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Managing the Extended R&D Supply Chain

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This article presents the R&D supply chain and manufacturing operations, from the manufacturing of Active Pharmaceutical Ingredients (APIs) through to the delivery of Investigational Medicinal Products (IMPs) at the clinical site and on to the patient.

Increasing Business Pressures

Most recent research on clinical trials focuses on the outsourced Research and Development (R&D) activities, such as data delivery, site conduct, and development. This article describes, for both sponsors and contractors, the clinical supply chain and manufacturing operations, from the manufacturing of Active Pharmaceutical Ingredients (APIs) through to the delivery of Investigational Medicinal Products (IMPs) at the clinical site and on to the patient.

Sponsors and contractors have undergone substantive change in recent years as the pharmaceutical industry and its needs have changed. New technologies and target diseases require more complex trials and in search of patient mass and lower cost, the clinical trial base has shifted toward markets such as India and China.

This has driven a drive for scale in some leading Clinical Research Organizations (CROs) and the emergence of truly global players, while others have responded by focusing in emerging markets, adding niche and specialized services and targeting selected disease areas.

Many traditional activities have shifted to CROs, often with very different risk and reward mechanisms. The redrawing of the activity map requires new and often more complex working practices involving multiple partners, often with differing motivations, and a consequent need to ensure that control is demonstrably sustained throughout the supply chain.

This puts increased demands on the CRO at a time when their finances are already under pressure, and the benefits are yet to be realized.

Sponsors remain accountable for their clinical trials and also need to rethink and/or develop the R&D supply chain.

Streamlining Clinical Trials

Clinical trials are an essential part of the drug development process and if run efficiently can provide the pharmaceutical/biotech company with a competitive advantage. Many internal

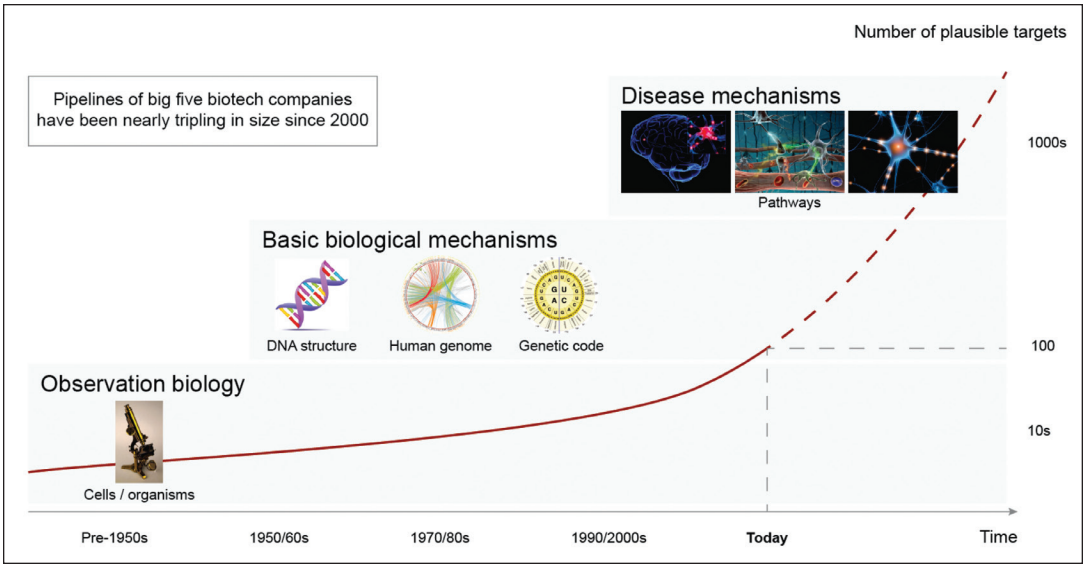

Figure 1. Increase in novel plausible targets will lead to rapid growth of clinical trial operations (Source: Lodestone).

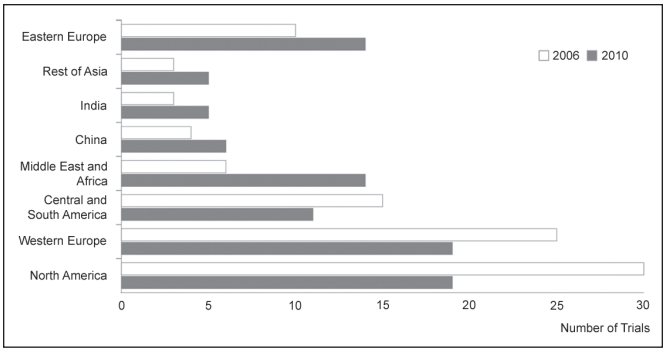

Figure 2. Evolution of trials from 2006 to 2010 by region – Source Gartner (Steven Lefebure).

and external company stakeholders point to developments costs as a barrier to innovation. The US Food and Drug Administration (FDA) has confirmed as part of its "Critical Path Initiative" that "streamlining clinical trials" is one of its key priorities.[1]

The shift toward global trials adds a further layer of complexity to the clinical supply chain[2]; therefore, companies must be able to manage both global and local regulatory requirements.

However, regulatory guidelines describe measures to protect patient safety, but not necessarily how to conduct trials. An effective operating model that supports integrated processes, inventory visibility, and compliance in manufacturing and distribution of clinical trial supplies becomes a priority. The integration of contractors in the R&D supply chain has been underestimated in many outsourcing strategies. Also contractors are not profitable enough to ensure sustainable growth and to put capabilities in place in order to deal with future challenges. This constitutes a considerable industry risk.

Future risk assessments need to differentiate between smaller life sciences companies and big pharmaceutical/biotech sponsors. Outsourcing of almost the complete study supply chain will be increasingly attractive to smaller companies who need the critical mass and footprint of global contractors. Big biotech and pharmaceutical sponsors require the highest levels of transparency and compliance in their global harmonized R&D supply chains, and will likely maintain clinical trials supply in-house in combination with outsourcing.

Contractors will make contributions in specific steps and they will need to establish new capabilities for collaborating with sponsors. Beside the externalization of physical manufacturing and logistics activities, outsourced services can be used for the coordination of stocks and enrollments at clinical sites. Their relationships and integration touch points are specific by category:

- API and DP contract manufacturing: prior to the point of finished goods packaging, the R&D supply chain employs a number of contract manufacturers for API and DP. Integration touch points between both parties include details about material inventory, including status, location, and quantity updates. The sponsor provides supply requirement plans and details about manufacturing orders, including bill of materials and detailed order instructions. The contractor is typically accountable for all ingredient batch traceability unless sponsor material is provided to the contractor.
- Third party logistics: API, raw materials, and drug product need to be moved through the supply chain. The transfer requests and confirmations are exchanged between sponsor and contractors. Also "cold chain aspects" are part of the information flow, especially the decision making in case of deviations.
- Contract packaging and labeling of clinical finished goods: the information exchange between sponsor and contractor is similar as for API and DP manufacturing. The blinding of IMP requires exchange of label samples and package numbers. Complex packaging designs and work instructions need to be specified and provided to co-packers for every clinical trial.
- Third party clinical finished goods distribution: clinical depots are located across the globe. Many low-volume pick, pack, and shipment operations (thousands of patients can participate in a study) are executed by multiple logistics providers. Inventory quantity, package numbers, and

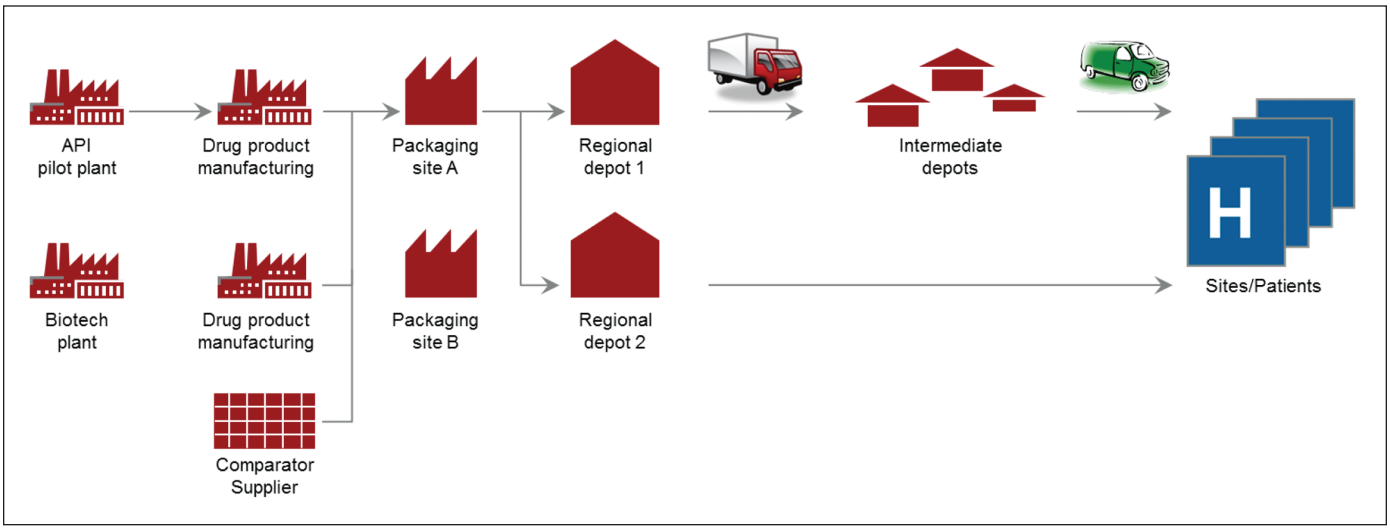

Figure 3. The R&D supply chain (Source: Lodestone).

status information are continuously shared for planning and traceability purposes. Also in this area, extensive cold chain information needs to be exchanged.

- Site stock control: stocks and enrollment information at clinical sites can be handled by external or internal monitors. Study teams need this information to manage the site supply which can be captured and exchanged in multiple ways. Drug Accountability (DA) systems and Interactive Response Technology (IRT) are typically used for high volume and global studies. Sponsors can use external service providers that provide this technology including the staff required to manage the IMP supply to and in the sites.

The Challenges of the R&D Supply Chain

Figure 3 shows the end to end supply chain. First, the API and DP manufacturing in the upstream part of the R&D supply chain is part of the "technical development" organization. It is a silo type organization with departments that have a science focus on the development of API and DP. "Manufacturing process science" is obviously a key deliverable from those departments, but world-class performance results in "manufacturing compliance, speed, and cost effectiveness" are still far from reality. Comparator drug manufacturing can be defined as a normal "DP manufacturer," but dynamics are different as DP is typically sourced via intermediate entities and it drives the study supply costs significantly. The packaging unit for IMP is dealing with blinding aspects of the trial.

Second, Figure 3 shows that components can be provided from different sources and IMP is transferred to a distribution network.

As depicted in Figure 3, further downstream in the R&D supply chain, a complex clinical distribution network is established for each study. The distribution ends at the patient visit in clinical centers or sites, potentially managed with interactive response technology from CROs or specific IRT service providers. This distribution network is also dealing with several complexity challenges that will be further described in this paragraph.

Regardless if the activity is internally executed or outsourced, sponsors and contractors need to overcome many operational challenges in forecasting and planning, manufacturing, and warehousing and distribution for active pharmaceutical ingredient, drug product, and clinical finished goods.

Forecasting and Planning

This process has different planning levels and horizons. It also has two modes: before and after study initiation. The following four factors are key challenges for ongoing trial forecasting and planning:

Long-term stability is a challenge as in many cases, API and drug product must be manufactured prior to the availability of long-term stability data.

Patient recruitment: when the trial begins, a range of factors inevitably alters original forecasts and impacts planning. Enrollment varies across sites owing to patient availability, withdrawals, study extensions, investigator performance, and other factors. The monitoring of patient enrollments is typical available information, but it is difficult to access by the R&D supply chain function. The actual enrollments should be considered to produce any demand data for re-supply of IMP. Otherwise planning becomes a very ineffective process. Figure 4 shows the generic profile of an actual enrollment rate that starts deviating from planned enrollments.

Inventory visibility at contractors is lacking when they keep the inventory for the sponsor in a single step without exchanging full data.

Integration of plans across manufacturing steps is a weakness in most end-to-end supply chains. As stated above, contractors only manage specific parts of the supply chain. Any lead time or delay of planning or status information can negatively impact the entire supply chain.

Chemical/Biotech Production, Pharmaceutical Production

The production of supplies for clinical use mirrors the manufacturing of commercial drugs in many ways. For example, all operations and processes must be fully compliant with current Good Manufacturing Practices (cGMPs), and are subject to audit by regulatory bodies such as the FDA.

However, clinical manufacturing – both internal and external – faces distinct challenges, including unreliable production or supply of API or biotech bulk and manufacture of different dosages and placebos. The "demand" is defined for R&D projects or studies driving either clinical or non-clinical demand. A non-clinical product is still in its "science status" meaning that the recipe is still dynamic. A clinical product has the purpose to be used for clinical trials; however, it can end up as a restricted for certain or all studies.

Clinical Packaging

Clinical packaging operations are in certain cases a commodity that is outsourced. For example, high volume open label study material is typically outsourced; however, subcontractors have still challenges to provide efficient and integrated solutions. Sponsors keep typically low volume studies in-house as the management costs for outsourcing would be too high, especially for complex studies. Beside this, they also have insourced the packaging to realize benefits from clinical supply chain integration.

Four supply chain integration challenges need consideration in the design and operation of the clinical packaging:

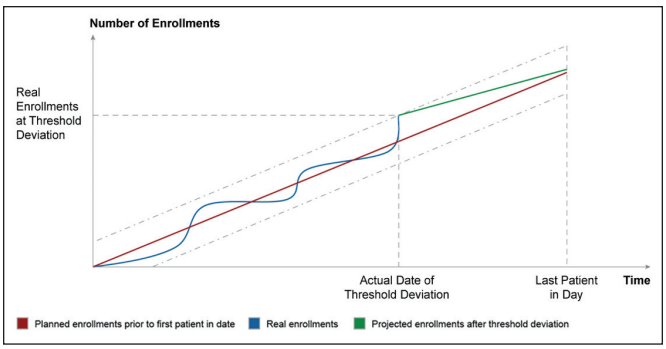

Figure 4. Actual versus planned enrollments (Source: Hoffmann-La Roche (Dr. Edwin Schiff)).

- Translation of protocols into packaging needs and obtaining approval from clinical operations on complex packaging designs is awkward. It requires several iterations to make sure that the designs match the needs. A protocol has typically multiple treatment groups, countries, and possibly different study phases. Different packaging types (e.g., comparator versus active, multiple visits) are used for the dispensing of IMP to patients. The IMP can have a bill of material with several levels and many components. Clinical supply coordinators have to make sure that the requirements from the study team are correctly translated into this packaging data. This information needs to be properly shared across departments and possibly company borders. As protocols are approved only a limited period before the first patient visit, it is important to ensure seamless data exchange, ideally with a graphical representation of the packaging design and labels in order to avoid misunderstandings between study team and packaging.
- A high volume of GMP information is required for a packaging order. Currently, companies need to re-enter such data multiple times due to separation of solutions. A packaging order is not a simple instruction to produce a quantity of a certain kit assembly by a due date. It is a very comprehensive set of GMP relevant information, for example: along with the various master label design information, each component label that is used in the kit needs to be printed with the package number of the kit. Work instructions - that are study and material specific - must describe in detail what needs to be executed by the packaging operator. A specific label must be applied on a component in the bill of material. The distribution center requires the link between the license plate number of the outer box carrying all package numbers. This high volume data generated by packaging is in many companies still manually registered. The cost of verifying the quality of multiple data sources is too high; therefore, a single entry and secure distribution of data needs to be implemented.
- Introduction of new packaging and labeling technologies to improve quality control. Reliable technologies are available on the market while many companies have still manual work methods, even for high volume packaging. For example, label print verification can be integrated in the label printing process. It provides automatic feedback for re-printing of labels. This avoids rework or correction during the packaging process. Also in-line printing of labels during packaging doesn't require witnessing by peers and post label reconciliation as the labels are only printed at the time that a kit is assembled.
- Re-labeling or over-labeling is necessary when a product is expired. The process starts with a shelf-life prolongation request and approval. Once the new retest date or use-by-date is approved, the data must be forwarded to multiple parties, such as the in-house or outsourced label room, internal or external packaging or distribution location where the IMP is located, quality people who review and approve the re-label operations, etc. Manual processes such as emails are error-prone and induce compliance risks; therefore, a validated system needs to be in place for this process.

Distribution

The shipment of IMP to many different countries became a highly niche and specialized operation. Many companies have still cumbersome processes:

- 24-hours-recall requires upstream tracking of API and DP batch information. Currently, distribution vendors don't have full visibility of the upstream supply chain for a recall which requires crisis teams and multiple data consolidations between sponsors and contractors.
- Drug accountability is still expensive and managed by study teams. There are limited solutions that approach the drug accountability with cross-study standardized processes.
- Distribution planning is typically managed by the study team and based on a single IRT/IxRS contract. Due to lack of cross-study inventory data at distribution depots, it is difficult to standardize replenishment planning.
- Expiry dating on the IMP label is complex in clinical trials as companies – especially in Europe – are still conservative in the interpretation of health authority guidelines. Health authorities are also challenging sponsors as their processes for expiry date updating, for example, audit trial, is poor.

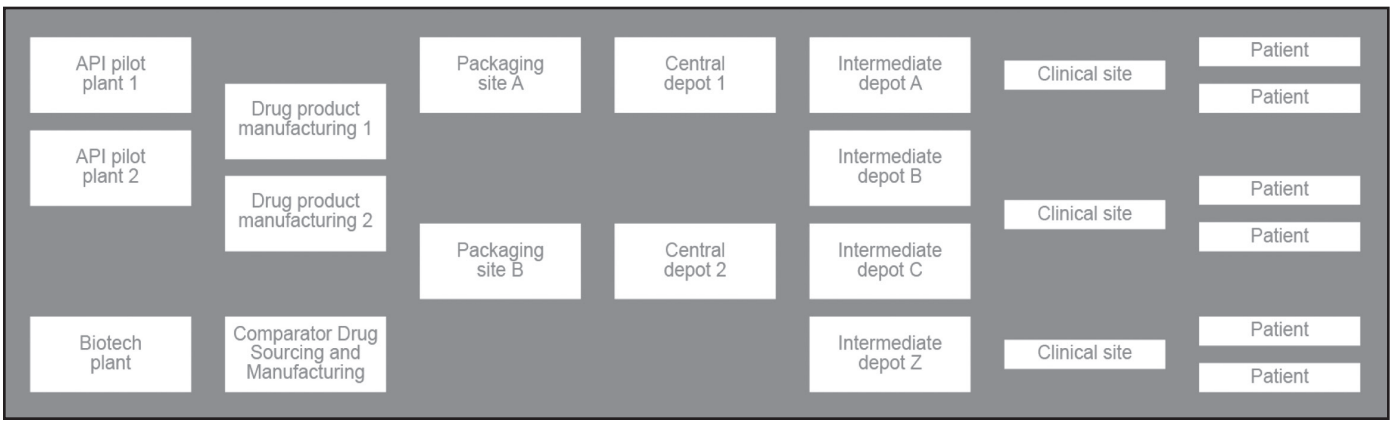

Figure 5. External R&D manufacturer with network of fully integrated supply partners (Source: Lodestone).

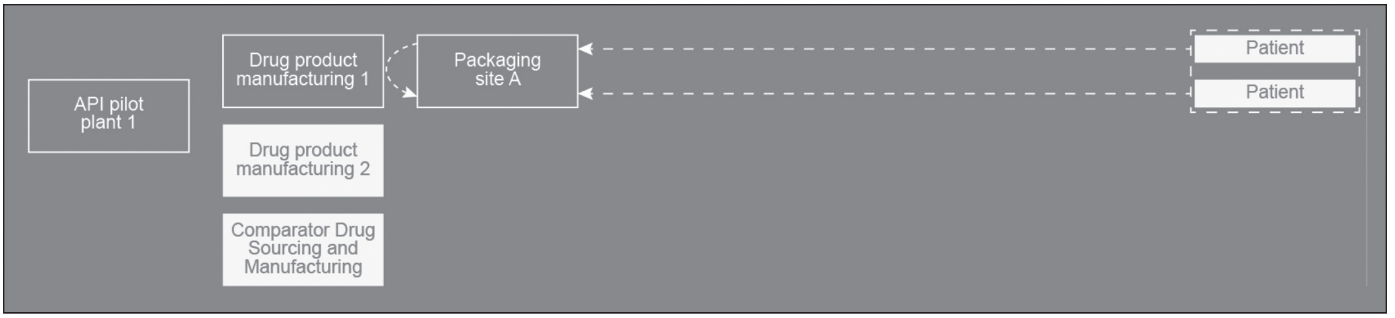

Figure 6. Patient oriented R&D supply chain (Source: Lodestone).

CTSM Process, Organization, and Technology Options

Sponsors have a broad range of clinical studies with different supply chain characteristics. As every sponsor company has different priorities, not "one solution will fit all needs." For the contractors, this means for sure that their capabilities will need to be multi-functional in order to be successful.

Different Supply Chain Models

Different models exist for rethinking of the R&D supply chain. In some companies, even multiple models should co-exist.

Externalized R&D Supply Chains

Sponsors can have specialist therapies that require outsourcing the entire physical R&D supply chain from production of the earliest technical batches to IMP packaging and distribution.

A number of small research firms have already taken the external route, but also large companies have announced plans to outsource a bigger share of their supply chain. It enables a sponsor to shift to a flexible cost base, reduce the risks associated with investing in new assets, and access new technologies and skills. For large biotech and pharmaceuticals, executing this strategy successfully involves building a network of fully integrated supply partners that exchange information seamlessly - *Figure 5*. Information of the R&D supply chain is virtualized as external organizations are enhancing and updating data. The sponsor needs still this virtual generated information to plan and to control the external supply chain. This will become one of the key challenges in the externalization as the number of studies is increasing and globalization is the overall industry trend.

Patient Oriented R&D Supply Chain

This supply chain is very innovative compared to actual clinical packaging and distribution solutions. Many companies are currently investigating this model in order to increase flexibility of patient delivery and to lower operational costs - *Figure 6*.

This model will require complete new ways of working in the production of drug product and IMP. This article highlights three building blocks as possible pillars for future solutions:

1. Drug product identification: the drug product has a unique code identifier to enable the compliance requirements in packaging blinding and ensuring correctness of treatments - *Figure 7*. Even the formulation of the drug product can become patient specific. The reader should remark here that this concept is not only about serializing the IMP and its components at the time of packaging. The drug product is serialized at the time of its production. This is not a common practice at the time of publication. Only pilots are implemented in the industry.
2. Zero-stocks: actual subject enrollment data in the site is continuously/real-time monitored and forwarded to the packaging organization in order to determine the actual IMP need at the packaging supply node. This is already a common practice at the moment of publication, but there are no pilots with zero IMP stock policies in hubs or intermediate depots.
3. Site and packaging control system: in this patient driven supply chain, systems such as IxRS will become obsolete and another solution will be required. A request is created and allocated to a single patient. The packaging order is directly linked to a patient.

