completely cleaned before they were provided for testing. The pixel means were re-assessed and the new values used as the basis of comparison for subsequently analyzed data.

Linearity

In order to evaluate the potential of this digital image processing method as a viable analytical technique for cleaning validation and verification activities, the linearity of the method was examined using a number of representative residues. In the following example, 1 ml of a final bulk formulation of a monoclonal antibody was spiked onto 2.5" × 2.5" 316L stainless steel coupons at five prepared aqueous dilutions ranging from 20 ppmC (parts per million Carbon) to 400 ppmC, and then allowed to dry under ambient conditions. These concentrations were selected in order to correlate to between 0.5 ppmC and 10 ppmC in a 40 ml Total Organic Carbon (TOC) swab sample, which brackets a range of concentrations typically used in allowable carryover limits. Coupons were then photographed using a high-resolution camera under controlled lighting conditions, and these images were then subjected to this digital image processing technique in order to generate the Pixel Mean X Area (PMXA) values. These resulting PMXA values were

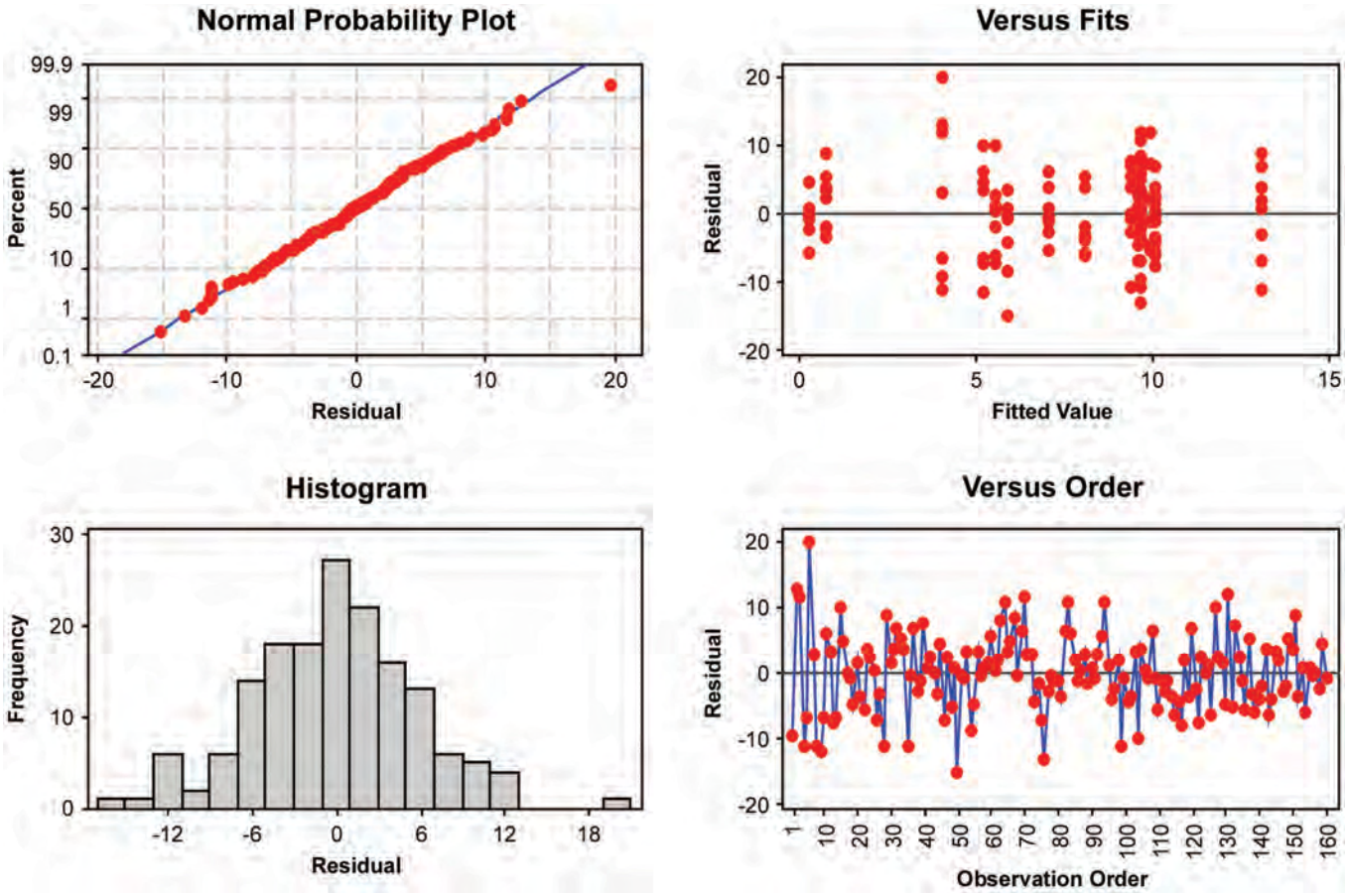

Figure 9. Residual plots for soil removal rate as determined through digital image processing.

plotted against the known concentrations prepared through precise dilutions, and this plot was then subjected to a linear regression as shown in Figure 11. The resulting regression coefficient (R2) value was 0.9969, which satisfies the criterion generally used for the response linearity of a validated analytical method (R2 ≥ 0.995).

Figure 10. Method Sensitivity – confirming cleanliness on control coupons.

Intermediate Precision

In order to evaluate to what degree the results from the digital image processing method vary between different opera-

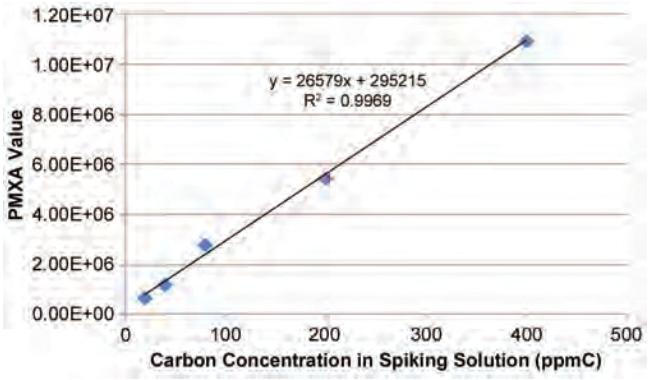

Figure 11. Method linearity response.

tors, two 316L stainless steel coupons were spiked with one of two different concentrations (40 ppmC and 400 ppmC) of a final bulk formulation of a monoclonal antibody. Once the solutions had dried on the coupons, they were analyzed using the digital image processing method by three different operators; one who had significant experience developing and performing this method, as well as two operators who were completely naïve to the method and had been given only a brief introduction and written instructions on how to execute the method. The resulting PMXA outputs were analyzed and found to have a Relative Standard Deviation (%RSD) of 9.4% for the coupon spiked with the 40 ppm solution and 20.4% for the coupon spiked with the 400 ppm carbon solution, as shown in Table A.