The above examples are "just" business methods and must be seen in an extended context. The supply chain organization will have to understand its role toward clinical operations in a much more broad sense as it needs to understand the patient behavior in the clinical site as the ultimate customer.

Full Service R&D Supply Chain

Companies have developed standardized processes with full

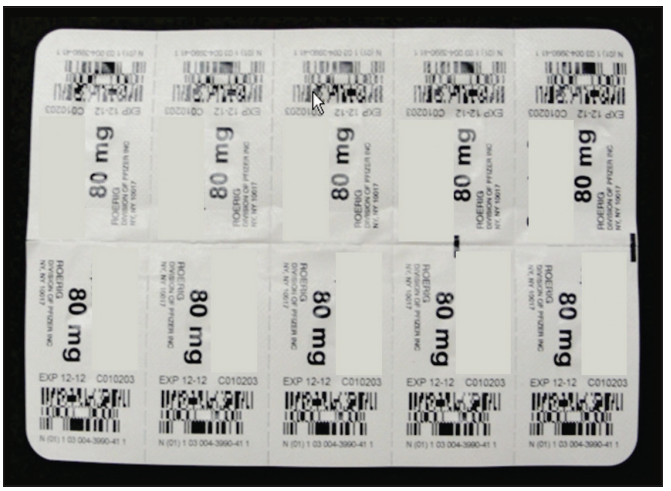

Figure 7. Coding of drug product and primary packs (Source: Lodestone).

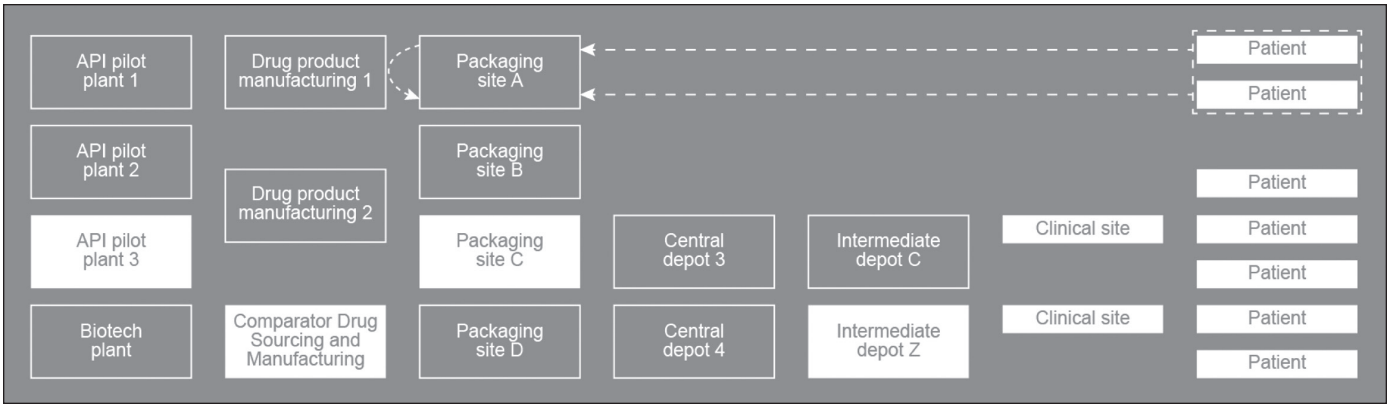

Figure 8. Full service R&D supply chain (Source: Lodestone).

internal accountability across multiple steps including the clinical distribution. The supply chain organization becomes a full service partner towards clinical operations - *Figure 8*.

Organizations that choose this option will have to make major cultural changes. A "supply chain organization" needs to manage demand and supply for multiple models and types of studies and establish contractor service level agreements. Such a supply chain has "cross-study" performance measurement, but it is able to manage the different types of studies within "channels," such as the patient oriented supply, direct to site shipment either from stock or on demand and conventional distribution through local depots, outsourcing of specific steps depending on study needs.

Direct to site shipment from regional hubs became already a more common approach in the last few years in order to eliminate the intermediate storage lead time at local or country specific depots; however, on-demand packaging has not been fully deployed across the industry. On-demand allows dynamic fulfillment of requests for a study at the moment that the order has been provided. The final IMP is not yet existing at the time of the request. The "stocking" of the drug product or other intermediate product form allows to create the final IMP in a very short lead time, either in a packaging center, regional hub, or final/country depot. The next paragraph will describe the on-demand method in more detail.

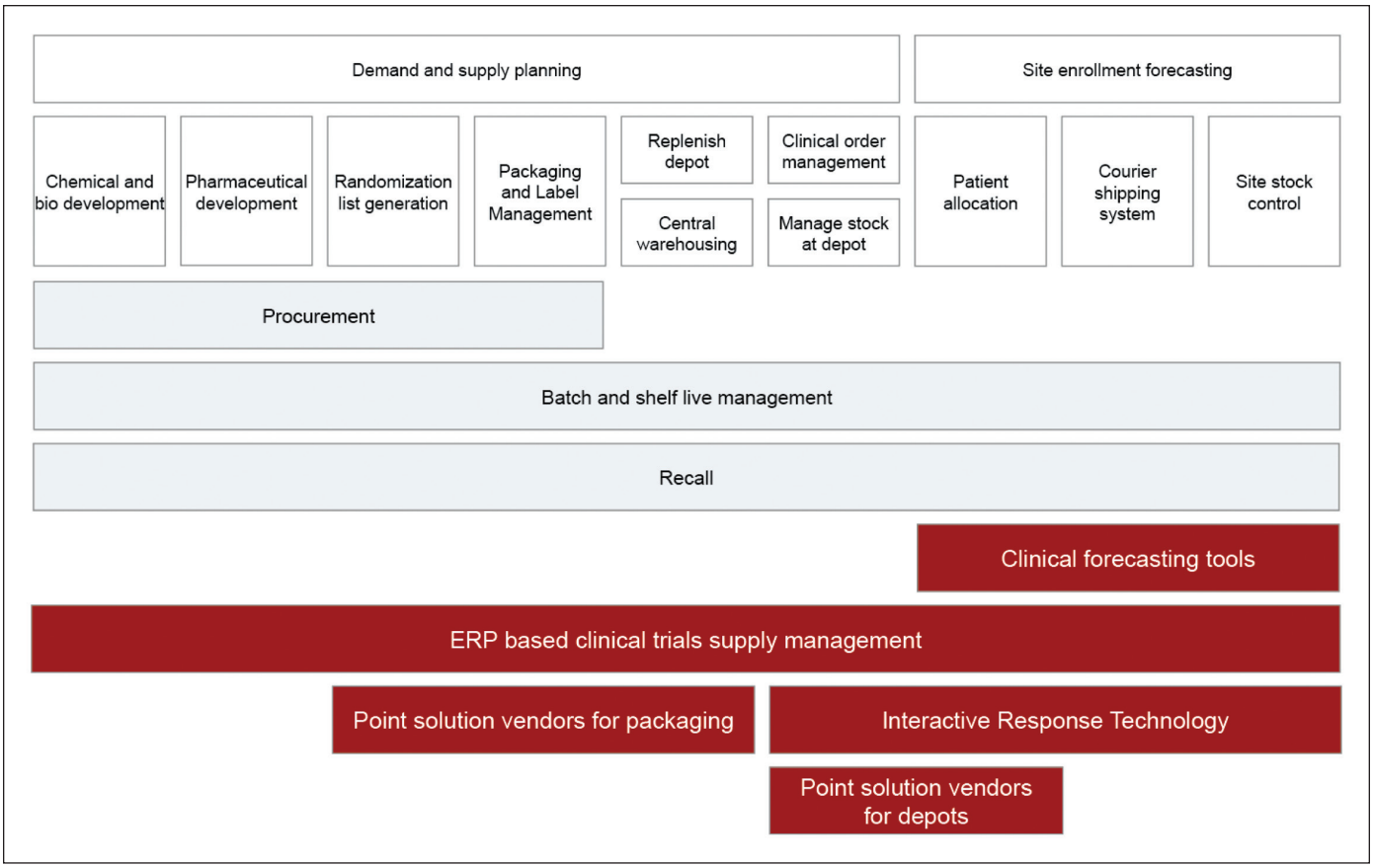

Figure 9. Solution map identifying roles of internal functions and contractors (Source: Lodestone).

Business Solutions Architecture for R&D Supply Chain

All above models will require major changes at sponsor and contractor, from an organizational and process perspective. There is no one single solution existing that matches above business requirements; therefore, an "architecture" needs to be developed as an integrated architecture of multiple systems using point solutions, IRT/IxRS providers, and ERP enterprise resource planning based CTSM solutions - *Figure 9*.

The solutions market for R&D supply chain is a niche domain. IRT systems and Drug Accountability systems cover only the downstream part of the supply chain. Many IRT vendors can offer bundled services, but operate only on study level. ERP-based CTSM solutions have broad functionality including down-stream distribution functionality for depot and site control; however, there are limited vendors who can deliver this capability. Point solution vendors provide user-friendly functionality, but do not enable end-to-end supply chain functionality.

Demand and Supply Planning

Although this article is advocating the need of on-demand packaging and labeling and the future development of a patient oriented supply chain solution, there is still the need for planning. Planning is not in contradiction with on-demand packaging. The right method must be deployed in the right supply chain segment.

Demand modeling functionality requires different horizons of forecasting. Long/medium-term clinical forecasting should be used for DS, DP, and/or IMP level planning with a make-to-stock strategy. The demand feeds conventional materials requirements planning while clinical batch data are considering study and country characteristics and the expiration of stocks. On the short term, the demand forecast is aggregated at each distribution point that is supplying to sites. Site level forecasting is even more granular.

A collaborative planning framework will empower clinical supply professionals to integrate the actions and objectives of their outsourced clinical logistics functions. Several functionalities are required to achieve this in clinical trials: what-if analyses, distribution replenishment planning, drug product planning enabling just-in-time packaging, batch data in supply plans.

The above topics have many different variants. Recent analysis with sponsor companies has proven that deterministic forecasting, overlaid with actual enrollment data from the sites, leads to reduced overage, minimal safety stocks, and supply lead time.

The deterministic forecasting feeds the replenishment planning for a depot or hub or complex distribution network that deals with many studies and sites. Replenishment planning is based on the following building blocks:

1. Safety stock algorithm: based on the study demand which considers all enrollments in all sites. So even if the number of sites is very high, the demand will consider all site needs, respectively also the safety stock in the depot will be relatively important.
2. Depot replenishment: the enrollments and all finished goods stocks are netted on a frequent, e.g., weekly basis. In case that the dispensing of stocks in a site is faster than expected (which is very unlikely as the actual enrollments are considered in the depot replenishment planning), there is still the use of safety stock in depot.
3. Site replenishment: the enrollments and site stocks are netted continuously, e.g., daily. This site replenishment process is cascading with the depot replenishment planning process.
4. Ad-hoc stock investigation: in case of exception handling, a total stock report provides details to take actions separately from above weekly and daily planning activities.
5. Clinical batch information is required for expiration, country and study restrictions.

The above forecasting and planning techniques can be complemented by stochastic forecasting. While deterministic forecasting is a frequent repeating process using average values, stochastistic forecasting takes into account the variability of clinical trial parameters such as titration/dropout and stratum. Variability has a significant impact on the clinical trial supply chain. The technique allows to reduce the overage and the risk of running out of stock. The main goals of a stochastic engine are to optimize costs, to define the optimal IMP safety stocks, and re-supply lot-sizes and frequencies; however, this technique is resource intensive in case it is used for all studies at a company.

As a summary, the best practice demand and supply planning framework has the following characteristics:

- Long/medium-term clinical forecasting
- Short term demand forecast at each distribution point and site level forecasting
- Deterministic forecasting complemented by stochastic forecasting for complex studies
- Replenishment planning at depot and site level
- Clinical batch data considering study and country characteristics and expiration data

Chemical/Biotech Production, Pharmaceutical Production

Process-order handling on the shop floor supports the need for GMP information. Shop-floor data collection systems, using barcode scanning devices, help to manage the execution of manufacturing and to automate traceability.

Batch management functionality covers the allocation and tracking of batches to process orders in every production step.

Moreover, the integration with external partners is critical to ensure visibility of inventory and traceability across the R&D supply chain.

Clinical Packaging and Labeling

First, this section highlights the specifics of clinical labeling, packaging, and randomization. Second, the importance of on-demand or just-in-time packaging is stressed in order to deal with future business trends. Finally, this evolution is put in

the context of the extended supply chain.

Labeling management is the design and approval of labels for a study and/or participating countries. Electronic routing and approval of labels is important due to the multiple hand-overs and iterations. Label variable data should be integrated with process order handling to ensure seamless data processing.

Packaging needs to deal with initial and on-going supply. At initial supply, the IMP is stored to deal with the uncertainty of unexpected demand as site activations are not 100% predictable. On-going supply needs to avoid any stock-out while expiration is a key constraint.

Creation and handling of randomization lists is complex as multiple parties need to be involved. The randomization solution could be incorporated in the packaging operations and provide access for the biostatistician and possibly IxRS vendor, or in general, the list must be electronically routed and approved by multiple stakeholders.

On-demand or just-in-time packaging will increase importance in the industry in order to reduce batch expiration and re-labeling costs. New trends in clinical studies will require that batches can be re-supplied more frequently or even immediately for a site request or individual patient need.

On-demand or just-in-time packaging allows dynamic fulfillment of IMP requests for a study. This means that IMP stocks are not on-hand available for the requester. This on-demand method can be deployed in many variants and combinations:

- Use at different location types: the method is not always executed in a packaging center facility. It can be used at hubs or local depots.
- Use of pooling: investigational medication product stocks will be stored independently of the protocols requiring it. At the receipt of order, the protocol is added to the IMP identification.
- Label printing only at receipt of site request: this method avoids use of expensive booklet labels (booklets are used in order to share stocks across countries).
- Use of on-hand stock of drug product or other intermediates: as IMP is immediately packed the drug product or other intermediates must be planned according to a make-to-stock strategy.

For the use of above methods, packaging and labeling operations are highly impacted. They require more advanced solutions, such as following solution building blocks:

1. Electronic batch recording will reduce the "records review" effort on the shop-floor and will shorten the lead times of batch record handling.
2. On-line printing prints the label during the packaging which eliminates the label room storage or external label printing services from a printer vendor, especially if the booklets are leading to high operating costs, label reconciliation tasks, and human witnessing of label application is also labor intensive.
3. Streamlined batch management is an advanced quality control method during the packaging and labeling across multiple orders to re-supply frequently. Orders are executed for multiple countries. The streamlined batch solution avoids that the sampling and batch record handling will lead to uneconomic packaging and quality operations. There is no industrial use of this method yet at the moment of publication; however, this new business method will only be used once the clinical supply business and regulatory agencies mature.

Seamless data exchange between contract packager and sponsor or direct access to sponsor processes provides information visibility. Conventional packaging, labeling, and randomization techniques requires frequent and complex exchange of above data contractors. Just-in-time packaging will even increase the complexity to this data exchange model.

Warehousing and Distribution

The integration between depot warehouse and order management needs to be automated for compliance and cost control. New techniques such as portal technology allows to connect the external partners to the sponsor inventory backbone.

Multi-level warehouse management and shipping is driven by consignment requests for serialized kits. This requires highly automated process controls to avoid errors when selecting multi-level kits.

Cold-chain shipper time measurement and temperature deviation logging are methods applied in cold material handling. Sponsor pipeline products are becoming increasingly cold chain with the influx of biomolecules and management of these items. Their temperature excursion is becoming increasingly costly. It is likely to become a burden for commercial sites as well as these products launch.

The cold chain solution is defining the allowable time by item for a batch operation, monitoring time of individual batch operations, monitoring the temperature along operation, and ensuring deviation logging and resolution. This solution becomes highly complicated in case that cumulating operation time over the lot genealogy is required.

Centralized un-blinding provides automatic alerts of an un-blinding event by fax or e-mail. Only specifically indicated study personnel have access to the un-blinded data.

Subject Enrollment and Site Stock Control

Site stock control is providing visibility on inventory information in sites. Employees managing inventories at sites can report inventory needs and current status by using IRT. Stock control triggers with parameters, such as level, buffer levels, and visit projection windows reduce waste. Information such as threshold days until stock-out and current screen-fail rate allows better prediction of site supply needs.

Patient allocation is the process of individual assignment to treatment arms and their respective kit type IDs. The patient code is also applied in medical records. Investigators furthermore maintain a patient diary to keep track of the patient's history and to improve advice during future visits.

Doctors and surgeons data is logged in databases. Patients can check the availability of the concerned doctors or surgeons using IRT.

New Technology Trends

This article highlighted new solutions and business methods that will gain importance for the extended R&D supply chain. New technology trends will change the way how sponsors and contractors will design solutions. There are already references in the industry about the use of R&D supply chain enterprise software. This trend is new as point solutions were not delivering transformational benefits.

Another technology to watch is the "cloud," especially for smaller companies that don't want to invest in assets for supply chain; however, there are no cases found in the industry at this moment of publication.

R&D Supply Chain Enterprise Software

The use of Enterprise Resource Planning (ERP) software has been identified by several biopharma companies as the appropriate technology for increasing transparency of demand and stock levels across the entire supply chain and to ensuring full compliance as well as backward and forward traceability. It is a capability that allows the consolidation of all business processes into a single enterprise-wide environment.

The competitive advantages are:

- Higher service level to the clinical site at optimal cost
- Greater supply responsiveness to changes in demand
- Increased efficiency due to streamlined business processes in the end-to-end supply chain
- Decrease waste due to forecasting techniques and planning of the supply chain including expiry dating visibility

The investment in such ERP depends on the need to modify it. Complex biopharma companies have specific requirements that cannot be standardized in the industry. In such case, the investment is very important and strategic. CROs and subcontractors have less need to modify such solutions which allow to limit the implementation costs.

The Cloud for BioPharma Validated Environments

Biopharma organizations' typical pain point in IT deployment is that it takes a huge amount of testing to fulfill all the computer validation requirements as per the 21 CFR Part 11 guidelines. Testing cycle contributes ~25% of the application deployment cost. The duration of an implementation project in life sciences organization is at least 15% longer than the similar project in other industries. So what are the ways to reduce these timelines, effort, and cost? The types of testing cycles involved in implementation for a life sciences organization are:

- Unit testing
- Informal screening of business scenarios
- End to end integration testing
- Performance testing
- User acceptance testing
- Day-in-a-life test

The formal screening of scenarios is to ensure satisfactory testing as per the regulatory needs and it consumes a lot of testing effort. The business scenarios which are GxP impacted have to be tested formally with extensive documentation which adds up to the testing effort.

Apart from it, it needs hardware to comply with certain installation qualifications which takes more time for environment preparation compared to environments in non-regulatory industries. The cloud eliminates the need of purchasing and maintaining own hardware; however, CROs or sponsors need to ensure that the environment comply with the Installation Qualification (IQ) , Operational Qualification (OQ), and Performance Qualification (PQ) requirements. Several service providers offer a specialized service for the CRO or sponsor reducing the time and cost of the environment preparation in the cloud. While doing so, the CRO or sponsor can proof its accountability, while leveraging external parties to get those requirements fulfilled. So cloud computing will reduce the cost of implementation projects in this matter.

This solution is certainly for fast growing companies that don't have the infrastructure in place or internal resources. In the long term, CROs and subcontractors need to integrate with their life sciences customers who are the sponsor of a clinical trial. Those sponsors have the need to integrate with their chemistry and pharmaceutical development, clinical packaging, and distribution. In the future, many sponsors want to exchange their data with CROs. Many CROs are not professionally organized for that and they will lose business due to lack of integration and transparency. CROs and subcontractors can increase their market share by using the cloud-based applications. First, it will show commitment to customers (big biopharma) as integration with their clients will become critical. Second, it will increase company profitability growth by enhancing CRO capabilities to obtain the sponsor's data and to provide full transparency to the sponsor.

Conclusions and Recommendations

A significant opportunity exists for life science sponsors and contractors to improve the efficiency and cost effectiveness of outsourced clinical supply activities. In the most successful cases, companies have started with a clear vision and a solid business case.

They have introduced a comprehensive program based on revised processes and new technologies supported by a change management program and organizational transformation. The vision should not be just another improvement, but a transformational answer to future trends, such as:

- Introduction of a planning framework that considers all elements of integrated planning: all demand and all supply sources. The key challenge is to capture all inventories including batch data across the supply chain.

- Health authority guidelines increasingly refer to opportunities to use "electronic means." A common hurdle to implement new solutions is the system validation. Vendors should mature further by providing "accelerators" for implementation.
- New adaptive study designs, new target diseases, and global studies will require on-demand labeling and packaging methods in order to keep operating costs under control. Methods like streamlined batch management will need to be used. This will require new interpretation of regulatory requirements.

As a conclusion, an integrated approach toward best in class internal and external CTSM processes supported by state of the art technology will result in higher compliance, shortened study timelines, and reduced R&D costs.

Acronyms

API	Active Pharmaceutical Ingredient
cGMP	current Good Manufacturing Practice
CMO	Contracting Manufacturing Organization
CRO	Contracting Research Organization
CTSM	Clinical Trial Supply Management
DP	Drug Product
ERP	Enterprise Resource Planning System
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
IRT	Interactive Response Technologies
JIT	Just-In-Time
I(W)VRS	Interactive Web/Voice Response Systems (also IxRS)
R&D	Research and Development
SAP	SAP is an ERP system that can be used as a platform to build a CTSM solution

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The Return on Investment (ROI) of Test Automation

by Stefan Münch, Peter Brandstetter, Konstantin Clevermann, Oliver Kieckhoefel, and Ernst Reiner Schäfer

This article presents a discussion on the considerations around the use of automated test tools vs. manual testing and provides an example of a calculation of Return on Investment (ROI). This article complements and expands on the information contained in the revised GAMP Good Practice Guide on Testing of GxP Systems, which is currently under development.

Background

In 2005, ISPE released the GAMP Good Practice Guide on Testing of GxP Systems. This Guide was provided electronically as a download available free of charge to ISPE members. It was made available in this format in recognition of the provisional status of the document, which captured the initial thoughts and concepts around testing GxP systems.