The %RSD of 9.4% is a level of variability between operators often seen in commonly utilized analytical techniques such as Total Organic Carbon (TOC) swab sampling. While the %RSD of 20.4% at the higher concentration is slightly greater than typically desired in a validated analytical method, this is still within a range of variability often used for intermediate precision acceptance criteria during analytical method validation. Furthermore, the variability observed between operators will likely be improved as the previously naïve operators gain additional experience in executing this method.

Spiking Concentration	%RSD
40 ppmC	9.4%
400 ppmC	20.4%

Table A. Intermediate precision data (N=3 Operators).

Critical Method Parameters

One critical parameter in developing the digital image processing method is properly establishing the color thresholds for filtering out any portions of the image that are not pertinent to the residue of interest. This involves filtering out the equipment surface in the background as well as any sort of glare off of the surface from the surrounding lighting. Since the image processing method functions by analyzing the intensity of each pixel, it is critical to adjust the filter thresholds to exclude any pixels from the analysis that are not considered part of the process residue.

Another critical parameter of this method is the light exposure present at the equipment surface. Bench scale laboratory studies have indicated that the results from this method are most consistent when the lighting exposure is well-controlled. In the experiments discussed above, the lighting was controlled at between 1200 to 1400 lux using a bench top photo studio, two halogen lamps, and a digital light meter. Ambient lighting in a manufacturing facility typically provides between 400 and 600 lux, although the application of additional lighting (either by fixed overhead tank lighting or a handheld flashlight), may increase this light exposure at the equipment surface to upwards of 1500 lux.

Digital image processing provides a rapid method for converting a qualitative image into quantitative data, and serves as a nonspecific approach to quantifying the surface area or mass of residue present.”

Conclusion

Digital image processing provides a rapid method for converting a qualitative image into quantitative data, and serves as a nonspecific approach to quantifying the surface area or mass of residue present. This approach has only been utilized in a laboratory bench-scale setting with two different types of steel alloys, though the robustness of this method will be challenged in future studies using other materials of construction such as glass and PTFE, as well as attempting to analyze photos of actual soiled equipment in full-scale manufacturing areas with varying magnitudes of light exposure.This digital image processing method has demonstrated linearity, repeatability, and intermediate precision on par with commonly utilized analytical techniques for cleaning validation and verification activities such as Total Organic Carbon (TOC) and High Performance Liquid Chromatography (HPLC) surface swab sampling. Although this method is still highly developmental and is yet to be tested or applied on actual process surfaces on the manufacturing floor, the accurate and repeatable experimental data generated using this method on a laboratory scale shows promising potential to eventually translate to full-scale process area applications.

References

1. Walsh, Andrew, “Cleaning Validation for the 21st Century: Overview of New ISPE Cleaning Guide,” Pharmaceutical Engineering, 31(6), November/December 2011.

2. Forsyth R.J., Van Nostrand, V., Martin, G.P., “Visible-Residue Limit for Cleaning Validation and its Potential Application in a Pharmaceutical Research Facility,” Pharmaceutical Technology. 28(10), 58-72 (2004).

3. Takahashi K, Nakazawa M, Watanabe Y., "DNAinsight: An Image Processing System for 2-D Gel Electrophoresis of Genomic DNA," Genome Infom Ser Workshop Genome Inform. 1997, Volume 8, pp. 135-146.

4. Kuehn M, et al., "Automated Confocal Laser Scanning Microscopy and Semiautomated Image Processing for Analysis of Biofilms." Applied and Environmental Microbiology, 64(11), Nov. 1998.

5. ICH Q11 – Development and Manufacture of Drug Substances, released November 2012, www.ich.org.

6. U.S. Food and Drug Administration. Guide to Inspections Validation of Cleaning Processes (7/93). Last updated 6/14/2010. Obtained from http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm.

About the Authors

Kelly Scalva is a Technical Proposal Engineer at Hyde Engineering & Consulting, Inc. She holds a BS in chemical and biological engineering from Colorado State University, and began her career with ChromaDex where she gained experience with multiple analytical methods employed for the analysis of oral solid dose FDA regulated therapeutics and vitamin supplements. She joined Hyde in 2011 where she was instrumental in helping Keith Bader, Director of Technology, set up Hyde's new CORE Lab, Scalva lead the lab until she was promoted to Engineer II. In the CORE Lab, she refined the procedures and methods employed for developmental cleaning studies. As a technical proposal engineer, she continues to use her engineering capabilities to ensure the technical accuracy, cost estimation, scheduling and compilation of proposals from each of Hyde's domestic and international regions. Scalva is a member of the Young Professionals group with ISPE and delivered a novel presentation at the 2013 ISPE Annual Meeting entitled, "Visual Image Processing for Bench-Scale Cleaning Studies," on the use of digital image processing for developmental cleaning studies. She was also a coauthor of a recently published article in the Journal of Validation Technology, "Translating Laboratory-Developed Visual Residues Limits to Process Area Applications," and recently presented the topic at the 2014 ISPE Annual Meeting. She also has been co-published previously in the 2013 Pharmaceutical Technology article entitled "Ruggedness of Visible Residue Limits for Cleaning-Part III: Visible Residue Limits for Different Materials of Construction." She can be contacted by email: kelly.scalva@hyde-ec.com.

Hyde Engineering + Consulting, 6260 Lookout Rd., Suite 120, Boulder, Colorado 80301 USA.

Steve Buckingham is an Engineer II at Hyde Engineering & Consulting Inc. He holds a MS in biotechnology from Northwestern University as well as a BS in chemical and biological engineering from the University of Colorado at Boulder. Buckingham began his career at CBR International Corp. in a technical consulting role, where he was responsible for drafting and submitting written responses to U.S. and European regulatory agencies on behalf of clients with regards to Chemistry, Manufacturing, and Controls (CMC) topics. He joined Hyde Engineering & Consulting in 2012 as a member of the newly-formed Hyde CORE laboratory in Boulder, Colorado, where his primary areas of expertise lie in analytical method development and validation, as well as performing IQ/OQ/PQ of laboratory equipment and instrumentation. He also recently presented at the 2014 ISPE Annual Meeting on the robustness of this digital image processing method and its capability to scale up adequately to pilot-scale and full-scale production equipment. He can be contacted by email: steve.buckingham@hyde-ec.com.

Hyde Engineering + Consulting, 280 South Taylor Ave., Suite 100, Louisville, Colorado 80027 USA.

Keith Bader is the Senior Director of Technology at Hyde Engineering & Consulting. He holds a BS in chemical engineering from the University of Colorado at Boulder. He began his career conducting government contract research in catalysts and advanced materials through SBIR grants. Following that, he joined Hyde Engineering & Consulting, Inc. in 1999 and worked in a variety of areas from control system development to cleaning validation. Through the years, he has provided high level consultation to Hyde's Engineering's clients in topic areas ranging from strategic quality and validation documentation architecture to detail oriented support, such as design of experiments and supporting study design. He has focused in recent years on the implementation of online instrumentation and process analytical technologies for clean in place systems, as well as the translation of bench scale cleaning process development data to full scale manufacturing systems. Leveraging this expertise, Bader founded Hyde's CORE Lab in 2012, a facility devoted to the development, exploration, and scale-up of cleaning processes for the pharmaceutical and biopharmaceutical industries. Bader also has published multiple journal and periodical articles as well as chapters in PAT Applied in Biopharmaceutical Process Development and Manufacturing: An Enabling Tool for Quality by Design by Duncan Lowe, and in Cleaning and Cleaning Validation, Volume 2, edited by Dr. Paul Pluta. He can be contacted by email: keith.bader@hyde-ec.com.

Hyde Engineering + Consulting, 6260 Lookout Rd., Suite 120, Boulder, Colorado 80301 USA.

ISPE Guidance Documents

Understanding the Development Process

You have all seen the ISPE publications – and perhaps wondered how they are developed? The oversight of the process is a task undertaken by the Guidance Documents Committee (GDC) led by Gloria Hall (ISPE Director of Publications) with the Chairperson this year, Jim Brinkman from Pfizer.

All of the committee members take their role seriously, as we believe that the ISPE documents are a key member benefit. The concepts behind the Guides are simple and embodied in the first Guide that ISPE produced – the ISPE Baseline® Pharmaceutical Engineering Guide, Volume 1 – Bulk Pharmaceutical Chemicals, International Society for Pharmaceutical Engineering (ISPE), First Edition, June 1996, www.ispe.org.

- Timely publication of material for the benefit of the public, members, and industry
- Clear definition of baseline standard through active engagement with regulators
- Reinforcing ISPE's reputation as a practical, pragmatic, "can-do" organization that delivers

This article provides an overview of the process, and also sets the stage for a regular item in PE describing the status of guidance documents in development, publicizing opportunities to contribute to new documents.

The overall process was recently streamlined in order to clarify and speed up document delivery from proposal to publication. Mapping this also allowed the committee to provide a simple process overview describing roles and responsibilities, so guidance document development teams could understand the overall process, and monitor their progress.

First Steps

The first step for any publication (excluding PE) is the development of a proposal to be submitted to Gloria Hall at ghall@ispe.org. The goals of the proposal document are:

- To provide a communication vehicle from the author to ISPE
- To assist the author in clarifying the goals and objectives of the document and the audience for the guidance document

Often when an individual is new to the process, the GDC can assist through the provision of a mentor to help an individual or team.

Publication Road Map

It is often more effective and helpful for guidance (especially on new and innovative topics) to be made available through a process of iterative publications as content matter matures. ISPE publishes two types of papers, each with a defined purpose:

Concept Paper

An ISPE Concept Paper establishes or clarifies a concept (or framework). Often a Concept Paper describes a potential solution or approach to an existing problem or area of discussion. A Concept Paper may solicit potential contributors and team members and may develop into Guidance Document.

Discussion Paper

An ISPE Discussion Paper promotes discussion and creates awareness. Often a Discussion Paper solicits feedback, gauges interest, explores feasibility, and seeks member or industry input. Discussion Papers may lead to a Concept Paper or Guidance Document.

Case Studies

ISPE Case Studies provide practical real-life examples, based on a project or the implementation of a concept. They provide information on the approach used and the challenges and implications of the implementation of the concept. Case studies can be stand-alone documents, be published as an article in Pharmaceutical Engineering, or associated with a guidance document.

(Knowledge Briefs are published by the Communities of Practice, not through the GDC, and provide a concise technical primer on a particular subject – e.g., blister packaging.)

Rather than always attempting to rush to publish a full final guidance document, there may be significant advantages in initially publishing articles and papers to

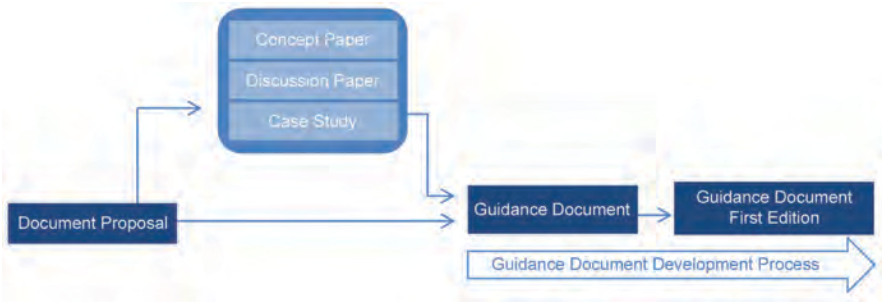

Figure 1. Publication roadmap.

ISPE Guidance Documents

Continued.

stimulate discussion, feedback, and refinement of ideas.

This process has several advantages. First, it allows industry quicker access to new ideas, and allows more rapid and wider feedback on such ideas. Second, it provides a series of distinct points for ISPE to make publication decisions (such as the appropriate guidance document category, how and where guidance is published and advertised, printed document or electronic document) based on an increasing understanding of value to the membership and to the industry as a whole.

The process also can help the authors develop a clearer understanding of the content and format for the final guidance document.

Guidance Documents

Guidance document are divided into categories depending on the intent:

ISPE Guides – provide the "what"

- Strategic in scope
- Wide ranging implications
- Define a framework for compliance in a particular area
- New and/or innovative concept or subject matter
- Areas of high compliance risk
- High potential product quality and patient safety impact
- High investment area

The Good Practice Guides provide the "how"

- "How To" practically implement approaches and principles defined in ISPE Guides
- Applying defined principles and frameworks in specific circumstances
- Typically technically based
- May suggest specific solutions where several approaches or outcomes may be valid

Handbooks

Provide a ready comprehensive reference with concise information on a particular topic, occupation, or process, structured for quick answers in a certain area.

The ISPE Guidance Document Series

ISPE documents may be stand alone or part an ISPE Series (or family) of documents. Each series may contain a combination of Guides and Good Practice Guides. Current ISPE Series are: ISPE Baseline® Guides, ISPE GAMP® Guides, and ISPE PQLI® Guides. These ISPE Guide Series are described below.