During the years since the document was written, there has been an increased focus on the use of risk-based approaches in industry, accompanied by a significant regulatory and industry activity affecting computerized systems, and much evolution in testing good practice, including:

- GAMP 5
- ICH Q8, Q9, Q10
- ASTM E2500
- Adoption and implementation of Process Analytical Technology (PAT) and Quality by Design (QbD)
- Increased industry focus on risk-based approaches
- Increased use of non-linear development lifecycles
- Increased use of computerized test tools
- Revised EU GMP Annex 11

A second edition of the Guide has been in preparation for the last year with the document substantially revised to provide definitive guidance around effective, risk-based testing of GxP systems. The new Guide contains pragmatic guidance on defining the scope of testing, the strategy, the test plan, recording the results, dealing with deviations and reporting the outcome. The central premise of the Guide is that the aim of testing is to discover defects in order to mitigate risk. It covers conventional linear sequential development methodologies as well as the iterative and incremental approaches. Practical guidance is included on the selection, benchmarking, assessment, control and use of automated testing tools. Appendices provide worked examples for different types of systems, focusing on the risks associated with any unique features of the system type along with suggestions on how to mitigate the risks. The examples cover systems applying PAT, cloud computing, packaged systems, analytical instruments, infrastructure, process control systems, configurable IT systems, and end user developed applications.

The GAMP D-A-CH Special Interest Group (SIG) on Test Automation, in combination with the GAMP Americas SIG on Test Automation, provided the key content of Appendix T11 "Automated Test Execution and Computerized Test Management Tools" in the upcoming second edition of the GAMP Good Practice Guide (GPG) on Testing of GxP Systems, which is currently in final review.[1]

In this article, the members of the GAMP D-A-CH SIG on Test Automation present a discussion on the considerations around the use of automated test tools vs. manual testing and provide an example of a calculation of Return on Investment (ROI). This article complements and expands on the information contained in the Good Practice Guide.

Introduction

The SIG is neither recommending nor advocating for test automation in general, but aims to highlight the benefits and risks of test automation, point out the differences between manual and automated testing, define criteria for selection and guidance for validation of test automation tools, and provide a model for calculating the ROI. While most aspects are fully covered in Appendix T11 of the above-mentioned GPG, the criteria and methods to calculate the ROI are unique to this article.

A key concept to consider before we start is the difference between two types of testing tools:

- **Test Management Tools** facilitate the task of test case and test script authoring, requirements management, review and approval, test execution, and test deviation management.
- **Test Automation Tools** assist in authoring or recording test scripts, automatically executing test scripts, and recording test evidence.

While this article focuses on tools for automated test execution, decision criteria for test management tools are addressed as well to complete the picture (see sidebar "Decision Criteria for Test"). Performance test tools that are being included in the GAMP Good Practice Guide on Testing of GxP Systems are not considered here.

Calculating the ROI for Test Automation Tools

An important aspect to be considered when planning the use of test automation tools is a calculation or estimation of the cost effects. These typically include initial costs for the assessment and set-up of the tool, the implementation of the tool infrastructure, training, and the initial creation of automated test scripts. In addition, specific parameters should be considered when calculating the return on investment.

This article gives an overview of the calculation and a description of a basic ROI model with further guidance on cost effects specific to regulated industries such as life sciences. In general, any suitable ROI model should assist in estimating the expected gains (or losses) for using test automation tools, especially when comparing costs and benefits to traditional manual testing. Regulatory requirements as well as industry-specific risks typically require a greater amount of testing and documentation of the software used to verify computerized systems, and this should be taken into account.

ROI calculation models can be found in various publications as well as in books and on the internet. These models typically take into account the more obvious factors, e.g., comparing the effort (or costs) for creating and executing automated test cases plus tool license costs versus the effort (or costs) for creating and executing manual test cases.

However, more complex and sometimes "hidden" costs need to be considered as well, e.g., follow-up costs caused by insufficient test coverage or failing to address multiple scenario boundary tests. These additional costs can often be reduced – or even completely avoided – by applying a comprehensive automated test suite with appropriate coverage. In addition to avoiding additional costs, a test suite also may help to increase confidence around excluding certain test cases. These additional factors have been included in the ROI model suggested by this article.

Manual vs. Automated Testing

A key decision significantly impacting the test strategy as well as the cost calculation is what types of tests will be executed, and of those, which will be automated. Obviously, some test types are more suitable for automation than others. Some tests cannot be automated at all except in combination with emulations or mock-ups (e.g., those involving interaction with real hardware, such as balances, scanners, or other devices), whereas other tests rely on test automation and cannot be executed manually (e.g., load and stress tests).

Suitability for Testing	Manual	Automated
Helping the development effort with smoke tests and unit tests	●	●●
Functional testing	●●	●●
Structural testing	●	●●
Automation of test input generation	○	●●
Installation and configuration testing	●●	●
Regression testing	●●	●●
Hardware testing (e.g., weigh balance interfaces)	●●	○
Load and performance testing	○	●●
Testing for race conditions	○	●●
Endurance/longevity testing	○	●●
Key: ●● = suitable ● = may be suitable ○ = not suitable		

Table A. The suitability of manual vs. automated testing for different test types.

Even more complex, a good ROI calculation needs to be able to handle mixed test modes as well, i.e., scenarios in which some tests are executed manually and some are automated. In real life scenarios, test automation often starts in a setup with existing manual tests, and consecutively automated tests either replace or complement the existing suite, so the ratio of manual vs. automated tests changes over time, impacting the ROI calculation. Test types that should be considered in different formulas include, but are not limited to those listed in Table A.

Formula – How to Calculate the ROI

The types of tests shown in Table A are usually related to different use cases or different life-cycle phases of the Application Under Test (AUT). This can be reflected in a powerful, yet flexible formula that needs to be adapted to a specific project and its current stage, thereby allowing to calculate the ROI per test type and under various constraints. It allows a stepwise or staged approach when introducing test automation into an existing manual testing scenario.

General Calculation: *Gain vs. Investment*:
The general formula for calculating the ROI is as follows:

$$\text{ROI} = \frac{\text{Benefit}}{\text{Investment}} = \frac{\text{Gain} - \text{Costs}}{\text{Investment}}$$

As expected, the ROI will be positive if the gain (here: savings)

exceeds the costs (that include the investment), and it will be negative if the costs are greater than the gain. In both cases, the relative difference between gain and costs in relation to the overall investment will determine the ROI.

Outside the life sciences industries, generally understood benchmarks are that automated test tools typically pay for themselves (achieve breakeven) by the second or third round of test execution (typically regression testing or development testing when used in non-linear software life cycles).

The initial direct costs of setting up an automated test tool are greater in the life sciences industry, because of the additional costs to assess, document, and control the tool. This typically achieves breakeven by the third or fourth testing cycle for new applications with the variation being due to various parameters discussed below.

Costs to Consider

When calculating the ROI for automated testing, both direct and indirect costs need to be taken into account. Direct costs are directly related to testing, whereas indirect costs originate from errors that have not been detected (e.g., increased support, bug fixing, recalls etc.). Obviously, the indirect costs are much harder to determine and can often only be estimated.

This section discusses various parameters and some suggestions that should be considered when calculating the ROI (as shown above). Although the basic formula is simple, i.e., *ROI = Benefit / Investment*, it can be quite challenging to properly calculate (or estimate) the gains and the investments.

Direct Costs

Tool costs (one-off costs relevant to the test automation tool):

- Tool acquisition and assessment costs

Factor	Description	Application-specific	Life Sciences-specific	Direction
Total # of test cases	# of tests to be executed (manual and automated).	Yes	No, but typically the test coverage is above average.	N
Total # of automated test cases	# of tests intended for automation.	Yes	No	I
# of executions per cycle	Average # of tests executed in each cycle.	Yes	Yes, typically more repetitions are needed.	G
# of testing cycles	# of cycles during ROI evaluation time (a cycle may be a week, a build, release, etc.).	Yes	No	G
Tester hourly rate	The average tester salary.	No	No	G
Failure cost	The predicted cost related to failures in production application functionality.	Yes	Yes, with product recalls as the worst case scenario.	G
Manual test execution and analysis time	The average time it takes to execute a manual test and analyze the results.	Yes	Yes, typically documentation overhead is above average.	G
Tool acquisition, assessment, and license costs	Test tool costs.	No (general)	No, although specific assessment activities may be needed.	I
Tool training costs	Cost of training resources to use the test tool.	No (general)	No, although qualification and training may require effort above average.	I
Test machine cost	Cost of machines used for unattended execution of automated tests (separate from machines used for manual test execution).	No (general)	No, standard hardware may be used.	I
Test automation environment activity period	The period of time that the test automation environment (incl. tools, machines, etc.) will be in use.	No (general)	Yes, typically applications will be used for longer than average.	G
Test development/debugging time	Script development time.	Yes	Yes, typically additional documentation and care is needed.	I
Automated test execution time	The average time it takes for a single automated test to execute.	Yes	No	N
Automated test cycle analysis time	The average time it takes to analyze the results of one full test cycle execution.	Yes	No, although additional documentation and care is needed.	I
Automated test cycle maintenance time	The average time it takes to perform script maintenance following each full test cycle execution.	Yes	Yes, typically additional documentation and care is needed.	I
Overnight execution?	Indicates whether tests are executed during the day, or also overnight.	No	No	N

Table B. Parameters for ROI calculation for automated test tools.

- Licenses for a test automation tool
- Initial training of core test automation team
- Initial configuration of the tool

Application-specific costs (relevant to each application being tested):

- Training of project-specific staff members
- Creation of a test automation framework with general functions/classes
- Creation of test data
- Creation of automated test cases
- Maintenance of automated test cases
- Execution of automated test cases
- Creation, maintenance, and execution of manual test cases (typically not all test cases will be automated)

Indirect Costs

Indirect costs may be included in the ROI calculation, too. Often, these costs need to be estimated based on experience from similar projects in the past:

- Increased risk of not detecting a failure before the application is used in production
- Costs originating from undetected failures

Parameters – Create Your Own Formula

The following parameters have initially been taken from a generally available ROI Calculator,[2] but have been analyzed, extended, and adapted for applications used in regulated industries. Three columns, "Application-specific," "Life Sciences-specific," and "Direction," as seen in Table B were added to provide guidance on which aspects to include in the ROI calculation and which ones to emphasize.

The added columns have the following meaning:

- **Application-specific**: is the factor specific for one application or is it of a more general nature and should therefore be distributed over several applications?
- **Life Sciences-specific**: parameters that require specific attention for applications used in regulated environments. This can be reflected by a relative weight in the formula.
- **Direction**: specifically, when automating tests, this factor is likely to increase Gains (G) or contribute to the Investments (I). In case that the difference is negligible, the factor is rated to be Neutral (N).

In Table B, the first three rows are used to explain the concept: The total number of test cases obviously depends on the Application Under Test (AUT), but is not necessarily life sciences-specific, and the number does not influence the ROI calculation, so it is neutral. The total number of automated test cases is also influenced by the AUT, and again regulatory aspects have no significant impact. Obviously, with more tests being automated, the investment in automation increases, as every test case requires specific effort, so when calculating the ROI, this is clearly an investment. However, with a higher number of executions per cycle, this investment in test automation will pay off so it will become a gain. The factor depends on the AUT (e.g., on the frequency and amount of changes), and with higher quality standards, more repetitions can be expected.

Example – Dispense Application

With the help of the direct and indirect costs and the parameters, the simple formula shown in "Formula – How to Calculate the ROI" can now be defined in more detail to calculate the ROI of test automation for a specific application.

The example as seen in Table C is based on having a dispense application (either stand-alone or as an integrated part of a more comprehensive Manufacturing Execution System (MES)) that has already been validated. Now a number of changes and enhancements are foreseen, so we wonder if automating a fair share of the existing test suite would be a good idea. In order to set up the formula and calculate the ROI, we need to act on a number of facts and assumptions. To simplify the example, not all the factors in Table B are used in Table C.

Starting with an existing suite of manual tests, the initial costs of executing one testing cycle can be calculated by using the numbers from above:

Test Execution Costs, manual only, per cycle =

$$EpC_{total} * Rate * Time_{man} = 25 * \frac{\$50}{hr} * 4\ hrs = \$5{,}000$$

It also can be assumed that one final test cycle with all available tests will be executed:

Factor	Abbreviation	Value
Total # of test cases	$NoTC_{total}$	45
Total # of automated test cases	$NoTC_{auto}$	36
Total # of manual test cases	$NoTC_{man}$	9
# of executions per cycle	EpC_{total}	25
# of executions per cycle, automated test cases	EpC_{auto}	21
# of executions per cycle, manual test cases	EpC_{man}	4
# of testing cycles	Cycles	variable
Tester hourly rate	Rate	$ 50/hr
Manual test execution and analysis time	$Time_{man}$	4 hrs
Tool acquisition, assessment, and license costs	$Costs_{tool}$	$ 15,000
Tool training costs	$Train_{tool}$	$ 8,000
Test machine cost	HW	$ 3,000
Test development/debugging time	$Time_{dev}$	8 hrs
Automated test cycle analysis time	$Time_{AutoFollowUp}$	0.5 hrs
Automated test cycle maintenance time	$Time_{AutoMaint}$	0.5 hrs

Table C. Example calculation.

Cycles	$Costs_{Auto}$ + $Costs_{Invest}$ = $Costs_{Total}$	$Costs_{Manual}$
5	$ 9,200 + $ 40,400 = $ 49,600	>> $ 29,000
10	$ 18,450 + $ 40,400 = $ 58,850	> $ 54,000
12	$ 22,150 + $ 40,400 = $ 62,550	< $ 64,000
15	$ 27,700 + $ 40,400 = $ 68,100	<< $ 79,000
20	$ 36,950 + $ 40,400 = $ 77,350	<< $ 104,000

Table D. Example costs for different scenarios.

Test Execution Costs, manual only, final test run =

$$NoTC_{total} * Rate * Time_{man} = 45 * \frac{\$50}{hr} * 4\ hrs = \$9{,}000$$

Both formulas can be combined so the costs of purely manual test execution can be calculated, depending on the number of testing cycles:

*Test execution costs with all tests being manual = $9,000 + (Cycles – 1) * $5,000*

The values returned for test execution costs with all tests being manual are in Table D as $Costs_{Manual}$.

For the calculation of the costs including test automation, again take the numbers from Table C, assuming that 36 of the overall 45 test cases will be automated. First, calculate the effort of the remaining (nine) manual test cases by using the above formulas. Assume that 21 of the 25 tests executed on average per cycle are made automated, leaving four manual tests:

Test Execution Costs,manual tests,per cycle =

$$EpC_{man} * Rate * Time_{man} = 4 * \frac{\$50}{hr} * 4\ hrs = \$800$$

For the final validation cycle, there are nine manual test cases (45 – 36) left:

Test Execution Costs,manual tests,final test =

$$NoTC_{man} * Rate * Time_{man} = 9 * \frac{\$50}{hr} * 4\ hrs = \$1{,}800$$

In addition, the costs for test automation need to be included. Start with the initial investments...

Initial Test Automation Investment = $Costs_{tool}$ + $Train_{tool}$ + HW = $15,000 + $8,000 + $3,000 = $26,000

...and the costs for the initial implementation:

Initial Test Automation Implementation =

$$NoTC_{auto} * Rate\ Time_{dev} = 36 * \frac{\$50}{hr} * 8\ hrs = \$14{,}400$$

The sum of Initial Test Automation Investment and Initial Test Automation Implementation are listed at $Costs_{Invest}$ in Table D.

For the calculation of the test automation costs per cycle, use the 21 automated tests on average:

$$Time_{auto} = Time_{AutoFollowUp} + Time_{AutoMaint} = 0.5\ hrs + 0.5\ hrs = 1\ hr$$

Test Automation Costs, per cycle =

$$EpC_{auto} * Rate * Time_{auto} = 21 * \frac{\$50}{hr} * 1\ hr = \$1{,}050$$

Finally, the numbers of manual and automated test execution need to be added to calculate the total costs per testing cycle:

Total Test Costs, per cycle = $800 + $1,050 = $1,850

Again, both numbers can be combined easily:

*Automated Test Execution Costs (21 auto, 4 manual per cycle) = $1,800 + (Cycles – 1) * $1,850*

With these formulas, calculate the costs if all tests are still manual (*n* cycles + *1* final test), and the overall costs for the automated approach with nine manual and 36 automated test cases – shown as $Costs_{Auto.}$ The total costs of the automated approach is given as $Costs_{Total}$.

As expected, the ROI is calculated accordingly by using the formula from above...

$$ROI_n = \frac{\text{Benefit}}{\text{Investment}} = \frac{\text{Gain} - \text{Costs}}{\text{Investment}}$$

...with the index *n* being the number of testing cycles, the saved costs for purely manual execution being the *Gain*, the overall costs for test execution (manual and automated) being the *Costs*, and the initial investment in test automation being the *Investment*:

Example calculation 1:

$$ROI_{10} = \frac{\$54{,}000 - \$58{,}850}{\$40{,}400} = \frac{(\$4{,}850)}{\$40{,}400} = -12\%$$

Example calculation 2:

$$ROI_{20} = \frac{\$104{,}000 - \$77{,}350}{\$40{,}400} = \frac{\$26{,}650}{\$40{,}400} = +66\%$$

In this example calculation, the breakeven will be at 12 cycles. This seems to be in contrast to Figure 1, but this number will go down quickly for all following applications, as the initial investment for licenses, training, and hardware is a one-time effect (see formula *Initial Test Automation Investment*).

Also, a conversion of existing tests has been assumed, but the ratio will become much more favorable for all new test cases, as here the cost for creating manual tests is contributing to the equation. Furthermore, costs that could back up the investment such as missed failures that made it to production are not included either. If only one issue were to be detected by automated tests that would otherwise have been missed, test automation becomes attractive very rapidly.

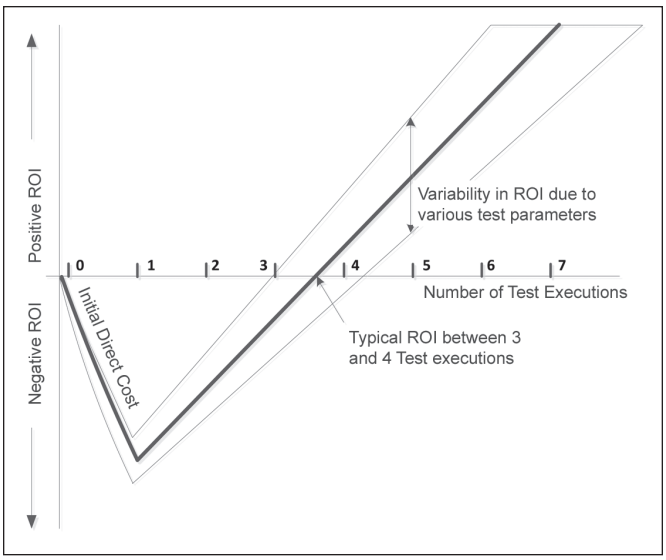

Figure 1. Typical Return on Investment (ROI) from the use of test automation tools.

Conclusion

In a world that is becoming more and more flexible and agile, automated test execution should be considered for applications used in regulated environments. While the initial effort seems – and often is – rather high, an automated test suite can provide numerous advantages as detailed in Appendix T11 of the upcoming second edition of the Good Practice Guide "Testing of GxP Systems." Although neither all benefits nor all negative aspects are quantifiable, it is worthwhile to calculate if – or when – investing in test automation will pay off. This article describes a general formula that can be adapted to any specific application or scenario, using direct and indirect costs and several parameters. With some experience, project or test managers will be able to estimate the investment needed and predict the point at which test automation will become profitable. The crucial aspect, of course, is to pay attention to all factors that contribute to the overall equation.

A spreadsheet containing the ROI model discussed in this website will be posted on the GAMP COP website for ISPE members to download and utilize.

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Decision Criteria for Test Management Tools

Planning and deciding on the use of test management tools depends on a calculation – or at least – a rough estimation of costs and an assessment of the quality of testing and test documentation. Setting up a general one-size-fits-all calculation model for the Return On Investment (ROI) is impossible, as the formula depends on which of the many features of test management will be used, and which testing aspects have to be covered using conventional (manual) testing methods. However, the following aspects may be taken into account when deciding for a specific scenario.

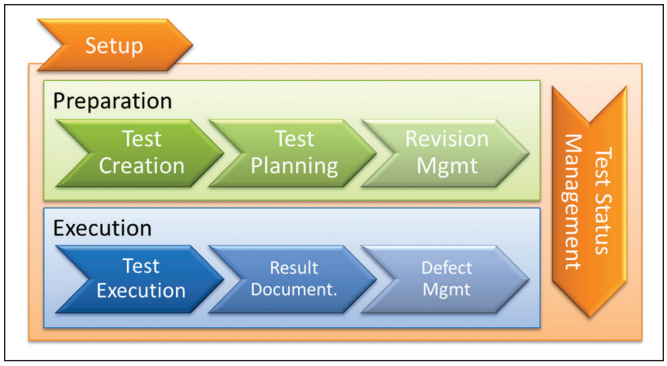

Figure 2. Test case life-cycle phases within a test management tool.

Setup

With Tool	w/o Tool
Significant efforts required to assess, implement, configure, and set up the tool (typically one-off effort). Users must be trained in the tool.	Lower efforts required, but storage location for test documentation needs to be defined.

Preparation

	With Tool	w/o Tool
Test Creation	Tools typically provide a clear structure that needs to be followed. This kind of consistency may require more effort initially, but does often provide quality gains. However, bulk changes may not be supported or require more effort.	Rules for templates and for structured test specifications should be defined. Users are typically more experienced in using office applications.
Test Planning	Test assignments and compilation of test sets/sessions are typically well-supported by the tool. A tool provides easier communication of responsibilities. Tools are especially useful for distributed teams.	Needs to be resolved organizationally.
Revision Mgmt	Typically, supported by the tool with minimal effort once versioning rules are defined.	Needs to be resolved organizationally (e.g., defined in an SOP).

Execution

	With Tool	w/o Tool
Test Execution Result Document.	Managing test execution and entering the results requires additional training. For trained users, entering test results and adding attachments is easier, as the tool provides guidance, thereby increasing quality and consistency. If the tool supports requirements, too, a traceability matrix can often be generated out of the box.	Finalizing the GMP-related test documentation, especially adding the appropriate attachments, is an error-prone activity that typically needs high effort. Creation of a traceability matrix requires effort and is an error-prone process.
Defect Mgmt	Results of failed tests can easily be added. A direct link (and tracing) to the defect management system is typically provided (in some tools, defect management is already built-in). Repeated test execution is supported through tight integration of test and defect management.	Typically, defect management (i.e., documenting, tracking etc.) requires additional effort.

Test Status Management

With Tool	w/o Tool
The current status of all test activities can be visualized any time. Many tools come with extensive reporting tools (e.g., dashboard). Especially for long test phases, high volumes, and distributed teams, a tool offers significant benefits.	The test status has to be calculated manually.