ISPE Baseline® Guides

ISPE Baseline® Guides establish a compliant minimum acceptable (baseline) approach to the topic area. Guides are developed in close collaboration with international regulators. ISPE Baseline® Guides are intended to:

- Provide a consistent and pragmatic interpretation of regulations
- Reduce costs while maintaining or improving product quality and consistency
- Prioritize facility and process design features based on

Document	Case Study	Concept Paper	Discussion Paper	ISPE Guides
Description	Provides real-life examples, based on a project or the implementation of a concept; supported by data and provides conclusions (500 – 1500 words)	Establishes or clarifies a concept; describes a potential solution or approach to an existing problem or area of discussion (10 – 20 pages)	Promotes discussion and creates awareness; solicits feedback, gauges interest; seeks member input (20 – 50 pages)	Baseline Guides, Good Practice Guides, and Handbooks (50 – 150 pages)
Publication Options	• Published on the ISPE website • Article in *Pharmaceutical Engineering* • Created to be an example for a Guidance Document	*Pharmaceutical Engineering* – print or electronic with links from the *ISPEAK* blog, or the monthly member gift. Published on the ISPE website; gauging interest in potential further guidance via an electronic form	Published on the ISPE web site, with an introduction and link from the *ISPEAK* blog, *Pharmaceutical Engineering* – electronic copy, or the monthly member gift. Can be linked to an electronic form or survey to obtain feedback	Print or electronic
Duration (Time in development)	4 – 6 weeks	8 – 12 weeks	4 – 8 weeks	12 – 18 months
Potential Reviewers	SMEs from relevant COPs, the Guidance Documents Committee	SMEs from relevant COPs, the Guidance Documents Committee	SMEs from relevant COPs, the Guidance Documents Committee	SMEs from relevant COPs, the Guidance Documents Committee
Status with ISPE	Statistics Discussion Paper Status	Peer reviewed and supported by ISPE	Seeks member / industry feedback	Peer reviewed and supported by ISPE

Table A: Types of documents.

Continued on page 90.

ISPE Guidance Documents

Continued from page 89.

their potential impact on product quality, minimizing unnecessary expense

ISPE GAMP® Guides

ISPE GAMP® Guides focus on compliance and validation of GxP regulated computerized systems by applying a flexible risk-based approach, and also enabling innovation and technological advance.

Documents in Development

- ISPE Baseline® Guides:
  - Science and Risk-Based Cleaning Process Development and Validation
  - Oral Solid Dosage Forms (Third Edition)
  - Sterile-Product Manufacturing Facilities (Third Edition)
- ISPE Good Practice Guides:
  - Controlled Temperature Chamber (CTC) Mapping
  - Decommissioning of Pharmaceutical Equipment and Facilities
  - Disposables / Single Use Technologies
  - HVAC (Second Edition)
  - HVAC and Process Equipment Filters
  - Manual Sampling
  - Operations Management
- GAMP® Good Practice Guides:
  - Global Information Systems Control and Compliance (Second Edition)
- GAMP® Essentials

Proposed Documents

- ISPE Baseline® Guides:
  - Active Pharmaceutical Ingredients API (Third Edition)
- GAMP® Good Practice Guides:
  - IT Infrastructure Control and Compliance (Second Edition)
  - A Risk-Based Approach to Compliant Electronic Records and Signatures (ER&S)
  - GAMP® Step-by-Step in Polish (may be a paper)
- ISPE Good Practice Guides:
  - Management of Engineering Guidance Documents
- Essentials
  - Commissioning and Qualification (C&Q)
  - Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)
  - Water
- Discussion Papers
  - Process Validation Lifecycle for Legacy Processes
  - Implementation of Lifecycle Validation Practices at Contract Manufacturing Organizations
  - Determination of Number of Process Performance Qualification Batches Using Statistical Tools

PQLI® Guides

Product Quality Lifecycle Implementation® (PQLI®) Good Practice Guides (GPGs) provide information on global solutions to implementation challenges of ICH guidance.

Key Roles

The Team Leader and Mentor are key roles in the production of an ISPE guidance documents. The Team Leader has the responsibility of ensuring that the document delivery team delivers a truly useful document, to the highest technical standards, in the time specified in the agreed plan. A document may have two Team Leaders to share the responsibility. A Team Leader should have the following attributes:

- Proven ability to deliver company policy or ISPE document
- Good, proactive, people, and project management skills
- Realistic, not over ambitious
- Technical credibility in the subject area

The role of Team Leader requires the support of their employer/organization for time and travel. Where the Team leader does not have a lot of experience working with ISPE, the GDC may provide a Mentor – the Mentor provides support and guidance to assist the Team Leader. The duties and responsibilities of this role include providing advice on typical issues arising when managing the development of a guidance document, and be available and willing to help the Team Leader (e.g., by telephone, face-to-face meetings, and e-mail). The Mentor also shares review and approval duties with the Team Leader at key points during guidance document delivery. A Mentor should have the following attributes:

- Proven ability to deliver company policy or ISPE document
- Experience of ISPE document delivery
- Dispute resolution skills
- Technical credibility in the topic area

Guidance Document Development Process

The Guidance Document Development Process consists of eight stages from Proposal to Layout, as shown below.

Stage 1 – Proposal

An Author/Team submits a proposal to the GDC. Note that the Team Lead is expected to be from Industry – if the Team Lead is a consultant or from a supplier company there has to be an industry co-lead.

The GDC confirms acceptance of the proposal, and

ISPE Guidance Documents

Continued.

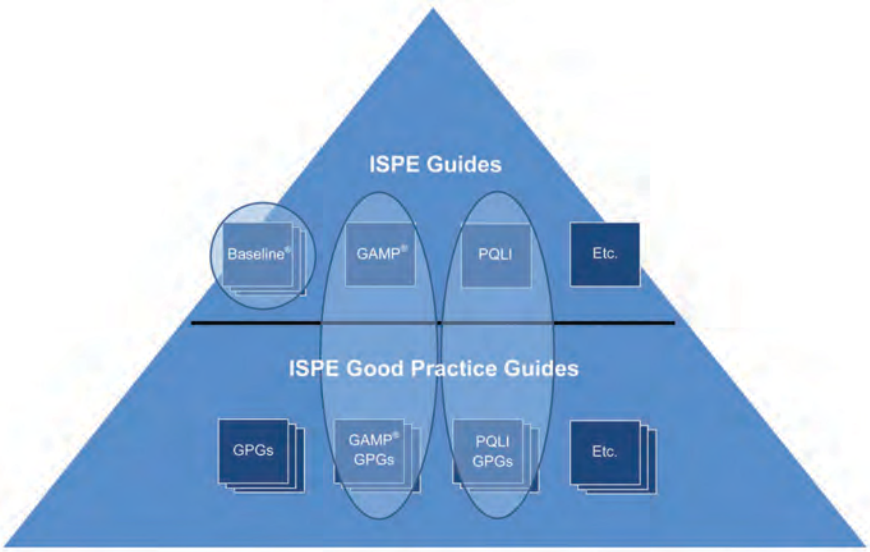

Figure 2. Hierarchy of ISPE publications.

advises on the type of publication – this may be the subject of discussion to obtain agreement; however, the GDC is the final authority. The Author may have a development team, or may ask GDC for help building the team.