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Harnessing Untapped Information for Enterprise Manufacturing Intelligence

by John Jackiw and Dr. Gilad Langer

This article presents a framework and industry best practices allowing for the definition of usable metrics and intelligence that employ all the available operational data in the organization from the shop floor activities to business operations.

Manufacturing Intelligence and Performance Management

It is sometimes said that accounting is the language of business and as such accounting allows us to describe and interpret business and its performance. What is then the language of manufacturing operations? Is it quality, operations, inventory, or something else? According to ISA-95, manufacturing needs quality, operations, inventory, and maintenance for an adequate description.[1] What does that mean and how can this help with the challenges of modern life sciences manufacturing business operations? The sheer volume of data and information that is generated from the factory floor can be overwhelming. What is missing is the ability to interpret this information and use it as the "language" of manufacturing, and in the absence of this "language," many organizations are sometimes driven to ignore it. The challenge is to provide a level of visibility that connects and relates the entire view of business, including finance, planning, the supply chain, and the multitudes of operational information that are available from manufacturing. This connected view yields aggregated accountability at any level of the organization.

The Manufacturing Enterprise Solutions Association (MESA) recently released the results of a survey titled "Pursuit of Performance Excellence: Business Success through Effective Plant Operations Metrics."[2] In this survey, the business movers are those companies that have improved more than 10% on average unit contribution margin and revenue per employee, and improved in their usage of fundamental metrics. These business movers show that measurement processes must be swift and deliver easy-to-digest, actionable information. The results clearly show that the business movers are finding value in connecting metrics from operations to financial and business metrics - *Figure 1.*

The "language" of manufacturing is often underutilized and misinterpreted by an organization's financial group. The everyday tasks in a manufacturing organization involve problem solving, decision making, and complex analysis that require:

1. All of the available information has to provide visibility to all aspects of the organization.
2. Data is combined from multiple sources and put into a common context.

Figure 2 depicts the typical relationship between financial data and manufacturing data in the context of the manufacturing business. The triangle represents all of the data available from a plant or facility with three main levels of data, each of which has different sources. The base represents the greatest amount of data from the manufacturing floor operations. The middle represents data that is aggregated and contextualized with financial information. Last, the top represents key aggregated information about the overall performance of the organization.

There is a tendency to use data

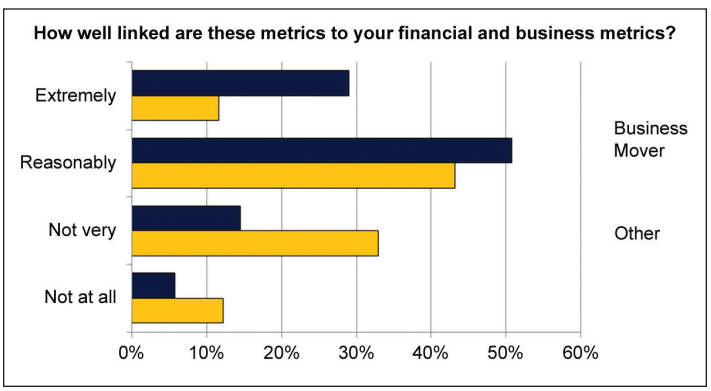

Figure 1. Comparison of business movers ability to link financial and operational metrics.[2]

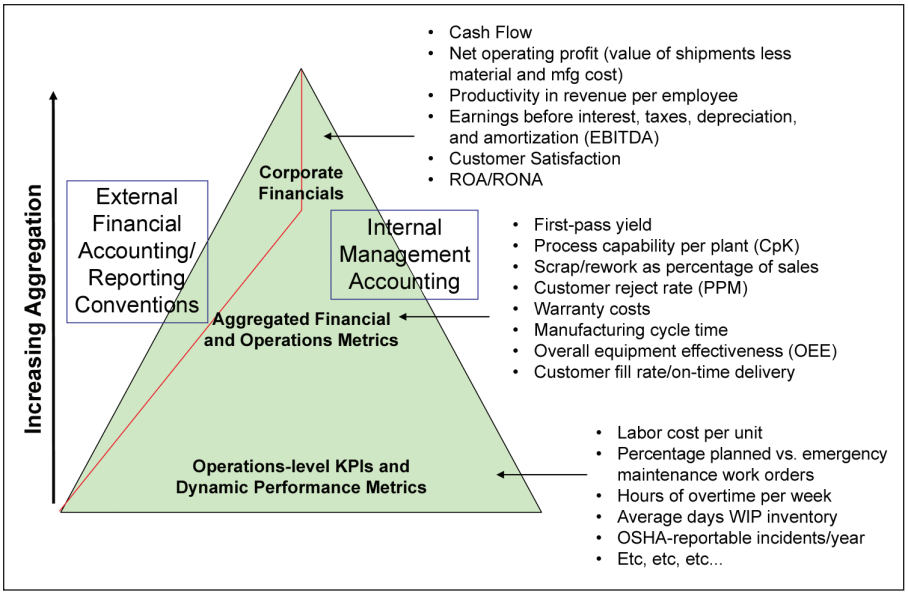

Figure 2. All the data available from a plant or facility.

that is readily available typically from a business system, such as Enterprise Resource Management (ERP), which invariably is financial information. This leads most organizations to focus on the financial data while ignoring operational data from the shop floor as indicated by the red line in Figure 2. This is typically the only information that is used to drive business decisions. Thus, a large portion of the available information from manufacturing is often ignored or underutilized for tactical and strategic decisions. This skewed view of a manufacturing organization causes the manufacturing operation to be regarded as a "black hole" where material goes in and product comes out. Yet, in reality, the manufacturing process is where value and quality are created, which are critical factors for any life science manufacturing business. The goal is to utilize all of the information and remove this "red line" of separation - *Figure 2.*

Using Business Goals to Define Metrics

In manufacturing, performance is ubiquitous be it financial or operational; therefore, it is important to measure performance. Performance in itself is an indicator of how well a goal is being met. These goals are the critical aspect of any business and can have varying degrees of granularity or scope. Commonly, goals used to run a manufacturing business are defined at a high-level and may include customer satisfaction, quality, regulatory compliance, supply chain responsiveness, resource usage, etc. However, these goals are too vague to be practical and need to be specified in an appropriate resolution in order to be useful. Frequently these vague goals are used directly to define specific metric targets and introduce the risk of measuring irrelevant performance and unwanted behavior.

A metric is a measure, and as such, it has to be interpreted relative to a baseline and in the context of what is being measured. This may seem trivial, but with the pressures of modern manufacturing business, this is sometimes forgotten. The question is what are we measuring and is it a good indicator of what we need? Often the measurement itself becomes the goal and this lack of clarity is a common symptom of flawed performance management. To quote Dr. Deming, "Running a company on visible figures alone is one of the seven deadly diseases of management." He also said that "You have to manage what you can't measure. You can't measure everything of importance to management, yet you must still manage those important things and take them into account to be successful."

So what do we measure? Manufacturing operations are complex and dynamic, and it is a challenge to account for metrics used to evaluate manufacturing performance. Manufacturing management is barraged with top down measurements, such as improve return on investment, maximize cash flow, reduce unit cost, and explain variances from overhead to material consumption. While they have every intention of being forward looking and forward thinking, manufacturing managers are often faced with too many daily pressures. Mining the manufacturing and enterprise systems for data while at the same time, maintaining plant production metrics can become overwhelming. Digesting the variety of metrics, such as quantity produced, throughput, quantity rejected, exception by batch, batch throughput by time, etc., is a challenge let alone analyzing cause and effect.

Manufacturers also must deal with the challenges of connecting the state of their shop floor with the business metrics. They have to understand the casual relationships that production performance has on the overall business. It is a common gripe of a production manager that they have to spend extra hours consolidating information from a multitude of systems to provide metric information and have to rely on administrative help to tie this information to the financial data in the ERP. Misunderstandings about performance occur because financial accounting and external reporting principles often do not reflect the reality of the plant. The continuous improvement process in manufacturing operations means a constant cycle of change and therefore need for information. Yet the information about the improvement cycles may not be exposed through all levels of the organization if it does not have a significant impact on the financial metrics. Most companies are still based on a set of very standard financial reports (financial accounting) that have little if anything to do with the work manufacturing operations is responsible for.

It is in the environment of the plant where cause and effect are the rule, and what is needed is a tool that relates the cause and effect reality of the plant floor to the financial layer of the enterprise. The missing element is best

practices that guide companies in the process of identifying and assembling the causal relationships thus linking business goals with operational metrics in an effective and practical manner. The practice of using metrics often focuses narrowly on a specific aspect of the manufacturing operations, such as engineering improvements, product development, process, or specific areas of improvement. The potential for these metrics to drive value up or down the internal and external supply chain is often overlooked. An important reason for using metrics is to empower people and focus on value creation, i.e., manufacturing operations, and provide them the required visibility into these so appropriate actions can be taken.

To exemplify this, examine the following scenario from a bioreactor process. There is an unexpected rise in Kilowatt hours consumed by the bioreactor agitation motor over a period of time. This information is interpreted in the following manner by different people across the organization and illustrates how a simple event can have an impact across different functions:

- Supervisor or Reactor Suite Manager – as a potential increase in speed of the agitation and therefore possible damage to the cell culture in the reactor.
  - Action: check agitation speed – take immediate corrective actions
- Maintenance Department – this could indicate mechanical wear of the agitator. Maintenance needs to prep for repair when the batch is completed.
  - Action: plan for a repair of the bioreactor and agitator part availability.
- Plant Manager – review the overall reactor and batch performance and begin to plan options that may require another batch run or other alternatives to satisfy order demand.
  - Action: keep the reactor running if possible. Plan for some downtime or low capacity run.
- Financial Managers – will see a costs increase for that batch lot number if the batch processing time is extended, increased consumption of electricity, and possibly lower yield.
  - Action: adjust forecast of the planned daily production and profitability reports.

Another example is production throughput as measured in tablets pressed per minute. This as a metric could be meaningless if tablets are rejected because of quality issues. The correct metric should be throughput of "quality" tablets. This is calculated from the two data points of tablet press speed and number of rejected tablets. This is a Key Performance Indicator (KPI) as opposed to the two independent data points and is used to drive value.

A Framework for Defining Metrics and Intelligence

During the mid-1990s, formal templates and scorecards for tracking performance were introduced and used by manufacturing organizations to create baseline benchmarks, identify potential problem areas, and prioritize plans for improvements. This process has evolved and become more formal in recent years with common best practices and various "types" of metrics identified for various

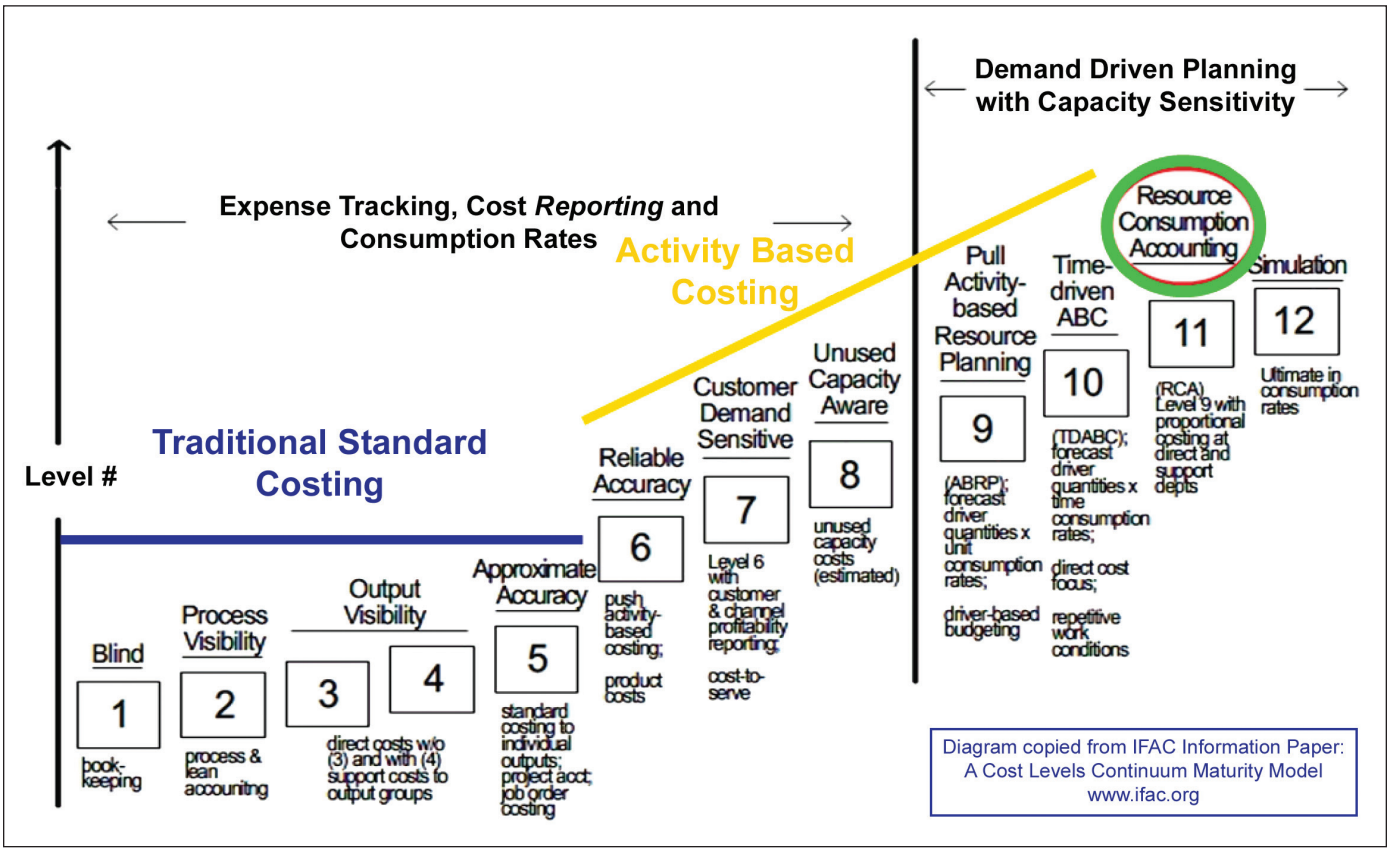

Figure 3. The Costing Continuum/Levels of Maturity.[7]

scenarios. Metrics are being used by all major industries, often as part of corporate initiatives involving lean, quality, ISO, or other improvement or compliance programs. The widespread use of metrics today often begins with product development, where engineering and manufacturing collaborate and use engineering systems and manufacturing systems for planning manufacturing processes and collecting performance results. As stated earlier, there is a clear need for an approach to identity and assemble operational data and the causal relationships that link operations metrics to business goals. The goal is to enable a better understanding of performance of the manufacturing business.

One such approach – the Resource Consumption Accounting (RCA) – was independently evaluated as illustrated in Figure 3. This approach begins by defining quantity structures and causal relationships to develop the connections from manufacturing operations to the financial layer.

RCA includes a three step approach that requires the cost model developer to obtain an intimate understanding of the manufacturing operations and that manufacturing operations management learns more about the overall business.

Step 1: define the organization's key strategic objectives, the critical and common decisions managers make, define the key value creating processes, the resources that directly contribute to final product, and what level of support they provide.

Define the manufacturing and business resources – know the plant, the business, the people, and the problems each are working with daily. This is a challenge since it requires realignment of the prevalent mindset and entails understanding all the different viewpoints and motivations in the organization, including the people in the financial department. It is critical to understand the responsibilities of each business area and stakeholder, including cost centers, capacities, assets, and the metrics each are held accountable for. The goal of this step is to define how value is generated from the resources (e.g., materials, equipment, facility, or plant) and identify misalignment in perception between manufacturing and business operations.

Step 2: define resource groups, metrics, measures and their relationships. This involves three sub-steps as follows:

A. Model the resources into their quantities (metrics), capacity, and where and how they are consumed. Quantities or metrics define what drives costs to the resources. This step should identify the metrics needed to measure performance of each resource and resource group.
B. Associate the quantities (metrics) with causal relationships by identifying how resources causally relate to where and how they are consumed or used.
C. Monetize the values of the quantities by adding the costs or monetize each unit or quantity identified in the model.

Step 3: visualize the model with a "storyboard." Figure 4 provides a holistic view of the plant and the business. This will give all the manufacturing and financial operations a clear and

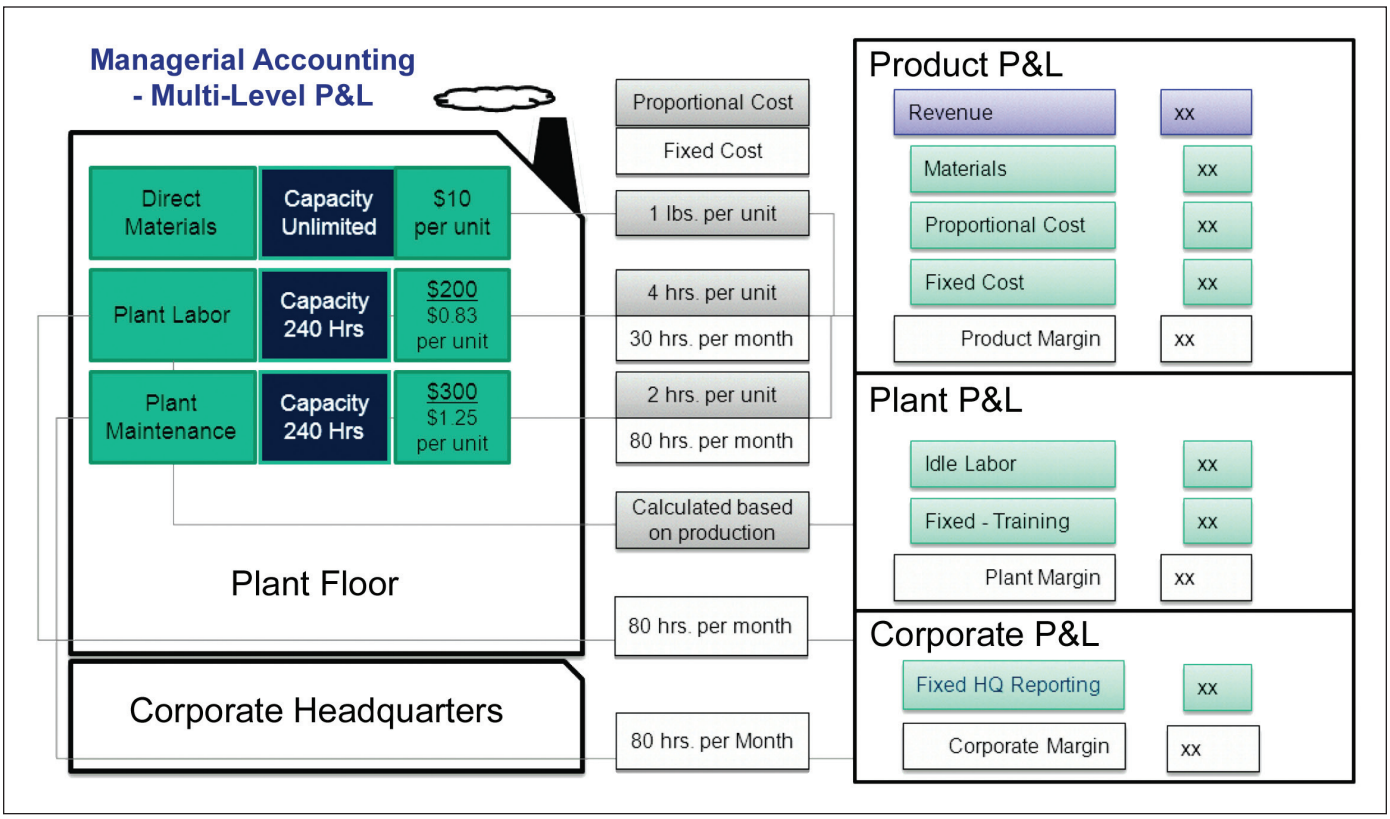

Figure 4. Example of storyboard.

candid perspective of the operational metrics that affect business and vice versa. It also allows a more granular and almost instant view of operational and financial data and metrics.

The simple example in Figure 4 shows a plant that is divided into three primary cost areas:

1. Raw materials
2. Production labor
3. Machine maintenance

In the center of the storyboard are the quantity structures that drive value to each of the cost centers, and their measureable units. The output from this story board is seen to the right and is:

- A standard corporate Profit and Loss (P&L) statement
- A breakdown of a more granular plant view of performance
- A more refined product, lot number, or SKU level performance statement

Defining Data and Information Requirements for Usable Metrics

Obtaining the required visibility into the performance of modern life sciences manufacturing operations with their inherent complexities is an important challenge that can only be addressed with information technology and manufacturing systems software applications. In the modern manufacturing plant data, information, and software systems exist in abundance; as exemplified, it is seemingly still a challenge to gain this required visibility into the performance of business operations. Data is being collected, sometimes in terabytes by different systems, yet it does not have the appropriate arrangement for effective decision support and analysis, i.e., intelligence. Even when the data is arranged in a usable format it is statically focused around a particular metric or problem.

Knowing the data exists, manufacturers are inclined to first consider the plethora of offerings with buzz words such as "metrics," "digital dashboards," and "business intelligence platforms" to address the manufacturing intelligence challenge. Yet, it is remarkable that one of the most commonly used tools to capture and manage information from the shop floor is the spreadsheet - typically Microsoft's Excel. In some cases, even with a major ERP system investment, the spreadsheet is still the primary source of timely data about manufacturing operations. In other cases, expensive solutions are put in place to capture and collect data from automated equipment, but fail to provide the information in a useable context and once again users resort to spreadsheets.

Why is it then that manufacturing organizations resort to spreadsheet solutions? It is typically not because of lack of understanding about information systems or the skills required to use these tools. It is because a spreadsheet provides the flexibility to manage and present manufacturing information in the most usable and advantageous manner. It is important to note that information use or "information consumption" is driven by the role a person plays in the overall operations. For example, a manufacturing manager's main focus can be productivity and quality. Hence, he will use information to obtain metrics about the value stream that he is trying to manage because he needs to know how the operation is performing in real time. This need is similar to that of a sport's team, where you know where you stand every second of the game. You don't have to wait until tomorrow morning's newspaper to know who won the game. Running a manufacturing operation without real time metrics is like bowling without being able to see the pins. You can see some of the action, you know that something happened, but you don't know what the result was.

It is critical to consider how people use information to solve problems and gauge performance. There is a clear need to provide effective and relevant information necessary to support the information consumed by the different roles in the manufacturing operations. As described in the sections above, identifying what needs to be measured is a fundamental principle, but it is not sufficient, the information also has to be arranged in a usable manner. Therefore, it is important to study and understand information consumption patterns by roles. Figure 5 exemplifies an information consumption pattern for a specific role.