Stage 2 – Plan

The Author/Team submits the guidance document plan to the GDC – the GDC provide feedback and comment on the plan based on their experience, allowing the plan to be revised. If acceptable to the GDC, the plan is approved for development.

Stage 3 – Draft 1

The team develops the initial draft – typically this has to be 80%-90% complete before moving to the next stage.

Stage 4 – Industry Review

This stage is considered critical to ensure that the guidance document reflects industry best practice. The document goes to volunteer reviewers who have demonstrated sufficient expertise in the topic area and to Subject Matter Experts (SMEs) proposed by the guidance document development team (the team) or associated COPs.

Stage 5 – Revise and Edit

Comments are received and processed by ISPE to remove non-technical comments, allowing the team to go through and respond to technical comments, revising the guide or replying to the comment – this process is overseen by the Team Leads and the ISPE Technical Writer. The ISPE Technical writer then goes through the document revising it to put it into the house style, adjusting the language to help readability for those whose first language is not English – this is a difficult process and is completed in conjunction with the team, so that the revisions do not impact the technical meaning of the content.

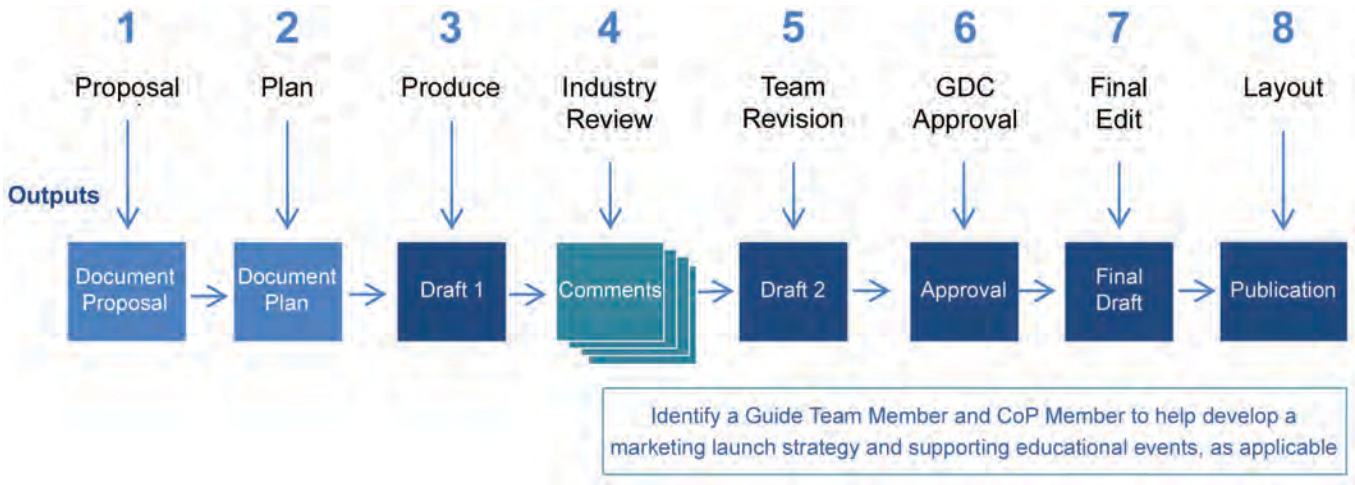

Figure 3. Guidance document development process stages.

Concludes on page 98.

2015 ISPE Europe Annual Conference

Driving Effectiveness in Pharmaceutical Operations with Integrated Quality

Join the 2015 ISPE Europe Annual Conference, taking place in Frankfurt, Germany on 4–7 May. If there is only one conference you attend, the ISPE Europe Annual Conference should be it. Gain a unique and forward looking insight into emerging regulatory developments, and learn how you can bring a new integrated perspective of regulation, technology and quality to drive increased production effectiveness. Network with industry experts and international regulators and bring a new level of expertise back to your organization.

Executive Forum – 4 May

During the Executive Forum, Senior Managers and Regulators will share their views on the pharmaceutical supply chain and ways to design it effectively. The invited speakers will discuss in detail about relevant industry and regulatory benchmarking case studies. The forum will enhance the cross-level dialogue between shop-floor, middle management, senior experts and top functional management and creates linkages between all stakeholders from related pharmaceutical functions such as drug development, quality, production, engineering and supply chain management.

Chair:

Dr. Thomas Zimmer, VP European Operations, ISPE

Speakers:

Professor Dr. Schubert Zsilavecs from the University of Frankfurt, will discuss the possibility of a reindustrialization of Europe and its implications for pharmaceutical production in the region.

Dr. Caitriona Fisher (Irish Health Products Regulatory Authority) who is a representative of the Benchmarking European Medicines Agencies (BEMA) Secretariat.

Paul Rutten from McKinsey an editor and co-author of the book, "Flawless: from Measuring Failure to Building Quality Robustness in Pharma," will share numerous benchmarking and pharmaceutical industry insights. The book will also be presented at the conference.

Dirk Pfitzer from Porsche Consulting will showcase areas of excellence as key success parameters in achieving quality. In his presentation Dirk will share a benchmark perspective of complexity and cost pressure between the automotive and pharma industries.

Conference Keynotes and Tracks

The 2015 ISPE Europe Annual Conference follows on the well attended 2014 conference and again showcase the latest technology trends, regulatory updates and developments in production, facility design and IT within the pharmaceutical business environment. Supported by the involvement of the EMA and MHRA, this conference will enable you to understand how best to bring together new regulatory expectations, new manufacturing technologies and your organization's quality system and quality culture to drive operational excellence to new heights.

Chair:

Jean-François Duliere, Pharmaceutical Process Technologist, Technip Life Sciences

Welcome Address:

Dr. Klaus Eichmueller, Darmstadt/Regierungspraesidium
John Bournas, CEO, ISPE

Keynote Speakers

In a few years a major portion of pharmaceutical drugs will consist of biopharmaceuticals. How can industry prepare for this challenge?