In this example, the production supervisor glances at his dashboard and observes that the cell density is not within acceptable limits. He immediately navigates to view the "cell density by time" trend over the last two weeks and observes a negative trend beginning around "Monday" that

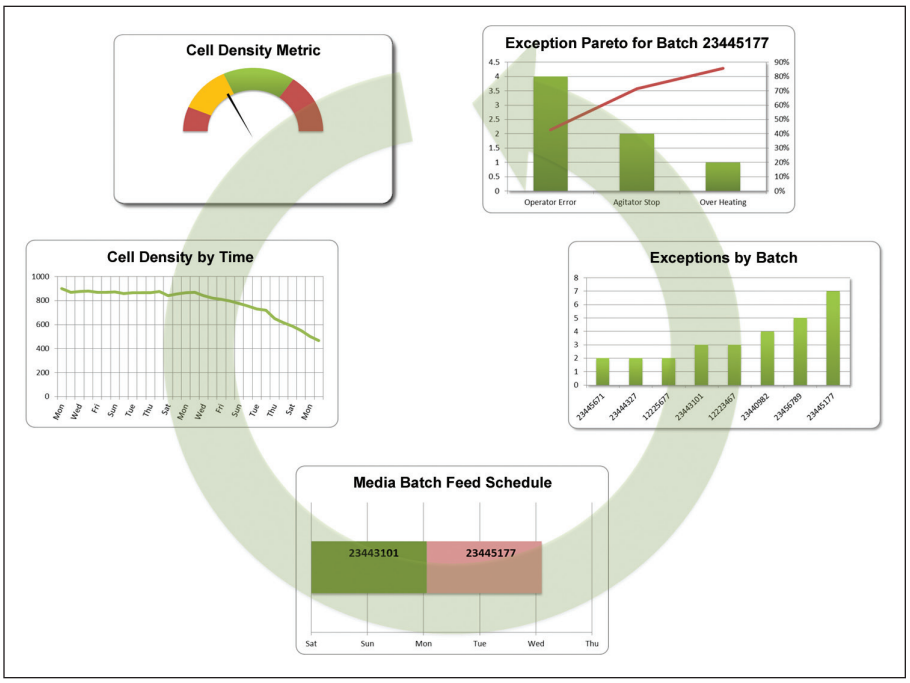

Figure 5. Example of information consumption scenario.

indicates something is seriously not in order.

To begin the analysis, he examines the "media batch feed schedule" to see if there is any correlation between the trend and the media that is being fed to the bioreactor. This action is obviously based on intuition possibly because he has seen that before. Seeing that there is a correlation between the change to a new media batch feed when the trend started he decides to take a look at the "exception by batch" information and notices that this specific batch had an unusual number of exceptions. He then dives deeper into the data by analyzing an exception Pareto for the suspect batch. He finds a high number of operator errors, which clearly highlights the root cause of the trend. Finally, since he is accountable for operational profits, he decides to take a look at the cost impact of this event in order to understand what the impact is to the plant's financial performance as seen in Figure 6. Unfortunately, the cost impact is substantial and thus he as to take action to mitigate this increased cost.

The scenario shows the power of "actionable intelligence." The supervisor has all the information he needs in order to quickly and effectively analyze the situation to determine root-cause and he can take action based on the results. The scenario that the supervisor decides to take in the example above is one of several that could have been used to detect and diagnose the cell density performance issue. It is this type of self-guided or self-serve analysis that really shows how information is consumed to meet a specific goal and should be the common pattern for the information required by a specific person or role. These requirements have direct bearing on the information context and data structures that must be provided, and the dimensions by which the metric is analyzed or "sliced and diced." Although this seems trivial at first the requirements that these analysis patterns have on the underlying information and data structures are significant and is a critical component of the system design. It is not enough just to collect the data; it has to be arranged in a manner that enables this unique type of analytic information consumption.

Experiences and best practices about information consumption are varied and differ from organization to organization. This in fact is a testament to the inherent challenge with this type of system; however, it is possible to compile a number of key points that are valuable when tasked with providing manufacturing intelligence.

- Performance management should be focused on the business processes and not a tool, system, or ability to see metrics or information. Focus on what the information tells you, rather than the way it is presented.
- Actionable intelligence is the ultimate goal of the information. The action to perform should be clearly evident, even intuitive after a short interpretation of the information.
- Defining relevant metrics is the toughest part of the exercise closely followed by identifying the data requirements.
  - Presentation and visualization of the information is the "minor" part of the battle and typically differs by users' needs.
  - Garbage in – garbage out applies universally, i.e., incorrect or inaccurate information presented in an appealing visual format is still incorrect. You must trust the information.
- Trends matter more than actual values. Humans have a natural ability to identify or observe patterns. Hence it is invaluable to include the trends exhibited by the information; in most cases, this elevates information to "actionable intelligence."
- The context of the information provides added value, isolating it can be detrimental. Context is a vital part of the analysis process and is another ingredient in the transformation of information to "actionable intelligence."
  - Understanding the source of the information enhances the ability of users to interpret context and patterns.
- The source of metrics information should be automated or computerized to prevent the possibilities of influence by "personal interpretations."
- It is critical information about the manufacturing operation is as close to real-time as possible. It is critical for diagnostic and analysis purposes to be able to react in an effective and timely manner to solve the operational problems as they occur.

It is common to see a multitude of reports, dashboards, and metrics in an

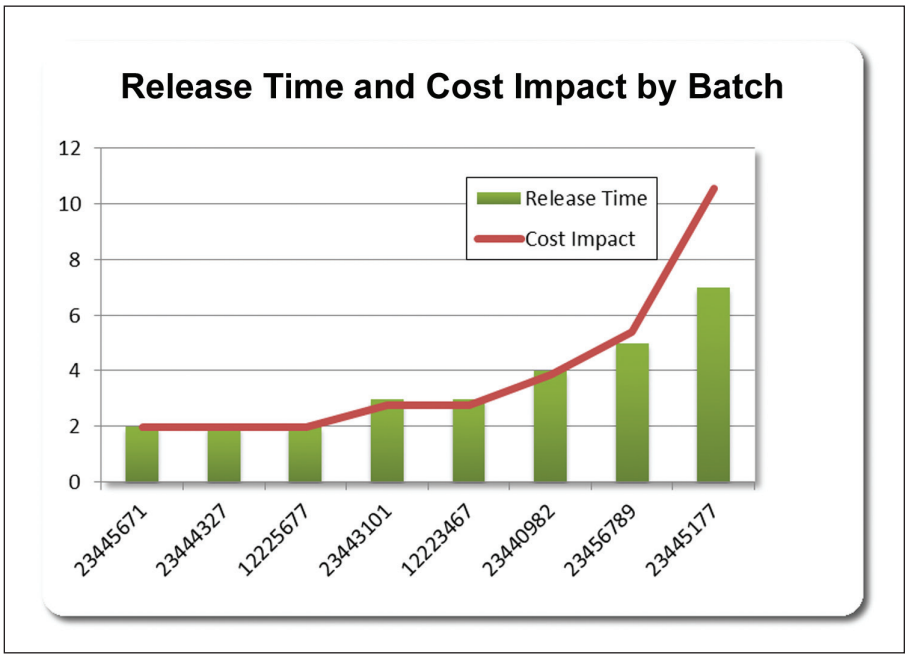

Figure 6. Cost impact analysis.

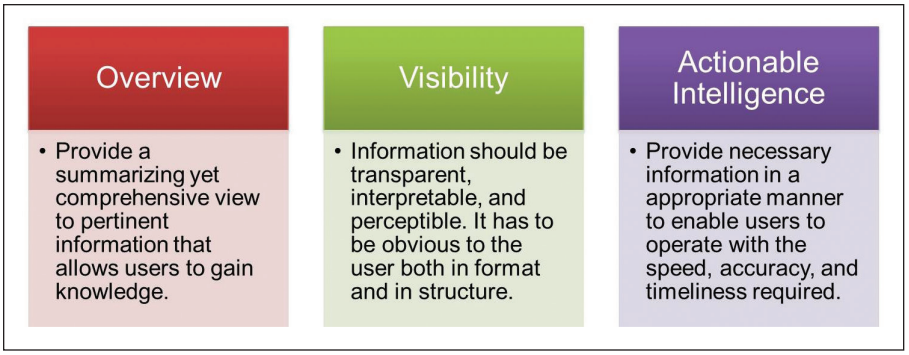

Figure 7. The three pillars of information consumption

organization. People will use data in any form in order to understand their performance and analyze problems. It is part of our creative nature and flexibility. Because a system constrains information to specific formats or simply lacks, it does not mean that business stops, people will strive to meet their goals regardless. Therefore, it is vital that metrics are driven by users' end goals and that the information that users need is provided in a manner that enable the dynamic and creative decision process. This puts a new dimension on the information structure design and the functionality of the information delivery solution that can provide true manufacturing intelligence. As a guiding principle, the manufacturing intelligence solution should provide overview, visibility, and actionable intelligence - *Figure 7*. These are considered the three pillars of information consumption and are meant as a guide when considering strategies for transformation of data to information and finally to actionable intelligence.

Summary and Conclusions

Performance indicates how manufacturing operations are progressing toward a goal, while intelligence aids in interpreting performance or lack of it. In simpler terms, intelligence is used to gauge and manage performance. This may seem straightforward, yet usable and useful manufacturing intelligence as it turns out is not easy to obtain both technically and operationally. Not only is it necessary to define what data is needed and how to transform it to information, there needs to be a definition of what is good performance and how can it be measured. This seems to be a universal challenge for manufacturing industries, not only the life sciences industries.

In recent years, manufacturers have gained substantial visibility about the performance of their manufacturing operations with the increased application of technology, but they still fall short of what is possible. Most manufacturing intelligence vendors are clearly aware of these needs and are working to bring applications with the flexibility and convenience that are really needed. The best way to guide the evolution of manufacturing intelligence solutions is to understand the true needs of the organization. This means a holistic view of the required intelligence that includes the appropriate scope and granularity of information linking operational shop floor metrics to financial metrics. It requires a mindset shift at all levels of the organization and best practices for utilizing more of the information to obtain and drive operational decisions.

Additionally, with the amount of available data growing daily we need new more robust methods to sift through the data to help us point the way to the value we all bring. The immense amount of data in a typical life science manufacturing organization is generally a hindrance to performance management. Companies know that they need to improve their performance and are actively pursuing operational excellence; however, it is a constant struggle to get a clear picture from the data and information in the different systems. The easiest system to get data from is typically the ERP and as such, there is a focus on the financial metrics, which do not necessarily give a complete picture of the performance of the organization. Knowing that, companies are looking for ways to link financial information with operational information. One approach that meets these needs is Resource Consumption Accounting (RCA). It provides a method to gain visibility of the linked information about operations on the factory floor to the financials.

Last, it is important to note that it is not enough to only link the data. The information has to be delivered in a manner where it can be consumed to drive performance. In order to do that, the behavior and creative way in which people operate has to be studied and used to design the appropriate functionality of the manufacturing intelligence solutions. Intelligence means that information must provide overview, visibility, and most importantly, actionable intelligence.

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PHARMACEUTICAL ENGINEERING Interviews

Larry Kranking, President and CEO, Coldstream Laboratories, Inc., Kentucky, USA

A longstanding ISPE Member and respected industry leader discusses his vision for Coldstream Laboratories and what it takes for start-up businesses to survive and succeed in today's market and regulatory environment. Kranking also shares his thoughts on why being a Member of ISPE is important today more than any other time in the history of the industry.

Larry Kranking has more than 40 years of experience in the pharmaceutical and regulated life sciences industry. Kranking holds an MBA in Pharmaceutical Marketing/Management and a BA in Sociology, Minor-Accounting/Business from Fairleigh Dickinson University.

Kranking's business/operations experience includes the start-up of cGMP manufacturing facilities for Boehringer Ingelheim and Esai Inc. that were defined by having a record of minimal 483 observations from the FDA (none at Esai Inc.) and no observations from international inspection agencies.

His record of accomplishments includes leading start-up pharmaceutical companies, implementing innovative regulatory strategies, expertise in efficiency improvements, and being a turn around expert in animal health, cGMP pharmaceutical and medical device operations. Kranking is an internationally recognized leader who has influenced the overall regulated environment by chairing a number of collaborative teams that included both industry and FDA scientists, engineers, and regulatory experts to develop the guidelines that define today's biopharmaceutical manufacturing world.

A longstanding Member of ISPE, Kranking took on many leadership roles, serving as President (1996-1997), founder and president of the New England Chapter, 1998 ISPE Member of the Year, chairman of the Chapter Committee, co-founder of the Scale-Up Post Approval Changes (SUPAC) Steering Committee, co-founder of the International Leadership Forum (ILF), and was appointed chair of the FDA SUPAC Similar Equipment Team.

Tell us about Coldstream Laboratories and why you decided to lead this company.

Coldstream Laboratories, Inc. develops and manufactures parenteral products in liquid and lyophilized dosage forms. We operate Kentucky's only sterile manufacturing facility. Coldstream offers fully integrated analytical chemistry services, formulation development, pharmaceutical manufacturing, and microbiology services.

Coldstream afforded me the opportunity to take my many years in the pharmaceutical business and create a winning team environment based on solid strategy to build a viable biopharmaceutical company meeting the vision of the University of Kentucky and the Commonwealth of Kentucky. I firmly believe that

culture trumps strategy. A dedicated workforce that believes in Coldstream's mission provides a better work environment and one that also gives back to the community. This is my passion at this stage in my career.

What trends are you seeing in contract manufacturing?

With the economic downturn over the past several years, large pharmaceutical companies have looked to outsource more and more of their manufacturing needs. The demand for contract manufacturing has increased substantially over the past several years and as big pharma seeks to cut costs, we are seeing that increase continue. Additionally, the demand for ANDA-associated production has increased as the generic industry segment grows especially in the highly potent and cytotoxic segment of the market – this is Coldstream's sweet spot.

What trends are you seeing in formulations, testing and GMP drug product production?

We are seeing a high demand for lyophilized formulations. We are also seeing an increased demand for nanoparticle formulations as well as antibody-drug conjugates. As mentioned before, the opportunities for generic drugs have grown substantially; therefore, many of our clients come to us seeking ANDA support. We also support a variety of emerging pharma companies with formulation development work on complex and difficult drug delivery processes for pre-IND and clinical supplies.

What technologies get you excited?

Whenever you can take a potentially life-saving drug product that previously was not capable of being provided safely to a patient and find the delivery mechanism through the marrying of basic science to the applied science, it is very exciting to me professionally. Our isolator technology allows flexibility in the types of products and technologies we can handle. Isolator technology has come a long way to not only protect the employee but also allows companies like Coldstream to handle highly potent products to meet the demands being formulated from cutting edge research. The biopharmaceutical companies of today have a better understanding of the science at the production floor level than ever before. We truly make better products today – that is exciting.

What kinds of efficiency improvements do you see for Coldstream Laboratories?

Coldstream is seeking to expand production through both an increase in physical production and laboratory space as well as increased efficiencies through new equipment. We are bringing a second filling line online in the coming months to allow increased batch sizes and a wider range of vial sizes. We are constantly improving with the addition of state-of-the-art laboratory equipment and software systems.

Efficiency improvement begins with training, so all employees working at Coldstream Laboratories have a training program developed to fully understand the theory and practical aspects of producing and testing the parenteral drugs manufactured by Coldstream. When the workforce is fully engaged in producing a high quality product first and foremost, then you develop effective efficiency models based on both workforce skill/knowledge and engineering capabilities of the process and equipment.

Could you tell us about Coldstream Laboratories' relationship with the University of Kentucky?

Coldstream Laboratories Inc. opened in 1991 as the Center for Pharmaceutical Science & Technology (CPST), a unit of the University of Kentucky (UK) College of Pharmacy. The CPST completed more than 200 development projects that led to clinical trials.

In February 2007, the University decided to spin off the CPST in to a private company, Coldstream Laboratories, Inc., in order to meet the demands from CPST clients and to integrate the Intellectual Properties being developed at UK. Coldstream Labs is privately held and wholly owned by the University of Kentucky Research Foundation.

What is unique about working for a company wholly owned by a university research foundation?

University activities are much smaller in scale and have a very long timeline and the focus is not so much on revenue as it is on basic science. Cultures are different at universities than a "for-profit" business venture. We have a unique opportunity to see what innovations are being developed and to formulate pharmaceuticals of the future into the long-range business plan. That glimpse into the future is very valuable from a science perspective, as it allows us to begin corporate structure planning to actually manufacture "future" drug products.

A significant part of your career has involved leading start-up companies. In today's market and regulatory environment, what major issues and regulations do start-up businesses need to focus on and what qualities do start-up businesses need to survive and succeed?

Leaders all have different styles and focus (passion) but what is paramount is that the leadership team must have a proper blend of diversity and experience to challenge each other, yet know when to yield to the best idea or plan of action going forward (many CEOs do not understand the "yield" part). Many start-up companies have issues because the Mission Statement and Company Values are not well-defined, hence decisions are not based from a solid framework or company structure. Once the moral and ethical standing of the company is agreed to, then the so-called regulatory burdens are not so onerous. Regulations are now more global (ICH) than regional and even though a company may only work within a certain region, if the focus is not on global regulations, they will constantly be challenged by clients or shareholders.

To survive and succeed in today's market, a company needs to have proper funding that allows them to grow and meet the constant changes in the biopharmaceutical landscape. This infers that the company has a solid strategy and business plan and the

ability to execute the plans effectively and efficiently, but be flexible enough to make course corrections along the way. The problem today is that funding is short-term focused yet in the biopharmaceutical industry everything takes much longer. ROI is normally 2-5 years depending on activity and for investors this is problematic. Bringing shareholders the vision for "playing" in the biopharmaceutical sandbox is the greatest challenge to leading start-ups.

"The industry needs ISPE more today than at any other time in the history of our industry. ISPE brings the thought leaders together (regulatory agencies and industry) to openly discuss the issues we are facing, facilitate defining solutions, then communicate a path forward. For a company like Coldstream, we do not have the resources to research all the activities nor the synergy that ISPE can create to reach the best solution and describe the best approach to implementing or learning from this synergy of ideas."

You have been an ISPE Member since 1981, including serving as President from 1996-1997; led and/or was instrumental in many groundbreaking initiatives benefiting Members and the industry (e.g. SUPAC, ILF, Chapters); and witnessed many changes within the organization and the industry. What changes in the industry are most notable to you in the last decade?

Manufacturing has become more of a strategic partner than ever before. Focus on QbD and PAT, combined with the realization that industry costs are more often associated with manufacturing rather than R&D, has companies looking at ways to maximize manufacturing as a strategic strength rather than a liability.

Quality of products is significantly better today. Companies are making the connection that poor quality is not a Quality Assurance issue, but rather a manufacturing issue. Root-cause analysis is delving into issue resolution in a manner that significantly reduces the probability of reoccurrence.

One other notable change is that FDA and other regulatory agencies from around the world are working with industry associations like ISPE to create a better understanding of what "true" quality means. Working together means that the regulations will not get harder to adhere to, but rather be developed in a smarter, more flexible manner. Innovation will be better utilized to yield safe, pure and significantly more effective products.

What are your thoughts on ISPE's approach to serving Members in an industry and regulatory environment undergoing tremendous change in the last decade?

ISPE's strategy is about the membership and the industry and is taking proactive initiatives to serve the industry. This means ISPE understands, better than any other organization or association, what the industry needs now and into the future. The biggest dilemma for industry is the time lag from time of discovery to product reaching the patient. Innovation opportunities are lost along the way. ISPE has committees that focus on the future of the industry and membership requirements and the International Leadership Forum (ILF) has a Global Positioning Strategy (GPS) that focuses on the future of the industry as well. This allows ISPE to move and facilitate what innovation looks like, create the dialogue or forum for the membership to discuss how to plan and/or implement innovation into the company's strategy thereby yielding significant benefits to the membership and the industry. Companies that cut back on sending employees to ISPE are losing an opportunity to keep innovation on the front burner and reduce costs while improving quality. This yields more profits to be used toward innovation – the improvement cycle of success.

How do you view ISPE's future in light of changes within the industry (e.g., outsourcing support other than core business, lack of funding to attend major society events)?

The industry needs ISPE more today than at any other time in the history of our industry. ISPE brings the thought leaders together (regulatory agencies and industry) to openly discuss the issues we are facing, facilitate defining solutions, then communicate a path forward. For a company like Coldstream, we do not have the resources to research all the activities nor the synergy that ISPE can create to reach the best solution and describe the best approach to implementing or learning from this synergy of ideas. Companies will learn that cutting back on training or networking is like cutting your sales force when sales decline – we must increase training and the skill and knowledge of the workforce if we are to continuously improve the company where we work and the industry in which we operate. At Coldstream Laboratories Inc. a significant portion of our budget is devoted to training.

How do you see ISPE assisting the industry and regulators in the years ahead?

ISPE has the ability to bring all the regulatory agencies together with industry representatives to discuss in a non-threating setting what is the best path forward for the benefit of the patients – the reason we do what we do for a living. ISPE will continue to lead the charge on fostering the collabora-

tion between all the entities in the biopharmaceutical industry because the one constant is that the industry will continue to change. We need to be vigilant at all times to what the changes are and how to react to the changes; that is what ISPE will continue to bring to the table.

What is your involvement now with ISPE?

I am a member of the ILF and chair the Supply Chain part of the Global Positioning Strategy for the ILF members. I am also on the Future Visioning Team (FVT) for ISPE that looks at the changes in the industry and offer advice to ISPE on direction that our membership will require to be ready for what the future holds for us all. I am also on the Facility of the Year committee, so all-in-all, still an active member. If one has a vision for growing and achieving greater responsibility in their profession then they must get involved in ISPE – involved, not sitting back and profiting from others' sweat equity.

What role has ISPE played in your career growth?

I look at the people in the industry whom I call friends and marvel at what they have all accomplished. When I started out so many years ago I met other "young" professionals and see them today as VP's and presidents; it is amazing. I cannot think of a problem I might encounter that I cannot pick up the phone and ask one of my friends how they resolved the issue. This is a true member benefit, but you only get that benefit from actively participating in ISPE.

As a seasoned veteran of the industry, what advice do you have for students and young professionals?

Get involved in a professional association to ensure that your learning never stops, your network continues to grow, and you have fun along the way. We may be competitors, but that does not mean you cannot help out your professional friend. I ask my staff and employees "what have you done today to make someone else be successful?" for when you help others be successful, you cannot help but be successful yourself.

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The Use of Acceptable Daily Exposures (ADEs) for Managing the Risk of Cross Contamination in Pharmaceutical Manufacturing

by Stephanie Wilkins and Julian Wilkins

This article presents a convincing justification for the use of Acceptable Daily Exposures (ADEs) to scientifically manage the risk of cross contamination in all types of bio/ pharmaceutical facilities.