Prof. Dr. Wolfram Carius, Senior Vice President Biopharma Strategy, Sanofi-Aventis Deutschland will share his experiences and thoughts.

Dr. Mary Oates, Vice President, Global Quality Operations, Pfizer, will discuss why quality culture will be a key success factor in operational excellence and how to effectively perform the change management to modernize quality culture principles in a whole organization.

Dr. Robert Nass, Head of Quality and Regulatory Management, Merck Serono will show how the right use of computerized systems, software and work principles with big data volumes, and data integrity contribute to the industrial success in the pharmaceutical industry.

5 – 6 May

Four Tracks, developed in conjunction with leading industry and regulatory experts, focused on evolving regulatory expectations and the challenges of implementation.

Track 1 – Managing Quality under the New Quality Paradigm

Track Leaders

Georges France, Region Head Quality Europe, Novartis, Switzerland
Ron Ogilvie, Senior Director, Global Chemistry, Manufacture and Controls, Pfizer, UK

This track will address manufacturing in the new quality paradigm and will examine lifecycle CMC management, from the ICH Q12 concepts, through the role of process knowledge in managing change to considering how the CMC submission can

Spotlighting the Aseptic Track at the 2015 Aseptic Processing Technology Conference

As you know, aseptic filling of parenterals coupled with maintaining compliance is one the most challenging tasks within pharmaceutical manufacturing. Therefore, the Aseptic Track at the 2015 Aseptic Processing Technology Conference on 23 – 24 February in Baltimore, Maryland, cannot be missed. In its 24th year, the conference's Aseptic Track includes a wide range of topics from filling accuracy and machine performance to maintaining a sterile and compliant process. Highlights of the Aseptic Track are:

- Exploring Active Pharmaceutical Ingredients (APIs) processing in two sessions - "High Potent Fill/ Finish 2.0," and "High Potent Fill/ Finish: Practical Aspects."
- Learning about Ampio Pharmaceuticals' liquid fill process which utilizes an automated closed system process, single use format with a minimal footprint in "Single Use Technology Considerations in an Aseptic Operation: Upstream Product Handling through Final Fill."
- Hearing lessons learned in the development of new blood plasma production facility in "Sterile Filling System – Aseptic Filling System that Minimizes Risk of Contamination."
- Discussing the design and execution of an external technology transfer project in "Management Lessons Learned from Technology Transfers of Lyophilized Drug Products."
- Gaining solutions for filling needle clogging under precisely controlled environmental condition in "Launching from a Pilot Plant – A valid option in a changing environment?"

In addition to the Aseptic Track sessions, the conference offers special sessions such as the newly added breakfast sessions. The ISPE Drug Shortages Task Team will host a breakfast session on Monday, 23 February on "How Improving Your Aseptic Processing Can Reduce Drug Shortages." Then on Tuesday, 24 February 2015, the ISPE Chesapeake Bay Chapter will host "Multi-Product Fill/ Finish Trends and Customer Expectations for Contract Manufacturers," over breakfast.

The sessions are just a few of the exciting opportunities to learn and network available during the conference.

For more information on the Aseptic Track or the conference, please visit the conference website at www.ispe.org/2015-aseptic-conference.

Europe Annual Conference

Continued.

optimally support lifecycle management. The sessions will also focus on the role of the Quality System in CMC lifecycle management, the role of the QP, and the importance of knowledge management in manufacturing.

Highlights

- Consideration of new lifecycle CMC concepts (per ICH Q12 concept paper).
- Deliberation of perspectives on the role of the quality system in lifecycle CMC management.
- Analysis on how knowledge management and submission content supports lifecycle CMC management.

Track 2 – Regulatory Trends and Developments in Europe and Beyond

Track Leaders

Bryan Wright, European Regulatory Affairs Advisor, ISPE, UK
Buket Hekiman, General Management, PharmaVision, Turkey

This track will consider the impact of the latest regulatory developments across Europe, including both industry and regulatory views. Topics covered will evaluate the role of EMA in harmonizing Good Manufacturing Practices (GMP) and the implications on both industry and national regulations. The track will also delve deeper on the topic of drug shortages, including latest updates from the ISPE drug shortages project and the implications and expectations of the EMA initiated plan to address shortages caused by manufacturing and quality problems.

Highlights

- Regulatory updates at EU and national levels, including discussions on the future regulatory directions.
- Oversight and vision of the supply chain from regulators' perspective in Germany and in the EU.
- Information on the proposed changes in Annex 1 of EU Guide and their possible effect on harmonizing the manufacture of sterile products.
- Presentation on the on-going updates on GMP Annexes 1, 15 and 16.

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Europe Annual Conference

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Track 3 – Facilities of the Future: Achieving Cost-Effective Manufacturing Flexibility

Track Leaders

Gert Moelgaard,Vice President, Strategic Development, NNE Pharmaplan, Denmark

Jean-Franols Dullere, Pharmaceutical Process Technologist, Technip Life Sciences, France

Pharmaceutical facilities of the future should be cost-effective in operations and at the same time fulfill the requirements of factory and process design in the pharmaceutical industry. Based on the successful track in 2014, the program will share experiences from commercial manufacturing with some of the new pharmaceutical manufacturing developments such as continuous manufacturing, advanced aseptic processing, lean GMP operations and quality by design application in commercial manufacturing.

The track will provide insight into the best ways to improve manufacturing productivity and achieve cost-effectiveness while maintaining high-quality standards, and give regulatory feedback on current manufacturing challenges.

Track 4 – IT innovation for Effective Business Solutions and Regulatory Compliance

Track Leaders

Chris Reid, Owner, Integrity Solutions Ltd, UK

Jens Seest, Global Head ERP Compliance and Training, Sandoz SHAPE Competence Center, Germany

This track will explore the exploitation of innovative automation and IT solutions in the effective management of pharmaceutical products throughout the product lifecycle. Sessions will address the use of state of the art technologies, solutions and services that bring about operational efficiencies and promote supply chain integrity. Presentations will showcase practical case studies that share the benefits and risks of exploiting innovative and emerging technologies, solutions and services.

Highlights

- Exposure to emerging technologies and the benefits and risks of implementing such technologies.
- Practical insight into implementation challenges.
- Risk-based strategies for dealing with regulatory impact.

Additional Conference Features

Poster Session

There will also be a Poster Session for young professionals to showcase their skills and knowledge.

Plant Tours

Optional plant tours at Sanofi Frankfurt and Dachser Intelligent Logistics Frankfurt are planned for 7 May. Secure your place now – spaces are limited!

Exhibition and Sponsorship Opportunities

Choose from a variety of exhibition and sponsorship packages to build brand awareness and increase exposure. For more information or to secure your place please contact John Phillips at jphillips@ispe.org, +1-813-960-2105 x242 www.ispe.org/2015-Europe-Annual-Conference/Exhibit-Sponsor.

For more information or to register, please visit the conference website at www.ispe.org/2015-Europe-Annual-Conference.

Announcing the 2015 ISPE Statisticians Forum

ISPE is pleased to announce the 2015 ISPE Statisticians Forum on 14 – 15 April 2015 in Silver Spring, Maryland. By participating in the Forum, participants will not only gain insights to improve the use of statistics in a company's processes, but also will contribute to the dialogue surrounding the interpretation and expectations from the FDA Process Validation Guidance, including topics related to:

- Global expectations
- Statistically based quality metrics reporting
- Sampling plans for Process Validation (PV)
- Changes in blend uniformity expectations
- Use of control limits
- Justifying batches

In addition, ISPE has added new and exciting opportunities including the Statistics Primer on Monday 13 April – a pre-conference program designed to serve as a refresher on statistical concepts and tools including normality tests, utilization of RQL vs. AQL for PV, impact of large non-normality, tolerance intervals and OC curves.

Participants will also dive deeper into statistical analysis with interactive participant polling throughout the event to benchmark Lifecycle to PV implementation. Lastly, an Integrated Case Study will be referenced throughout the conference to illustrate statistical options for each stage of the PV lifecycle.

For more information or to register, please visit the conference website at www.ispe.org/2015-statistician-forum.

Learning Opportunities Abound at PACK EXPO East

PACK EXPO East offers free educational opportunities that enrich your knowledge of the latest industry advances and your exploration of the show floor.

A World-Class Conference Program – Low-cost, convenient and timely sessions

Learn the latest trends, best practices and practical applications of technology relevant to the pharmaceutical packaging in twelve convenient education sessions. International Society for Pharmaceutical Engineering (ISPE), global leader in pharmaceutical manufacturing solutions, brings you a world of knowledge in the PACK EXPO EAST conference program.

Innovation Stage – Free 30-Minute Seminars

Conveniently located on the show floor, Innovation Stage is the site of educational talks on breakthrough technologies and techniques, presented by the industry's leading companies.

In-Booth Education – The Straight Scoop from Engineers

Many exhibitors offer in-depth demonstrations about their products, allowing you to make better buying decisions and better leverage the benefits of the technologies you own. These sessions are a major benefit of seeing vendors in person—you can't get insight like this from salespeople over the phone!

Education Focused on Manufacturing Excellence

Building on the success of their world-class conference program at Pharma EXPO, the International Society for Pharmaceutical Engineering (ISPE) will bring educational opportunities to PACK EXPO East. You can expect quality sessions that cover best practices in manufacturing operations, new technologies and tools for achieving regulatory compliance and advances in pharmaceutical packaging.

ISPE leads scientific, technical and regulatory advancement throughout the entire pharmaceutical lifecycle.

Conference Tracks

Choose from 12 substantive sessions categorized into three topic tracks—one track for each day.

Monday, February 16 – Manufacturing Operations
Tuesday, February 17 – Pharmaceutical Packaging
Wednesday, February 18 – Compliance Trends

Pricing Levels

Affordable pricing options give you the flexibility to choose the amount of time you spend in conference sessions versus on the show floor. Are your interests focused on one particular track? Choose the **Day Pass**. Is your schedule already

Concludes on page 98.

Announcing the 2015 ISPE Quality Metrics Summit

ISPE is pleased to announce the 2015 ISPE Quality Metrics Summit on 21 – 22 April 2015 in Baltimore, Maryland. The summit will provide the initial report of the ISPE Quality Metrics Pilot Program. During the event, attendees will hear the real-life experiences of the 18 companies and 44 individual sites participating in the ISPE Quality Metrics Pilot Program.

In addition, the summit will provide a forum for discussion of the FDA proposed metrics during the Federal Register notice commenting period where attendees will be able to provide input to FDA on the proposed metrics set in two ways – direct dialog with FDA senior metrics representatives during panels and breakouts sessions, and by contributing to industry's collective response to the FDA draft metrics. As a participant, you will:

- Receive a copy of the ISPE Quality Metrics Report
- Understand how quality and other business metrics are used in industry to drive efficiency and continual improvement
- Gain an overview of the FDASIA and its extension to a quality metrics program
- Examine the objectives of a quality metrics program from an FDA perspective – understand what FDA is aiming to achieve
- Hear experiences from the ISPE Pilot Program relating to Data Collection, Submission, and Benchmarking
- Debate and provide input to FDA proposals based on their company and ISPE experience
- Help develop industry response to implementation of FDA proposals
- Form proposals for implementing a quality metrics program which can be taken back, discussed with colleagues and management, and implemented

Look for more information coming soon on the ISPE website.

Architects, Engineers, Constructors

CRB, 7410 N.W. Tiffany Springs Pkwy., Ste. 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

NNE Pharmaplan, Nybrovej 80, 2820 Gentofte, Denmark. +45 4444 7777. See our ad in this issue.

Pharmadule Morimatsu AB, DanvikCenter 28, SE – 13130 Nacka, Sweden. +46 (0)8 587 42 000. See our ad in this issue.

Biopharmaceuticals / Biotechnology

Eli Lilly S.A. Irish Branch, www.lilly.ie. See our ad in this issue.

Consulting

PharmEng Technology, 2501 Blue Ridge Road, Suite 250, Raleigh, NC 27607. (416) 385-3922. See our ad in this issue

Dust Collection Systems and Equipment

Camfil Air Pollution Control, 3505 S. Airport Dr., Jonesboro, AR 72401. (870) 933-8048. See our ad in this issue.

Information Technology

Ing. Punzenberger COPA-DATA GmbH, Karolingerstrasse 7b, Salzburg, Austria 5020. +43 662 43 10 02-0. See our ad in this issue.

Zenith Technologies, The Genesis Centre, Garrett Field, Birchwood, Warrington, United KingdomWA3 7BH. See our ad in this issue.

Instrumentation

Bürkert Fluid Control Systems, Christian-Bürkert-Strasse 13-17, D-74653 Ingelfingen, Germany. +49 (0)7940 100. See our ad in this issue.

Endress+Hauser, Kägenstrasse 2, 4153 Reinach, Switzerland. +41 61 715 75 75. See our ad in this issue.

Pumps

Alfa Laval, Inc., 5400 International Trade Dr., Richmond, VA 23231. (804) 222-5300. See our ad in this issue.