Introduction

ISPE's Risk-MaPP Baseline Guide® has brought the term ADE to the forefront for the management of cross contamination in pharmaceutical manufacturing facilities. ADE refers to an acceptable daily exposure which is defined as a daily dose of a substance below which no adverse effects are expected by any route, even if exposure occurs for a lifetime.[1] By this definition, the ADE is a conservative value and is protective of all populations (including infants, elderly, ill, etc.) by any route of administration.

Once an ADE has been established for a compound, this value can be used to set limits for cleaning validation (rinse and swab) limits and cross contamination limits. ADEs are established by qualified toxicologists who reference all safety data for the compound in question to set the various factors needed in the calculation of the ADE. The safety data can include data generated from clinical trials used to support drug applications, package inserts for commercial products, and various resources that provide information on drug safety such as PubMed.[2] For a more detailed understanding of how ADEs are established, refer to the Risk Identification section of the Risk-MaPP Baseline Guide®.

Although the term ADE[3] is fairly new, several companies have been using health-based limits for a while and many companies are now getting ADEs developed so that their cross contamination risk management program is based on scientific data linked to the protection of the patient. Note that one of the primary principles of quality risk management as stated in ICH Q9[4] is that the "evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient." Companies are realizing this principle by incorporating the ADE into the company's risk management program.

Cleaning and Cleaning Validation

Retention is where product residue is left behind on product contact parts of equipment. The potential carry-over of the retained residue to the next product can be a major source of cross contamination. The purpose of cleaning and cleaning validation is to minimize this source of potential cross contamination so that there will be no adverse effects to the patient.

Traditionally, cleaning validation limits have been based on either not more than 1/1000th of a therapeutic dose or 10 ppm of the previous product in the maximum daily dose of the subsequent product and typically firms will use the lower of the two values. While these methods were the best information at the time of their inception (early 90s), they do not take into account the potential harm to the patient.[5] The therapeutic dose by definition is an amount that provides an effect to the patient, not a safe level for anyone. Using a safety factor of 1000 has not been scientifically proven to equate to a no adverse effect level for all compounds. The 10 ppm limit is not correlated to the safety of the product at all. The 1/1000th of therapeutic dose or 10 ppm methods are not linked to patient safety and therefore are not scientific based methods for setting the cleaning limits.

As discussed previously, the ADE is based on scientific data analyzed by toxicologists to set safe levels for long term exposure without adverse effects. Using the ADE to set cleaning limits provides the scientific justification as the basis for the limits as required by the FDA.[6]

The use of ADE values to determine cleaning limits is gaining acceptance from the pharmaceutical industry and more importantly the regulatory bodies. For example, at the ISPE Risk-MaPP launch sessions in Brussels September 2010, the presentation by Catherine Lefebvre of Agence française de sécurité sanitaire des produits de santé (AFSSAPs) – the French Agency for the Safety of Health Products stated:

> *"Some MSs are considering that the approach with the ADI is an improvement for risk evaluation over the arbitrary appoach of 1/1000th of the lowest clinical dose or 10 ppm."*[7]

MSs refers to the member states of the European Medicines Agency (EMA) and Acceptable Daily Intake (ADI) is synonymous with ADE.

In October of 2011, the EMA Safety Working Party in response to a request from the EMA GMP/GDP Inspectors Working Group published their Concept Paper on "the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities" where they state:

> *"Currently toxicological data are not always used in establishing limits for cross-contamination. In some cases arbitrary limits such as 1/1000th of the lowest clinical dose or 10ppm are used as limits for cleaning validation. These limits do not take account of the available pharmacological/ toxicological data and possible duration of exposure and may be too restrictive or not restrictive enough. A more scientific approach based on current available pharmacological and toxicological information is required to establish threshold values to be used as part of the overall quality risk management in shared facilities."*[8]

Selecting Cleaning Limits

In some cases, the acceptance limit calculated with the ADE may be significantly higher than the limit calculated with either the 1/1000th of therapeutic dose or 10 ppm. Many are tempted to set the cleaning limits based on the lowest value determined by using the ADE, 1/1000th of a therapeutic dose or 10 ppm methods because many feel lowering the limit makes the process more robust. But in actuality by artificially lowering the limit the process may be more prone to failures. First remember that the ADE is a very conservative value set on data that is used to approve the product, support labeling claims and is evaluated by toxicologists. This is a safe limit. Lowering the limit does not make the limit "safer," but it does tend to bring the limit down to the level of the data, hence a larger probability of failure. The best way to have a more robust process is to improve the process (clean better),

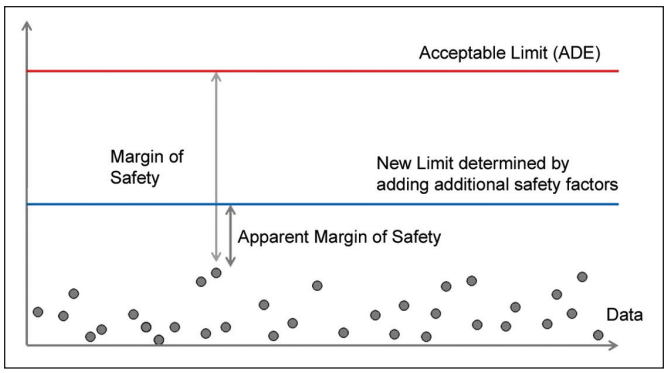

Figure 1.

not lower the limits. The margin of safety for the process is determined by the difference between the highest data point to the acceptance limit. As shown in Figure 1, the margin of safety is actually reduced when the limit is artificially lowered.

Some companies also may use the LD50 to set the cleaning limit by calculating an ADI based on modifying the LD50 by a safety factor to determine a No Observed Effect Level (NOEL). The LD50 represents the lethal dose of 50% of the test population. This method is described in the APIC's "Guide to Cleaning Validation in API Plants" and "Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants"[9] where the underlying document that is referenced for this approach clearly states that using the LD50 to determine the NOEL to calculate the ADI is an interim approach and is not a substitute for actual testing for the NOEL.[10] Clearly, there are adverse effects before death so the use of this value to set safe cleaning limits is not scientifically valid nor is it a safe value.

There may be situations where the limit calculated with the ADE is a large value that would not be acceptable as a carry over to another product even though it will be considered a safe amount. In these situations, visually clean would become the overriding acceptance value where the visual detection threshold is typically 4 mcg/cm^2 or less.[11] In these cases, using visual inspection as the method of detection can significantly save time and cost since analytical methods are not necessary because the visual threshold is more stringent than the calculated acceptance limit (safe limit).

Verification that equipment is clean to the required limit is necessary after each cleaning prior to using the equipment for the next product. It is important to note the distinction between cleaning validation which proves that a particular method will in fact clean to the necessary levels and cleaning verification which shows that the cleaning did in fact clean to the necessary levels. This distinction becomes much more necessary with manual systems. Automated systems should in fact perform as validated unless there is a failure that is usually noted by the equipment as an alarm condition. Manual systems are variable just by virtue of human nature. In manual situations, it is more important to verify the equipment is clean to the necessary limits each time. So it becomes advantageous to have limits that are above the visual threshold so that visual inspection can safely be

the verification method. When limits are below the visual threshold, other methods are necessary to prove the cleaning is meeting the requirements.

As more data are collected on the actual results of the cleanings, statistical analysis should be used to help determine the process control limit[12] where the process naturally works, alert limits where the process begins to veer out of the normal operating range, and action limits where the process is trending out of control, but still well within the overall acceptance limits. The advantage of this type of hierarchy of limits is that remediation can be implemented well before the process is out of control and far from the acceptance limit. This also minimizes the number of cleaning validation failures that require extensive root cause analysis and justification on acceptability of the product affected by the failure.

Cross Contamination

ADEs can be used to assess the risk of cross contamination by several methods. The true test is to analyze product for the presence of the previous product. This is not really an ideal situation as it is akin to testing quality into the product. Obviously, it is preferred to build quality into the system. Processes can be and should be challenged for their ability to minimize the risk of cross contamination through several testing scenarios that can then provide some scientific basis to predict the likelihood of the risk of cross contamination.

One test is similar to surrogate testing containment systems where a surrogate material is processed and testing is in place to determine the level of containment the system provides. To adapt this testing scenario for determining the risk of cross contamination, a placebo should be processed into final dosage form after the surrogate also has been processed into final dosage form with the required cleaning processes between the two "products" and then the placebo is analyzed for the presence of the surrogate.[13]For the test to be meaningful, a statistically relevant number of samples should be analyzed. A statistical analysis should be used to determine the process capability of the system. The system should then be routinely monitored against this process capability and similar to the cleaning systems outlined above, alert and alarm limits can be set and monitored where the actual acceptance limit based on the ADE is well above these limits.

Another testing scenario is to collect data relative to the potential for mechanical and airborne transfer in the facility. Care should be taken when obtaining data to support the potential occurrence of cross contamination due to mechanical and airborne transfer as merely determining the presence via air sampling or swab samples does not indicate that cross contamination by these routes is inevitable. Some companies are gathering and analyzing data to assist them in creating databases that are used to help predict the likelihood of mechanical or airborne transfer leading to an increased risk of cross contamination.

In addition, it is necessary to prove whatever systems are in place to manage the risk of cross contamination are working as intended and are indeed supporting the management of cross contamination. The FDA is citing firms for the lack of monitoring for cross contamination. Some firms assume this means testing the product for the presence of another product. This should be a last resort scenario. Firms should be monitoring the systems in place to manage the risk of cross contamination. For example, containment systems if used should be challenged to prove that they are containing to the levels needed. Pressure cascades are often used as a means to managing the risk of cross contamination and as such verification that the necessary cascades are in place is also needed as well as proving the pressure cascades are indeed managing the risk. These systems should be challenged at regular intervals as part of the ongoing monitoring requirements for the management of cross contamination. The key to success is to use science as the basis.

Conclusion

ADEs should be used as the basis for cross contamination limits as they are protective of patient health, are conservative and are scientifically derived. In many cases, the ADE derived limit provides a large margin of safety from actual results. In cleaning, the ADE derived limits also allows more compounds to have acceptable limits above the threshold for visual detection so that analytical methods are not necessary to determine if the equipment is adequately cleaned. In some cases, the limit may be significantly above the ADE so that visual inspection also may be considered for the validated method.[14]

It may be tempting to set cleaning validation limits based on the lowest of the following criterion:

- ADE based limit
- 1/1000th of therapeutic dose method
- 10 ppm in the rinse water
- LD50

This will not lead to safer, better cleaning, but actually to increased failures as the limits will start to approach the level of the data leaving no apparent safety margin. It has already been stated that the ADE is a very conservative number based on the adverse effects that could occur to a patient, so why is there a need to add additional conservatism to this limit? The best way to protect the patient from inadequate cleaning is to actually clean better.

In many cases, the ADE derived limit will actually be higher than the limits calculated using the 1/1000th of therapeutic dose or 10 ppm and in some cases, it will be much higher. In all cases where the ADE value is higher than the more traditional methods, the visual detection threshold will actually override and become the acceptance limit. Following this thought process based on documented visual threshold limits, the highest limit for cleaning would be 4 mcg/cm2.[15]

In addition, with release of the FDA's new Process Validation Guide, the use of statistical analysis to determine operating parameters is gaining more momentum. As data is collected on the performance of the cross contamination management program, they can be statistically analyzed to determine process control limits where the process typically

performs as well as alert and action limits where notification and remediation should occur if the performance veers to these limits.

By using the ADE as the basis for setting cleaning validation and cross contamination limits not only will patients be protected from the risk of cross contamination, there is opportunity to be more cost efficient especially in the cleaning and cleaning validation processes.

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Stephanie Wilkins, PE, Lean Six Sigma Green Belt, has more than 25 years of professional experience in project management, engineering, and validation solutions for the pharmaceutical/biotech industry, including research, development, pilot plant, and manufacturing facilities. She is President of PharmaConsult US, Inc, which provides cross contamination and containment consulting to the pharmaceutical industry. Wilkins is the Co-Chair of the ISPE Risk-MaPP Baseline® Guide Task Team, ISPE faculty member for training on Risk-MaPP, and was a member of the ISPE International Board of Directors. Wilkins is a technical reviewer for Pharmaceutical Engineering magazine, and she has contributed articles, given lectures, and organized courses for ISPE. Wilkins graduated from the Pennsylvania State University with a Bachelor of Architectural Engineering. She can be contacted by telephone: +1-908-575-7745 or email: stephanie.wilkins@pharmaconsultus.com.

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Julian Wilkins is Founder and Vice President with PharmaConsult US, Inc. In 1991, he founded a UK based isolator company for the emerging need for pharmaceutical containment. The company carried out many projects worldwide for aseptic and potent containment at all scales of pharmaceutical operation. He moved to the US in 1997 and set up PharmaConsult US in 1999. Since its formation, the company has provided independent advice, design, and support for containment projects, including Bristol-Myers Squibb, Chiron, GSK, Merck, Pfizer, Roche Colorado, Sanofi Sythelabo, Tyco/ Mallinckrodt, and Wyeth. Wilkins is also an adjunct professor at Steven's Institute in the Pharmaceutical Manufacturing Engineering Master's program. Wilkins is a core team member of the Risk-MaPP Baseline® Guide Team. Wilkins is a past recipient of the prestigious ISPE Member of the Year award. He has spoken at many seminars worldwide on the subject of containment and has contributed articles and chapters to periodicals and books on containment. He can be contacted by telephone: +1-908-575-7745 or email: julian.wilkins@pharmaconsultus.com.

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This article presents the results of a survey conducted by the ISPE United Kingdom/Ireland PAT COP.

The Business Benefits of Quality by Design (QbD)

by Theodora Kourti and Bruce Davis

Introduction

The business case for Quality by Design (QbD) was a hot discussion topic during a meeting of the Process Analytical Technology Community of Practice of United Kingdom/Ireland (PAT COP UK/IR). The discussion concluded with a plan to conduct a survey that would aim to gather actual experiences, examples and candid industry opinions on the business benefits of QbD. The questions were designed to cover a wide range of issues, including the use of modelling and PAT tools. A standardized set of interview questions were produced and sent out with a letter to individuals that agreed to be interviewed. All questions that would lead to commercial bias from vendors, suppliers, or pharmaceutical companies were avoided. The survey topics are listed in Table A.

Survey Topics

• Elements of QbD
  - Does the company apply elements of QbD?
  - What business units apply QbD, i.e., new/legacy products; R&D/manufacturing?
• Drivers for QbD, i.e., regulatory, management, other?
• Benefits of QbD, including metrics and possible examples, i.e., regulatory flexibility, cost reduction?
• Additional level of resources and cultural changes to achieve QbD
• Regulatory flexibility, i.e., experiences from QbD interactions/filings
• QbD for in-licensed products and third party manufacturers
• Use of modelling in QbD
• Regulatory response to modelling
• PAT tools to support QbD
• Desired sensor technology
• Future of QbD in your company (interviewees opinion)

Table A. Survey Topics.

Some of the interviews were conducted with individuals by telephone, while others were conducted with a group of company employees representing different business units who compiled their answers and replied by mail to one questionnaire. Written answers also were produced for the telephone interviews and these were approved by the interviewees. Interviewees were from development, manufacturing and regulatory while the companies range from large and small, both small molecule and biotech.

In total, we received 15 completed questionnaires from 12 companies. The responses were received between November 2010 and September 2011. The companies agreed to have their names listed, but it was agreed that the identity of the individuals or relation between company name and answer would not be revealed. Not all of the comments presented here represent "company" views; some are the opinions of the individuals interviewed. One company response indicated *"…that they do not apply QbD…"* and this company is not named here as it would be uniquely identifiable. The company deals with early stage cell development and their answer was that *"Customers do not ask for QbD."* The other 11 companies, listed in Table B, have adopted the use of QbD elements to varying degrees.

Companies in the Survey
1. Abbott (USA)
2. AstraZeneca (UK)
3. Bristol Myers Squibb (UK and USA)
4. GSK (USA)
5. Jazz Pharmaceuticals Inc. (USA)
6. Eli Lilly and Company (USA)
7. Merck (USA and Ireland)
8. Pfizer (USA, 2)
9. Centocor Biologics (J&J) (Ireland)
10. Vertex Pharmaceuticals (USA)
11. United Therapeutics Inc (USA)

Table B. Companies Interviewed that Perform Elements of QbD. Where there are two locations mentioned it indicates that we received a completed questionnaire from each location; from one company we received two completed questionnaires from different groups in the USA (14 questionnaires in total).

Presenting the Outcome of the Survey

The survey responses provided a great deal of revealing material. The interviewees provided candid answers, including interesting case studies and examples. Presenting the answers has not been an easy task because we wanted to retain the richness of the answers as much as possible. So instead of providing charts with numbers, we chose to present the answers in the narrative form. The answers from the companies for most of the questions are listed in Tables, edited for briefness, but presented in such a way that they reflect the context in which they were given. For example, nine out of the eleven companies indicated that *"increased process capability, process robustness, and reduced atypicals"* was seen as a benefit. Rather than simply putting the number (9/11) next to this benefit we also listed the comments associated with the benefit, for example:

- *Cpk has increased significantly; demonstrated increased process capability by comparison of Cpk values for legacy products versus QbD products.*
- *Zero batch failures in a year compared to high batch failures in the past.*
- *Processes are more robust.*
- *Batch failures have been reduced significantly.*
- *Certainly, we see improved process robustness and the potential for improved manufacturing efficiency worldwide.*
- *Improved process robustness; reduced variability.*
- *Amount of rejected batches is below industry norms.*

In addition, we chose two companies (which we designate as A&B) and we list the answers from interviewees of these companies at separate tables, to the extent that the answers do not identify the company. The objective of this approach was to help the reader develop an appreciation of the responses from interviewees from the same company to several questions. For example, if the interviewees from one company report certain benefits from QbD, what did they tell us about requirements for resources for the same company? What about dealing with third party manufacturers? What type of modelling was used in the QbD framework by this same company? Both companies A& B have embraced QbD as a way of working. For one of them, it was indicated that *"Our intent is that 100% of our products will follow the QbD framework"* while for the other company, it was stated that *"QbD principles (i.e., science- and risk-based approach leading to product and process understanding) are embedded in all that the company does. It is part of the company philosophy and the way of working."*

We encourage the readers to read the document as a whole, rather looking at isolated tables, so that they can get a better appreciation of the relationships between answers but more importantly of the overall prevailing feeling about QbD.

Embracing the QbD Framework

Eleven out of the twelve companies had used elements of QbD to various degrees. Three small companies demonstrated an impressive QbD record, and the company philosophy is to embrace QbD long term.

The responses from the large pharmaceutical companies and the number of applications in QbD vary, as shown from the following answers:

- *Our **intent** is that 100% of our products will follow the QbD framework.*
- *Filed one product with QbD and **intend** to do all time.*
- *Filed one product and **selectively** apply QbD elements to others.*

Overall, interviewees from ten companies indicated that it is their company's intention to apply QbD to **all** new products; one company seems to apply elements of QbD selectively. Five companies also apply QbD on existing products especially when there is transfer to a new site. QbD is applied to both development and manufacturing; when the companies use third parties to manufacture their products, the elements of QbD applied depend on the company, as discussed later in this article.

Elements of QbD

Interviewees were asked to list the elements of QbD that were applied in their company. Table C provides the answers from companies A and B. The answers from other companies were similar and frequent reference was made to the following:

- Principles and concepts as defined in ICH Q8, Q9, and Q10; risk-based approach
- Real Time Release Testing (RTRT)
- Extensive use of statistical and mathematical modelling
- PAT tools
- Ensuring link to in-vivo understanding
- Risk assessments; Critical Quality Attributes (CQA) risk assessments
- Fundamental process understanding; full mechanistic understanding
- Using science to improve product and process understanding

Elements of QbD Applied in the Company
Company A
• The principles and concepts as defined in ICH Q8, Q9, and Q10 and step 3 of ICH Q11, and all of our products are intended to follow this framework. The science- and risk-based framework and advanced understanding of defining design spaces based on both first principles and empirical understanding. In addition, advanced use of enhanced control strategies has increased, integrating PAT with technology platforms. Modelling is actively used for scale-up and scale down and to confirm our technical understanding.
Company B
• QbD principles (i.e., science- and risk-based approach leading to product and process understanding) are embedded in all that the company does. It is part of the company philosophy and the way of working. The company is aware of ICH Q8/Q9/Q10 terminology and recognizes the value in use of a common language across the industry. We recognize that during development, data is sparse so we want to build in maximum flexibility and uncover all potential problems during development.

Table C. Elements of QbD – Companies A&B.

Drivers for QbD
Company A
• The opportunity in QbD was to showcase a lot of the technical and risk-based approaches we were already doing and extend their practice deeper into our development and supply framework. We felt from a patient's perspective, this was the right thing to do. We see this as a win-win-win for the pharmaceutical industry, health authorities around the world and patients/customers.
Company B
• It's the company philosophy to use QbD principles. It is not for regulatory reasons. • The key drivers are being able to produce the product and reliability of supply. We concentrate on "getting the product right."

Table D. Drivers for QbD – Companies A&B.

- Quality Target Product Profile (QTPP) (patient centered design)
- Quality Risk Management (QRM)
- Multi-factorial Design of Experiments (DoEs); parameter risk assessments and prioritizations
- Use of modelling and PAT to guide process development and scale-up
- Integrated control strategies
- Design space
- Raw material attributes and relation to quality

Drivers for QbD

There were several reasons identified as the drivers for embracing QbD, including senior management and the need to standardize approaches, while the FDA pilot served as a driver for some companies. However, the main driver for continuing QbD was identified as *"process and product understanding and improvement in process robustness."*

This response was provided by every single interviewee in different parts of the interview. The answer to whether the reason they started QbD was *regulatory pressure* was negative from all of those interviewed. *Regulatory flexibility* was not a strong driver either and was only mentioned as the driver by few companies. Table D provides the answers from companies A and B, while Table E provides the responses for the rest of the companies.

Drivers for QbD
• As part of the FDA Pilot program in 2004 • It was not done for regulatory pressure, but it was recognized that the regulators would be inspecting the manufacturing site and so the company wanted to achieve a high level of confidence from the regulators regarding the site's approach and capability. • It is company policy now, but the history is that the approach was driven by a relative small group of like-minded individuals (in early stages using PAT tools to enhance product understanding) and the approach was later accepted by the company as an improved way to work for development of new products; we were involved in the FDA pilot program and learned from this. • From senior management – no pressure from regulatory authorities; the company is a science-based company and applies these principles from late Phase II. • At early stage, because of the regulatory climate and drive from the FDA. Management policy lead. Now fully integrated as part of our work • QbD is being used to get a standardized approach across the organization to technology transfer and the introduction of new products/molecules. • The promise of regulatory flexibility was the drive initially. Currently, it is becoming a norm for developing new products within the firm. Additionally, this (science-based approach) is an expectation from major regulatory agencies. • The primary driver for the application of QbD is the need to improve product and process robustness and enhance process understanding. Improved product and process understanding enables further changes to a product throughout its lifecycle, including the increase ease in technology transfers between sites. Regulatory flexibility is also a benefit, but lack of global harmonization limits this currently. • A desire for improved product and process understanding; a more systematic approach across the development portfolio; to continue to improve patient safety and efficiency; to improve manufacturing efficiency; and to improve development efficiency. • QbD implementation aligned with an internal redesign of the product development process in which QbD deliverables were imbedded into the process. QbD was viewed as an enabler of increased process and product understanding and improved regulatory submissions.

Table E. Drivers for QbD – Rest of Companies.

Benefits of QbD

The following statements reflect the feeling among the interviewees regarding the overall benefit of QbD:

- *"There has been a knowledge adjustment; undoubtedly applying a QbD process in development has improved process*

QbD Benefits
Company A
Benefits from Cost Savings • Saved more than $60 million • QbD processes have "zero process atypicals" to date • Saved API costs in technology transfer • Advanced enhanced control strategies with global regulatory acceptance that provided greater manufacturing flexibility
Benefits in Process Understanding • Greater process understanding and greater assurance of product quality • We gained experience following the science- and risk-based framework and advanced our understanding of defining design spaces based first principles and mechanistic understanding. • Advanced use of enhanced control strategies by integrating PAT in our technology platforms.
Benefits in Work Practices • Manufacturing is closer to development • Improved internal business processes (e.g., technical reviews are much more integrated) • API and Formulation Development are much closer as a lot of the QbD work is done jointly • Ensuring we have adaptable quality systems to support advanced scientific concepts and enhanced control strategies (e.g., predictive modelling and PAT) • We highlight that QbD also can be another mechanism to unleash the scientific and innovative creativity of our scientists
Company B
Benefits from Cost Savings • QbD processes have "zero process atypicals; we used to have processes with high batch failures in a year" • Improved product quality • Improved product robustness • A stable product with a long shelf life
Benefits in Process Understanding • Greater process understanding • Improved formulation design: - Simplifying the number of unit operations. - In development, we have taken on more complex formulations and made them work (e.g., one development provided a stable product with a long shelf life, whereas initially this was not the case). This was achieved by thorough investigation and understanding of the processes involved.

Table F. Benefits of QbD – Companies A&B.

QbD Benefits

Improved Process and Product Knowledge and Understanding
- It has meant clearer understanding of what matters, improved understanding of the specifications; we are proposing more meaningful specifications
- Advanced our understanding of defining design spaces based on first principles and mechanistic understanding
- Helping manufacturing sites understand the potential impact of some changes they might want to make
- Achieved in some cases full mechanistic understanding which we didn't have in the past

Improvement in Product Quality and Product Robustness/Reproducibility
- Corresponding improvement in product quality has been clearly demonstrated
- Improved product robustness
- Gain also has been in robustness (e.g., avoid bio-equivalence failures)
- Improved product reproducibility

Improved Control Strategy
- Better process control with on-line techniques demonstrated and established. Have gone through the challenge of validating on-line sensors
- Advanced use of enhanced control strategies by integrating PAT in our technology platforms
- Advanced enhanced control strategies with global regulatory acceptance that provided greater manufacturing flexibility
- Ensuring we have adaptable quality systems to support advanced scientific concepts and enhanced control strategies (e.g., predictive modelling and PAT)
- Control strategy is more holistic than just specifications on drug substance and drug product; the control strategies have become more explicit, are more integrated across the entire process, and are focused on patient impact (CQAs)

Fast and Reliably to Market
- QbD is viewed as a means of reliably getting products to the market.
- The specific site believes that they have a head start on the other sites and competitors having been through the QbD /tech transfer process before

Increased Process Capability/Process Robustness; Reduced Atypicals
- Cpk has increased significantly; we have demonstrated increase process capability by comparison of Cpk values for legacy products versus QbD products
- In the manufacturing process, we used to have high batch failures in a year, and now we have zero.
- Processes are more robust
- Batch fails have been reduced significantly
- Certainly, we see improved process robustness and the potential for improved manufacturing efficiency worldwide
- Improve process robustness; reduced variability
- Amount of rejected batches is below industry norms
- Reduced number of deviations per batch for QbD products.
- Increased process knowledge and efficiency/robustness.
- Implications of process robustness leading to process validation
- QbD processes have zero process atypicals to date

Reduce Impact of Raw Material Variability
- Variability in raw materials has been detected and impact reduced using QbD principles
- Batch fails due to raw materials have been reduced significantly
- Broadened the acceptable range of raw materials and developed knowledge of sensitive areas which are then highlighted
- Better understanding of material quality requirements

Improved Product Stability
- A stable product with a long shelf life
- Greater shelf life stability achieved

Improved Scale Up Efficiency/Speed
- Applied a blending PAT tool that improved scale-up understanding and efficiency
- Improved scale-up speed (due to science-based approach)

Standardize Ways of Working
- Streamlining the process
- Standardizing the platform for bringing new products on stream

Improved Development Capability, Speed, and Formulation Design
- ***Better development processes has been our main gain***
  - More structured and using science to improve product and process understanding
- ***Capability of development has improved***
  - There has been a step change in the capability of the development organization
- ***Speedy development***
  - Develop a formulation in six weeks rather than six months using knowledge base
  - Reduced experimentation time
- ***Improved development efficiency***
  - Drug Product Development has data (metrics) that demonstrated improved development efficiency
- ***Fast tech transfer to manufacturing***
  - Our overall goal: double the number of products introduced in half the time taken
- ***Improved formulation design***
  - Simplifying the number of unit operations
  - Converting a cold chain product into a room temperature product
  - In development, we have taken on more complex formulations and made them work, e.g., one development provided a stable product with a long shelf life, whereas initially this was not the case. This was achieved by thorough investigation and understanding of degradation processes.

Cost Reduction Benefits
- ***Saved more than $60 million***
- ***Leaner and more agile supply chain; reduced stocks***
  - Main benefit is having a leaner and more agile supply chain; reduced cost of supply; drug product has gained via shorter supply chains and we measure this.
  - RTRT has given benefits on improved supply chain.
  - Significant stock improvements involving tens of millions of dollars
- ***Saved API costs in technology transfer***
- ***Savings due to reduced number of investigations***
  - Improved process robustness improves indirect product costs (investigation time, rejects, etc.)
- ***Reduced development cost***
- ***Reduction in lab expenses for each batch, as a result of RTRT***
  - RTRT has had a positive impact on direct product costs due to the reduction in lab expenses for each batch.

Yield Increase
- We are now measurably producing more product.

Engaging Science in Profitable Ways
- We gained experience following the science- and risk-based framework and advanced our understanding of defining design spaces based first principles and mechanistic understanding.
- Has provided an awareness of application of PAT methods. (Before QbD, it was somewhat weaker). Use of PAT has provided enhanced understanding of the process. *(See detailed section in PAT later).*
- Due to PAT, testing moved upstream and RTRT enabled. *(See effect on cost reduction).*

Improvement in Collaboration between Business Units and Enhanced Work Practices
- Two way feedback between R&D formulation and manufacturing/commercial: interchange/discussion on the key parameters to deliver a robust product to manufacture
- Closer cooperation between development and commercial operations (improved relationships and links)
- Manufacturing is closer to development
- API and Formulation development are much closer as a lot of the QbD work is done jointly
- Internal business processes (e.g., technical reviews) are much more integrated
- Better understanding of the process and control strategies for an individual project has lead to a greater shared knowledge resulting in a more consistent approach across functions and projects
- Skill development, e.g., bringing in new skills such as modelling, chemometrics
- We highlight that QbD also can be another mechanism to unleash the scientific and innovative creativity of our scientists

Table G. Benefits of QbD – All Companies. The table includes answers from A&B to provide a complete picture of the benefits mentioned. Comments under each benefit are verbatim comments from companies.

Additional Resources
Company A
• There is pre-investment in training and methodology/tool development. • If done well, with strong alignment and support across the entire company, the resource commitment is not as large as one might think. • Return on investment is evidenced by the business benefits obtained to date.
Company B
• No additional resource • From the outset, we set out to recruit people that have these skills. We expect them to use these skills to ensure products are well understood.

Table H. Additional Level of Resources to Enable QbD – Companies A&B.

and product knowledge and understanding."–This comment reflects the view by all interviewed.

- *"Control strategy is more holistic than just specifications on drug substance and drug product; improved process understanding and implications on process robustness leading to process validation (PV). The control strategies have become more explicit, are more integrated across the entire process, and are focused on patient impact (CQAs). This has lead to a better understanding of the process and will lead to higher quality products."*

- *"Greater process understanding and a corresponding improved product quality has been clearly demonstrated. We have demonstrated increased process capability by comparison of Cpk values for legacy products versus QbD products. This same improvement is also demonstrated through reduced number of deviations per batch for QbD products. While improved process robustness improves indirect product costs (investigation time, rejects, etc.), RTRT has had a positive impact on direct product costs due to the reduction in lab expenses for each batch."*

- *"We gained experience following the science- and risk-based framework and advanced our understanding of defining design spaces based on first principles and mechanistic understanding."*

Table F provides the benefits listed by the interviewees for the two companies, A and B; Table G provides the benefits for all of the companies. Some companies provided monetary values. Savings in inventory due to Real Time Release Testing (RTRT) and the cost reduction of API in technology transfer were mentioned. Another very frequent response was the ability to deal with more complex formulations due to better understanding, for example:

- *"Converting a cold chain product into a room temperature product"*
- *"We have taken on complex formulations and made them work (a stable product with a long shelf life, whereas initially this was not the case)"*
- *"Simplifying the number of unit operations"*

"Improvement of process and product understanding" was mentioned in 14 out of 14 questionnaires, as the main benefit of QbD.

A set of metrics was provided together with the questionnaire, which may be used to demonstrate "hard" QbD benefits. The interviewees were asked to consider these metrics when answering. This Table is shown in Appendix I. Most of the companies were not able to provide information based on those metrics, at this point in the interview, but some mentioned that they were developing metrics of their own. Any metrics that were provided are shown in Table G.

Table G lists the benefits by categories. *Shelf life stability improvement* has been mentioned very frequently as

Additional Resources
• The first prototype obviously expends a higher cost. No cost analysis was undertaken because the practices tend to be intrinsic to the way the company has always worked. • We have no additional resource, but from the outset we set out to use QbD principles and it was part of the process for designing and specifying equipment. • I don't believe it is more expensive (we haven't measured it with metrics), but the capability of development has improved. Processes are more robust. • Initial training and developing the approach has been a significant cost in time (which has been costed using Effort Tracking System). For the ongoing application of these techniques, the additional effort is almost negligible. • As a personal impression (and we haven't done a cost analysis), the cost and resource in the long term do provide a good return, but one has to appreciate that the benefits only come two to three years post launch. • Skill development, e.g., bringing in new skills such as modelling, statistics • No additional resources because QbD is embedded in the production process. It was a good return of investment; we believe that the amount of rejected batches is below industry norms. • We believe that a more appropriate view is that QbD is a transfer of resources from a down-stream corrective mode to an upstream proactive mode; QbD approaches have already demonstrated that they result in more robust product and processes which reduces the resources needed to investigations, corrective actions and product rejects in commercial operations. • Added a dedicated Risk Assessment Department • In drug substance development, mix of chemists/engineers has shifted toward engineers, but no overall increase in resources. In drug product development, mix of pharmaceutical scientist, engineers, and analytical chemist have been important to implement the process; we have not changed these ratios. Have not increased resources. No Data for ROI. • QbD provides a good ROI. • A cross-functional governance team was formed to drive implementation of QbD. This governance team launched various project teams to address certain topics. After the project phase was completed, the associated headcount needs were absorbed into normal business. Continuous improvement of our programs is being managed through both base headcount as well as continuous improvement (6 sigma) headcount. QbD is considered to provide a good return on investment; however, an overall cost analysis has not been performed. • For product development, there has been an increase in the degree of experimentation required to define the design space; however, this has not translated to additional people resources. Some resources are required to increase capability, e.g., chemometrics, modelling, PAT. • From a manufacturing perspective, the additional level of resource is minimal. QbD has manufacturing more involved earlier in the development process which has tended to shift the resource timing and focus, but the "net add" is minimal. Also, during process installation phases (commissioning and qualification), there is some minimal incremental effort increase. As for good investment, it is too early to tell. The benefit has not yet been realized due to minimal experience.

Table I. Additional Level of Resources to Enable QbD – Rest of the Companies.

Regulatory Interactions
Company A
• Regulatory flexibility is not our primary driver for adopting QbD. QbD is a core element to our overall company Quality Strategy. We have had some regulatory flexibility, but it has been limited to date. • Regulatory improvements are harder to quantify than the benefits secured by science and risk based product and process development. • We have used predictive models in QbD applications and have been successful with regulatory acceptance. • We developed advanced enhanced control strategies with global regulatory acceptance that provided greater manufacturing flexibility
Company B
• It's the company philosophy to use QbD principles. It is not for regulatory reasons. • We have only indirect examples of regulatory flexibility gains. We have products pending approval. • We use QbD principles not as much for regulatory flexibility, but to ensure we can have the product produced and back on the rails if anything unexpectedly goes wrong.

Table J. Regulatory Interactions and QbD – Companies A&B.

a benefit; the same applies to *increase speed of scale-up. Increased process capability, reduced number of deviations, zero atypicals* were used to describe improvement in process robustness. Other benefits were listed that reflect ways of working in the company. The reader will find a plethora of benefits ranging from monetary benefits, to ways of working, to speed to market.

Regulatory Interactions
• Regulatory flexibility would be considered a benefit, but is not a determining factor in the application of QbD principles. • A definite regulatory benefit is that QbD provides for a more comprehensive CMC submission and rationale. • No data on regulatory flexibility, but not expected. • We do see regulatory flexibility gains, in the sense of giving the regulators confidence that we really understand our products and processes. Regulators will normally keep peeling back layers to investigate. With a QbD approach, when they see these principles being used, their confidence is increased and they realise they don't need to look further. • The biggest battles are with our internal regulators – and the external regulators. Internal regulators say we don't want to open up the file and yet, when we do, in order to use a new approach, in practice it takes longer to gain approval and yet the new approach is clearly much better than the conventional. • These are great guidances (i.e., reference to QbD principles), but there is sometimes a disconnect between top level/central regulatory messages compared to local demands. In practice, we have to get approval and so we don't have any leverage to say no to the local demands. • It has meant more questions and challenges from regulators. • Timeline for approval – much reduced. • The regulatory flexibility is brought mainly via approval of design space. Design space was approved in all major markets. Some other countries have granted further flexibility. • Some flexibility in post-approval changes has been experienced, but more global harmonization and acceptance is needed to fully realize the potential for continuous improvement. • QbD submission requires a full explanation that requires learning from company and regulators – a relationship building exercise. • QbD filing may not be realizing as much freedom as was expected. There is a gradual learning on the level of detail required in filing. • Improvements have arisen: having CQAs and CPPs is providing assistance in dealing with regulation. • More documentation and elaboration are needed for the CMC section; usually we get asked for more data. • The focus of the site regulatory inspections has shifted to include a blend of review and quality systems type issues. This has lead in some instances to a lack of clarity of what should be in the submission and what is managed within the company's quality system.

Table K. Regulatory Interactions and QbD – Rest of the Companies.

Additional Level of Resources to Achieve QbD

The additional resources required to work in a QbD framework did not seem to be of concern and the overall philosophy of the companies that embraced QbD seems to be summarized by the following statement:

> *"We believe that a more appropriate view is that QbD is a transfer of resources from a downstream corrective mode to an upstream proactive mode."*

The answers from companies A and B are shown in Table H and other sample answers from the rest of the companies are shown in Table I. In general, the feeling was that the Return on Investment (ROI) is very high for the investment to be a matter of concern.

QbD and Regulatory Interactions

Regulatory flexibility was **not** the main driver for QbD adoption according to the responses in all of the questionnaires. According to one interviewee, *"QbD has been worth doing irrespective of the regulatory position."*

The following statement recognizes the fact that both the industry and the regulators are learning from the process and the advancement of QbD is dependent upon building relationships with each other.

> *"QbD submission requires a full explanation that requires learning from company and regulators – a relationship building exercise."*

There are strong examples cited by some interviewees where regulatory approval was achieved for their companies:

QbD for In-Licensed and Third Parties
Company A
• We apply QbD elements with CMOs and for in-licensed products. The former has primarily been accomplished through DoE driven protocols.
Company B
• For in-licensed products, we find we have to do more work in-house to ensure the formulation meets QbD principles. • For contract manufacturing, it is difficult to get companies to do fundamental work. We find it best if we set out our expectations early and then expect them to meet these. We employ our own specialists who know how to manage the external supply base. We often have to put our own resources into contractors to manage the early stages of a contract and ensure the product will be made successfully. We expect for example use of control charts by the third party. We do have a philosophy to build long term relationships with many third party manufacturers. - For manufacturing, we have quarterly meetings with our contractors and collect the usual metrics such as yield, customer complaints, etc. - We find drug substance third parties entities are more sophisticated when it comes to PAT and modelling than drug product ones, as the latter seem less flexible to new approaches. - Third party manufacturers would expect us to pay them to develop their own use of PAT tools; it is hard to justify for us.

Table L. QbD for In-Licensed and Third Party Manufacturers – Companies A&B.

In-Licensed and QbD
• Often we carry out further development work (DOE) to ensure robustness of the product, before putting it into commercial manufacturing; we have improved bought-in products this way. • If they are acquired early, then they would be part of the QbD development process; sometimes they are acquired too late to be influenced by QbD principles, other than by post-approval. • We apply QbD for in-licensed. • Some limited aspects (CQA and DOEs) applied to in-licensed product; an assessment of the QbD elements during due diligences for in-licensing candidates is often done, but is not an expectation. • We apply QbD for in-licensed, for drug substance (could not comment about drug product); ensure we are involved in the development and understanding of products using QbD tools and develop risk assessment based on this knowledge. • We apply QbD (Interviewee was not able to provide details, but he believes it is based on the overall company's QbD approach.) • Intent would be to make use of these approaches with in-licensed products, but timeline will determine whether that is achievable, both for drug substance and drug product. • In-licensed product to be filed, all based on risk assessment; in some cases, the partner or originating company also has taken a QbD approach. Where this is not the case, QbD principals are applied to in-licensed products according to a risk-based approach. The risk analysis will consider the current level of process robustness, the level of process understanding, as well as the expected time remaining to gain approval. In many cases, QbD approaches are applied to certain higher risk areas of the process, as opposed to a more holistic approach for a fully in-house developed product. In some cases, it also may be determined that a product developed by a partner is suitable for launch, but that additional process improvements can be gained post-launch. In these cases, QbD tools are applied during the commercial phase of the products lifecycle
Third Party and QbD
• QbD is applied. An example where we imposed QbD principles: they (third party) didn't believe they had a problem, as their processes on average yielded 95% or better. But they couldn't explain why some batches yield was 99% and some 96% so we insisted on investigating this to find root cause. The process is now more consistent and more productive. • We don't have our own plants and we use external third parties for manufacturer of our products. QbD is done for this purpose • Generally, they (third parties) are not expected to apply QbD principles. • Third party contractors: QbD is applied but on a case by case basis. Main area is aspects of control that we expect or want. • Third party contractors, they do not need to be QbD enabled; they are required to work within the boundaries of the license. • QbD is applied; this has primarily been accomplished through DoE driven protocols. • QbD is applied; interviewee was not able to comment too much on how this is being done, but he believes it is based on the overall company's QbD approach.

Table M. QbD for In-Licensed Products and Third Party Manufacturers – Rest of Companies.

- Advanced control strategies (global acceptance)
- Predictive models
- Design space (approval by all major markets)

There are still concerns for the following issues:

- Lack of harmonization
- Lack of clarity as to what should be in the submission and what is managed within the company's quality system
- Lack of flexibility for post approval changes to realize the potential of continual improvement.
- Amount of data required for a QbD submission

Use of Modelling
Company A

• Models have been used for direct prediction of CPPs/CQAs.
• Predictive models for assessing stability of the product.
• Verification at commercial scale
  - For PAT models, yes.
  - For first principle or mechanistic models, no.

Company B
• Models have been used in development. • Kinetic modelling for improving stability: understand rate of formation of degradants. • Simulations of what we expect dosage form to be in the human body – IVIVC models • Manufacturing have used a lot of DOE (re-establish operating range if changes are made to the process) • Have used models or earlier analysis to push testing as early as possible in the process rather than (testing) the final product.

Table N. Use of Modelling in QbD – Companies A&B.

QbD for In-Licensed Products and Third Party Manufacturers

When asked whether their company applies QbD principles for in-licensed products, the interviewees gave a variety of answers; however, the following sentence captures a reasonable argument of when a company would consider QbD:

> *"If the in-licensed products are acquired early, they would be part of the QbD development process; sometimes they are acquired too late to be influenced by QbD principles, other than by post-approval."*

For third parties, some companies do not expect QbD; however, some are keen to provide support to the third parties:

> *"We often have to put our own resources into contractors to manage the early stages of a contract and ensure the product will be made successfully."*

> *"We used an external contract manufacturer, and much to their chagrin, we imposed QbD principles on them. They didn't believe they had a problem, as their processes on average yielded 95% or better. But they couldn't explain why some batches yield was 99% and some 96%, so we insisted on investigating this to find root cause. The process is now more consistent and more productive."*

The responses from companies A and B are listed in Table L. Responses from the rest of the companies can be found in Table M.

Use of Modelling in QbD

It became evident from the responses that all the eleven companies are using Design of Experiments (DOE) and empirical modelling. Mechanistic/first principles models are also used by the majority of companies (9 out of 11). Use of modelling in existing products also has been mentioned as for example, *"composition of an oral solid formulation was modified, based on a model."* A company mentioned that *"the use of both empirical and mechanistic models has improved*

Use of Modelling
• Composition of an oral solid formulation was modified, based on a model • Model used for RTRT • For adjusting process parameters (in feed forward mode) • For energy input to granulation
• PAT models • DOE to establish design space
• Use of modelling in development is increasing, e.g., predicting operating space. • Haven't got to the stage where it is being used for release.
• Extensive use of models • Models are used at full scale and developed with data from clinical batches at full scale.
• Small scales (e.g., viral spiking and viral removal studies) are being carried out in downstream processing. Model studies have not been used for upstream (cell culturing and bio-fermentation) processes.
• Modelling and PAT were used to guide process development. • Modelling was used to predict scale-up parameters.
• Both mechanistic and empirical (statistical) models have been developed and used to improve product and process understanding • For PAT based methods • Development of design space • Deliver early warning of problems (drug substance) but not being deployed in RTRT at present. • RTRT models have been deployed in drug product manufacturing.
• Extensive use of modelling across the company including the investigation and demonstration of scale independence • Statistical and mechanistic models are employed based on suitability to a particular product or process.
• Significant use of DOE modelling • Use of engineering first principles and modelling • Statistical and first principles models are primarily used to define and describe the design space and justify experiments and scales selected to map the design space.