Fristam Pumps USA, 2410 Parview Rd., Middleton, WI 53562. (800) 841-5001. See our ad in this issue.

LEWA-Nikkiso America, 132 Hopping Brook Road, Holliston, MA 01746. (508) 893-3218. See our ad in this issue.

Watson Marlow, 37 Upton Technology Park, Wilmington, MA 01887. (800) 282-8823. See our ad in this issue.

Software/Hardware Products

Computational Dynamics, Ltd., 60 Broadhollow Road, Melville, NY. (631) 549-2300. See our ad in this issue.

Software Simulation and Processing Systems

Intelligen, Inc., 2326 Morse Ave., Scotch Plains, NJ 07076. (908) 654-0088. See our ad in this issue.

Tray Systems

Hurst Corporation, P.O. Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Validation Services

Azzur Group, LLC, 726 Fitzwatertown Rd., Ste. 6, Willow Grove, PA 19090. (215) 322-8322. See our ad in this issue.

Commissioning Agents, Inc., 652 N. Girls School Rd., Indianapolis, IN 46214. (317) 271-6082. See our ad in this issue.

ProPharma Group, Inc., 10975 Benson Drive., Ste. 330, Corporate Woods Bldg. 12, Overland Park, KS 66210. (913) 661-1662. See our ad in the issue.

Valves/Pipes/Fittings

Crane ChemPharma & Energy, 4444 Cooper Road, Cincinnati, OH 45242. +01 513 745 6021. See our ad in this issue.

Water Treatment and Purification

ELETTRACQUA Srl, Via Adamoli 513, 16165 Genoa, Italy. +39 010 8300014. See our ad in this issue.

Mar Cor Purification, 160 Stedman Street, Lowell, MA 01851. (978) 453-9600. See our ad in this issue.

INTRODUCING

PACK EXPO East

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advertiser's index

ISPE update

ISPE Guidance Documents

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Stage 6 – GDC Approved Document

This edited version is provided to the GDC for final review (hopefully) to approve the technical content – each member of the GDC is responsible to check or get a company SME to check that the content is technically acceptable.

Stage 7 – Final Edit

Any revisions suggested by the GDC are incorporated (as appropriate) and the technical content finalized.

Stage 8 – Layout and Cover

The final stage sees the text beautified to provide the layout for either an electronic or print document – graphics may be redrawn and the permissions to use any graphics are checked, acknowledgements and references are checked, and the final document sent to the team for review.

Each of these stages has defined gatekeeper who approves moving on to the next stage. These are shown below.

Summary

The combination of the overall publication roadmap and the streamlined process for the development of guidance documents should bring benefits to ISPE, the membership, and the industry. Guidance documents should help make the most relevant and useful guidance available in a timely manner, facilitating the exchange of ideas and practical experience, while also upholding ISPE's reputation for technical excellence.

...PACK EXPO East

Continued from page 95.

packed with supplier meetings? Pick a few can't-miss sessions for the **Per-Session rate**.

	Before January 21	After January 21 – Onsite
Day Pass	$125.00	$150.00
Per Session	$75.00	$100.00

Questions on the conference program? Please contact:

- Julianne Rill, Associate Director Continuing Education, ISPE, Email: jrill@ispe.org, Tel: 813-610-7133
- Jennifer Bayne, Conference Speaker Coordinator, ISPE, Email: jbayne@ispe.org, Tel: 813-960-2105, ext. 216

2015 ISPE Europe Annual Conference

Driving Effectiveness in Pharmaceutical Operations with Integrated Quality

4-7 May 2015
Frankfurt, Germany
Steigenberger Airport Hotel

Don't miss out!

Executive Forum to enhance the cross-level dialogue between shop floor, middle management senior experts and top functional management.

Four Tracks covering the milestones of the pharmaceutical lifecycle:

1 – Managing Quality under the New Quality Paradigm
2 – Regulatory Trends and Developments in Europe and Beyond
3 – Facilities of the Future: Achieving Cost-Effective Manufacturing Flexibility
4 – IT Innovation for Effective Business Solutions and Regulatory Compliance

Exhibition with top suppliers and solution providers.

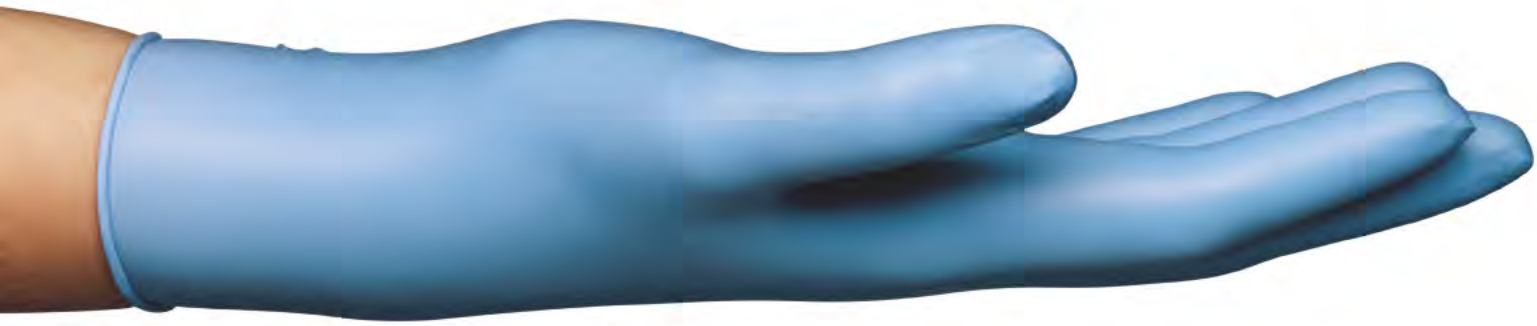
Student Poster Session featuring presentations from students in Europe.

Optional Plant Tours
at Sanofi Frankfurt and Dachser Intelligent Logistics, Frankfurt.

Early Bird Discounts until 10 February

www.ISPE.org/2015-Europe-Annual-Conference

Elevate your mixing performance



Alfa Laval's magnetic mixers are an attractive proposition. What lifts them above the pack is the levitating design. The impeller floats on a powerful magnetic field, and there is no contact between bearing surfaces. With no friction, the impeller can safely run dry, mixing right down to the last drop for the highest possible yield. The eight-wing impeller is gentle on your product and delivers efficient mixing from as low as 10 rpm all the way up to 600 rpm. The levitating design also makes these mixers supremely hygienic; there is no product stagnation between bearing surfaces and cleaning fluid can flow freely.

Learn more at
www.alfalaval.com/biopharm

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