Table O. Use of Modelling in Rest of Companies – Grouped to Indicate Use by Company.

product stability." Comments related to use modelling by the two companies A and B are shown in Table N. Examples of modelling use from the rest of the companies, grouped by company, are given in Table O.

Comments related to the acceptance of modelling use by the regulatory agencies are listed in Table P. Please note that the different level of scrutiny described by some interviewees is related to the impact of the models involved in their submissions; according to ICH points to consider for modelling [1], models that are used as sole predictors of quality (i.e., for product release) are considered high impact and therefore a higher level of scrutiny may be expected.

Modelling and Regulatory Interactions
• We have used predictive models in QbD applications and have been successful with regulatory acceptance. • Small scales (e.g., viral spiking and viral removal studies) are being carried out in downstream processing. Regulators have accepted model data. • Regulators have demonstrated their acceptance of the concept of modelling although they expect the use of a model to be strongly justified for each instance of its use. • We have experienced challenges, e.g., for mechanistic understanding. Challenge also has been verifying model at scale. Regulators want data to show it works at full scale, though level of this scrutiny depends on what the model is being used for, e.g., more scrutiny if being used for release testing. • Use of model for post-approval flexibility was not accepted by regulators. The regulators do expect to see model verification studies at commercial scale. • The regulatory agencies have struggled to understand and accept the validity and scalability of the models (interpolation versus extrapolation). • Statistical and first principles models are primarily used (in our company) to define and describe the design space and justify experiments and scales selected to map the design space. Regulators have stated that this approach seems acceptable and full scale verification is not required; however, this is yet to be verified. • We have experienced challenges (for modelling) with inexperienced regulators, but for those with experience and understanding of models, the models have been accepted.

Table P. Regulatory Response to Modelling – All Companies.

Use of PAT to Support QbD

All the eleven companies use PAT. The majority of the companies answered that they use PAT both in R&D to gain product and process understanding and also in manufacturing. Only two companies answered that although they use PAT in R&D, they rarely use PAT in manufacturing. One of them uses it mainly in drug substance manufacturing. *"We rarely use it in manufacturing, as conventional end product testing is a lot cheaper than using PAT tools for our products today. We have used PAT tools more in drug substance (where it has been longer established by the industry) and less so in drug product."* The other company uses third party manufacturing so the comment was *"Third party manufacturers would expect us to pay them to develop their own use of PAT tools so it is hard to justify for us."*

The thought process behind PAT choices is accurately reflected in the following statement:

> *"PAT tools are used in various applications including development and commercial control strategies. In a development setting, PAT tools can be used to gain process understanding and may not be necessary in the commercial setting. In other cases, PAT tools may be appropriate as an element of the commercial control strategy. These decisions are based on risk assessments of the specific product and process."*

Desirable PAT Sensors
• A means of 100% integrity check of sealing on aluminium overwrapping pouches for BFS. • Non-destructive way to measure tablet properties and an efficient at line HPLC measurement • Not fully utilizing all the available PAT devices commercially available for manufacturing environment • A tool to measure residual ethanol in wet granulation would be useful • One area we struggled with somewhat was in dry granulation (roller compaction) – ribbon porosity is difficult to measure on-line, this is a gap in the market. Apart from this, most tools are available, but are expensive to operate and validate. • Lack of sensors in vaccines and biologics. For small molecule solid dosage forms we lack suitable on-line technology (including sensors) for degradate and impurity analysis. Accurate moisture sensors. • Sensors to examine resin contamination. • Non-destructive measurement of oxygen/water in opaque blisters or tablet bottles. More specific and sensitive sensors for reaction monitoring applications. • Microbial counts in process streams – rapid fluorescent method being examined. Rapid and robust cell density measurement linked to automated sampler.

Table Q. Desired Sensor Technology not Currently Available – All Companies.

The Future of QbD
• It will continue – it is part of our company's way of working. • QbD will be the norm within 10 years and manufacturing efficiency will be significantly improved – but remember we're not a commodity industry. • I think it will continue to grow and become more embedded as it is applied more in production we will get better at it. We will use more prior knowledge and more risk-based approaches. • QbD will become the norm. • Quality by design is already expanding its scope into new paradigms such as RTRT, continuous quality verification, analytical QbD, lean stability approaches and others. We expect this trend to continue. • We will continue using QbD principles to guide the development and manufacturing of commercial APIs, but how QbD plays out in registration remains to be determined. In drug product, we are constantly reviewing our QbD implementation process to determine how the process and underlying tools can be improved to make the implementation as practical as possible. • I am a supporter of QbD as it brings enhanced product and process understanding internally. The biggest risk is that people will give up if we don't see movement from the regulators and all this benefit will be lost. It is very disappointing to have to say that at the moment while I fully support QbD as a development principle, I cannot see a logical business case to justify including this information in a regulatory submission. • Since we are not driven to do QbD solely for regulatory benefits, we see QbD as the way we will develop and supply all our products. • The value of the QbD principles is clear and will continue to be integrated into the product development processes. It provides a systematic approach to product development, a common language, increased integration of patient requirements, and an advanced control strategy for increased process and product understanding, and a strong rationale for the control strategy. • QbD will be a far bigger part of operations and activity at the site now. Six sigma to align with QbD with PAT as the enabler is the approach being pursued.

Table R. Response to the question *"What is the Future of QbD?"* – All Companies.

Desirable New PAT Sensors

The interviewees were asked for a "wish list" of sensors that could be applicable for PAT at their businesses and that are not currently available; this list is given in Table Q. The following two statements summarize the overall feeling about the state of PAT in the pharmaceutical industry:

> *"As a general statement, our experience has shown that PAT tools are more advanced than our current understanding of how to fully utilize them. PAT tools are typically developed and implemented outside of the pharmaceutical industry and then adapted to the pharmaceutical setting. This implication is that our ability to utilize new approaches often lags behind the technologies themselves."*

> *"In the future, if one established 'real QbD,' this would mean flexible manufacturing processes that responded to these tests to feed forward/feedback, i.e., attribute based controls to assure product output would be of the required quality, even though input materials varied."*

The Future of QbD

Overall, the interviewees indicated positively that QbD is here to stay, not for regulatory flexibility but because it is the right thing to do. This is evidenced from the responses listed in Table R. The following statements summarize the feeling:

> *"The value of the QbD principles is clear and will continue to be integrated into the product development processes. It provides a systematic approach to product development, a common language, increased integration of patient requirements, and an advanced control strategy for increased process and product understanding, and a strong rationale for the control strategy"*

> *"Quality by design is already expanding its scope into new paradigms such as RTRT, continuous quality verification, analytical QbD, lean stability approaches and others. We expect this trend to continue."*

Concluding Remarks

QbD seems strongly embedded in the companies interviewed. The benefits realized have met the expectations set by companies when they embraced QbD *"...improved product and process understanding; a more systematic approach across the development portfolio; continue to improve patient safety and efficiency; improve manufacturing efficiency; and improve development efficiency."* Additionally, significant cost benefits have been reported from QbD developed products. QbD is being applied in development and manufacturing, in new and also established products. No significant overall increase in resources is expected, but a shift from resource upstream and requirement of additional skills (e.g., statisticians, chemometricians) and multi-disciplinary working. The use of models and PAT is commonplace. For in-licensed products and third party manufacturing, the degree of QbD implementation is varying. The opinion about the future of QbD is unanimous: QbD is here to stay.

Reference

1. ICH Quality Implementation Working Group Points to Consider (R2); ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation, Document date: 6 December 2011, can be downloaded from http://www.ich.org.

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Appendix I: ISPE PAT COP: Business Case for Quality by Design				
Business Benefit Category	**Sub-Category**	**Metric**	**Benchmark (Traditional)**	**Benchmark (QbD)**
Robustness	Process Performance, CpK (for all end of process and within process measurements	CpK		
	Reduced OOS Product	Batch Fails		
	Re-Work/processing			
	Acceptable Range of Raw Material Specification			
	Time on incident analysis	Manhours		
Production Cycle Time	Cycle Times (Predictable) (for each individual production unit and across whole process)	Cycle Time, Average and Std Dev		
	Work in Progress			
	JIT, RFT , Reduced Inventory	£		
Manufacturing Efficiency	Energy Efficiency	Cost per Unit		
	Reduced Cycle Times	Time		
	Reduced Cleaning/Setup times	Time		
	Reduced Manpower	£		
	Stock Turn			
	Right First Time	%		
	Overal Equipment Effectiveness	%		
	Yield	%		
Speend to Market and Sustainability	Reduced time from filing to market			
	Regulatory Flexibility (through improved Process monitoring and understanding)			
	Continuous Improvement (Operational Excellence activities)			
	Cumulative Benefits year on year			
	Quantify reduced or increased documentation			
	Process Development Time (Stage 1, 2, 3)			
	Risk Assessment (Time, People, etc.)			
Return on Capital Employed or ROI	Initial Capital Costs	£		
	Lifecycle Capital Costs	£		
	Cost of QC	£		
	New Product Efficiency	%		
	Product Extensions (speed to market)	IRR		
Strategic	Diversity – able to produce products at different sites worldwide			
	Showcase	Number of Publications? PR		
	Transferability (through Improved Process Understanding)			
	Environmental Benefits	Carbon Footprint		
	Regulatory Agency Interaction			
	Process Understanding of material, offering flexibility in supply chain	Reduced Risk		
	Real Time Release	Reduced Cost of QC		

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Rouge: the Intrinsic Phenomenon in 316L Stainless Steel – a Key Material for Biopharmaceutical Facilities

by Michelle M. Gonzalez, P.E.

This article will try to demystify the presence of rouge in 316L stainless steel; its unavoidable link with iron; regulatory mandates; detection and monitoring; and the resulting dilemma, removal from or analytical management of process systems.

Introduction

Because the biopharmaceutical industry has been a major driver of technological change in health care, producing unprecedented benefits by improving and saving human and animal lives around the world, materials and methods utilized in the construction of their manufacturing facilities play a major role in the production and delivery of safe and effective medicines and medical devices.

Traditionally, the preferred material for the manufacturing of tubing/piping, fittings, valves, vessels, and other components utilized in drug/product processing facilities throughout the world has been the austenitic, Type 316L (low carbon) stainless steel (UNS S31603); characteristically non-magnetic, not hardenable by heat treatment, and *the most corrosion resistant* among the martensitic, ferritic, and austenitic groups.

Two critical facts to keep in mind when discussing this particular alloy and the issue of rouge are:

1. Its predominant composition element is iron.
2. In nature, iron and rust (rouge) are "intrinsically" tied to each other. (See Rouge Composition and Classification).

Rouge – What Is It?

"Rouge" in high purity biopharmaceutical processing systems is a general term used to describe a variety of discolorations on the metal product contact surfaces.

While having always prompted a great deal of concern, much discussion, and proprietary analysis, the issue of rouge has yet to fully reveal itself to the life sciences industry. Its chemistry is understood, its formation is the subject of theories as diverse as there are colors to identify it; it is generally agreed under what conditions it is more likely to appear and progress, but what is not well known is, where specifically originates in diverse systems, what are the specific causes for its appearance, and to what extent may be deleterious to product contact surface finishes or their cleanability. More importantly, there is the need to clearly understand if the presence of rouge in any product contact surface may contaminate the flowing product in such a way to prove dangerous or even fatal to humans and/or animals, and whether there are specific governmental rules/mandates addressing this phenomenon and all its real or perceived associated repercussions. (*See Rouge and Regulatory Stances*).

Rouge in a process system operating under a single set of fluid service conditions is an anomaly, the cause of which can be attributed to multiple factors rather than resulting from one single originating source.

The propagation of rouge is generally believed to be dependent upon the following four major factors:

1. Material of Construction – variability of factors in the manufacturing of stainless steel components within a process system may be the source in some instances (e.g., sulfur content, alloy composition, traces of non-signature elements from scrap material, microstructure quality, type of thermomechanical processes, mill surface conditioning, etc.); however, it may not necessarily be the entire cause.
2. System Dynamics – how the system was constructed (e.g., welding and welding condi-

tions, material storage conditions, installation environment, grinding, buffing, passivation state, and treatment, etc.).

3. Process Environment – what process service conditions the system is exposed to (e.g., corrosive process fluids, such as halides or bleach, temperature gradients, pressure gradients, mechanical stresses, high shear environments, high flow velocities, stagnant flow areas, redox potential, system age, etc.).
4. Maintenance and Repairs – these system interventions are an opportunity to either minimize the onset of rouge or conversely, set the stage for its formation. During these functions, the various product contact surfaces may be compromised by use of dissimilar materials, scratches, welding residues, derouging (remediation) treatments, faulty passivation treatments, etc., making the base material susceptible to corrosive processes, and possibly, prompting the appearance of rouge.

Rouge – What It Is Not?

Rouge is not corrosion; it is the observed evidence of it. "Corrosion" is the chemical or electrochemical interaction between a metal and its environment, which results in undesirable changes in the properties of the metal.

As mentioned in the Introduction to this article, it is very important to remember that corrosion resistance is one of the main reasons why austenitic stainless steels are used in the life sciences systems. If corrosion may be a threat at all to any system, it is a matter of technical responsibility to choose the appropriate material at the design stages of that system.

Classification of corrosion is based on the appearance of the corroded metal and the specific cause for its presence, which can be either a chemical dissolution of the metal or an electrically (galvanic) driven process. Additionally, whether the corrosion is derived from an active oxide layer metal, such as iron, zinc, aluminum, and copper (anodic or least noble end in the galvanic series of metals and alloys), or a passive oxide layer metal, such as stainless steel, titanium, gold, and silver (cathodic or noble end in the galvanic series) should be considered.

Following are the most commonly recognized corrosion types:

- *General or Uniform Corrosion – the relatively uniform reduction of thickness across the entire surface of a corroding material*. It is expressed as "rate" measured in mm/year or mils/year. Uniform corrosion can occur from an overall breakdown of the passive layer (see passive layer and passivation); the "rate" of corrosion is influenced by material composition, fluid concentration, temperature, velocity, and stresses in the metal surfaces subjected to attack.

- *Galvanic Corrosion* – sometimes called *dissimilar metal corrosion, galvanic corrosion is an electrically driven process by which the materials in contact with each other oxidize or corrode*. There are three conditions that must exist for galvanic corrosion to occur:
  - The presence of two electromechanically dissimilar metals
  - An electrically conductive path between the two metals
  - A conductive path for the metal ions to move from the more anodic metal to the more cathodic metal.

If any of these three conditions does not exist, galvanic corrosion will not occur.

- *Crevice Corrosion* – considered a form of galvanic corrosion, crevice corrosion is *a localized corrosion of a metal surface at or immediately adjacent to an area that is shielded from full exposure to the environment because of close proximity between the metal and the surface of another material*. To function as a corrosion site, a crevice has to be of sufficient width to permit entry of the corrodent, but sufficiently narrow to ensure the corrodent remains stagnant.

- *Pitting Corrosion* – is another form of galvanic corrosion and *is an extremely localized type leading to the creation of small pits or holes at the surface of the metal*. Pitting corrosion is the most common failure mode for austenitic stainless steels. For specific acceptance criteria of pits in the surface of stainless steel components utilized in the life sciences industry, refer to the *ASME Bioprocessing Equipment (BPE) International Standard*.

- *Stress-Corrosion Cracking* – a type of corrosion that *occurs because of sudden failure of normally ductile metals subjected to a constant tensile stress in a corrosive environment, particularly at elevated temperatures*. Particular austenitic stainless steels alloys crack in the presence of chlorides, which limit their usefulness for being in contact with solutions (including water) with greater than a few ppm content of chlorides at temperatures above 50ºC (122ºF).

- *Intergranular Corrosion – a form of relatively rapid and localized corrosion associated with a defective microstructure known as carbide precipitation*. When austenitic stainless steels have been exposed to high temperatures and allowed to cool at a relatively slow rate, such as occurs after welding, the chromium and carbon in the steel combine to form chromium carbide particles along the grain boundaries; the formation of these carbide particles depletes the surrounding metal of chromium and reduces its corrosion resistance, allowing preferential corrosion along the grain boundaries. Steel in this condition is referred to as "sensitized."

The solution to corrosion problems can often be obtained through careful observation of corroded test specimens or failed equipment. For more information, refer to the *ASME BPE International Standard,* Nonmandatory Appendix F, "Corrosion Testing."

Rouge Composition and Classification

The following discussion will look at the raw materials of rouge, which are iron and oxygen. Iron is the major element (approximately 60% to 63%) found in the composition of 316L stainless steel throughout the various applicable standards or specifications (tubing has been chosen as the example for this article), while oxygen is present in all aerated fluids, water, and steam. Not all rouge being equal in composition, a general identification/classification has been adopted as follows:

- Iron oxide or ferrous oxide (FeO) has been identified as being the most prevalent among other oxides and hydroxides found in the *migratory rouge (Class I* rouge).
- Iron oxide or ferric oxide (hematite) (Fe_2O_3) has been identified as the most prevalent agent in *in-situ oxidation of non-passive surfaces (Class II* rouge).
- Iron sesquioxide (Fe_3O_4), an extremely stable form of magnetite that initiates as a stable surface oxidation film and that is rarely particulate in nature, has been identified as *black oxide produced by hot-oxidation (Class III* rouge).

It must be understood that the existing rouge classification (Class I, Class II, and Class III) is not an industry regulatory standard, but rather a valuable practice adopted by the industry at large, and based on analytical observations and technical processes originally presented in October, 1999 at the Validation Council, a Division of the Institute for International Research, New York, NY.[1]

Rouge and the Key Role of Chromium

To fully understand the interaction between 316L stainless steel and biopharmaceutical processes, it also is necessary to learn about the other two major elements in 316L stainless steel. They are:

- Chromium (approximately 16% to 20% depending on technical organization standard/specification) which gives the stainless steel its corrosion resistance and participates in the formation of a complex chromium oxide layer known as the "*passive layer*" – not "passive film" – on the surface of the alloy.

- Nickel (approximately 10% to 15% depending on technical organization standard/specification) stabilizes the austenitic structure so the alloy is non-magnetic and ductile over a wide range of temperatures.

The balance of elements that are part of the 316L stainless steel base material include molybdenum, manganese, silicon, phosphorus, carbon, sulfur, and in some related alloys, nitrogen and copper as seen in Table A.

Passive Layer and Passivation

The forming of the passive layer is a naturally occurring phenomenon when the surface of stainless steel is exposed to air, aerated water, or any oxidizing atmosphere.

The mentioned natural process is known as "*oxidation*," which is a common form of electrochemical reaction where one element yields an electron, while at the same time, another substance absorbs an electron; the complete process constitutes a "redox" reaction, which in this case, is the combining of oxygen with various elements and compounds in metals or alloys in interaction with their environment, such as exposure or use.

Once the layer has formed, the metal surface becomes "*passivated*" and the oxidation process will slow down to inconsequential limits. This layer consists primarily of chromium oxide, a mixture of iron oxides and iron hydroxides, and small quantities of nickel hydroxides; its precise thickness and constitution cannot, generally, be predicted or calculated. However, this chromium rich layer being the key defense or barrier against corrosion for the base metal, and considering its extreme thinness (normally measured in Angstroms) and relative fragility, is not impregnable; airborne impurities, high temperatures, lack of oxygen, surface conditions, and other direct contact materials can compromise its integrity causing the material to lose its ability to ward off corrosive processes.

Element	ASTM A 270	DIN 17457	BS316S12	EN DIN 1.4404	EN DIN 1.4435
C	0.035 max.	0.03 max.	0.03 max.	0.03 max.	0.03 max.
Cr	16.0 – 20.0	16.5 – 18.0	16.5 – 18.5	16.5 – 18.5	17.0 – 19.0
Mn	2.0 max	2.0 max	0.50 – 2.0 max.	2.0 max	2.0 max
Mo	2.0 – 3.0	2.5 – 3.0	2.25 – 3.00	2.0 – 2.5	2.5 – 3.0
Ni	10.0 – 14.0	12.5 – 15.0	11.0 – 14.0	10.0 – 13.0	12.5 – 15.0
P	0.045 max.	0.04 max.	0.045 max.	0.045 max.	0.045 max.
Si	1.0 max.	0.75 max.	0.20 – 1.0 max.	1.0 max.	1.0 max.
S	0.005 – 0.017	0.03 max.	0.03 max.	0.015 max.	0.015 max.
N				0.11 max.	0.11 max.
Fe	Balance	Balance	Balance	Balance	Balance

Table A. 316L Stainless Steel tubing chemical composition – comparison.

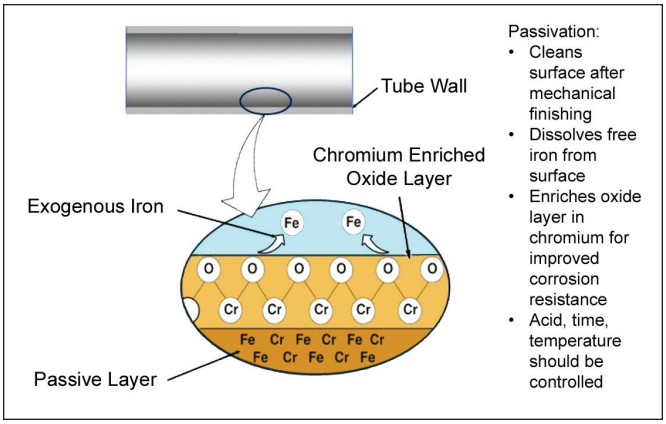

Figure 1. Passivation – how it works.

In a process system, the passive layer is the product of the interaction between the stainless steel basic material and the corresponding flowing solutions. A well passivated system will show rouge after a time, as the passive layer characteristics will change to the appropriate level resulting from the equilibrium between the flowing product and the corresponding product contact surfaces.

The passive layer may be artificially enriched by a treatment known as "*passivation*" that removes exogenous iron or iron compounds from the surface of stainless steel by means of a chemical dissolution, most typically, an acid solution that will remove the surface contamination and potentially augment the passive layer, but will not affect the base metal itself. Since the top layer of iron is removed, passivation diminishes surface discoloration as shown in Figure 1. The passivation treatments are generally applied after completion of construction/fabrication of new systems or the installation/replacement of new components (tubing/piping, fittings, valves, vessels, etc.) within an existing system; these procedures ensure that all product contact surfaces that may have been disturbed during the course of construction/change functions, are appropriately protected. Some of the most commonly utilized passivation treatments, applied for limited time periods, include the use of specific percentages of nitric acid; phosphoric acid; phosphoric acid blends; citric acid; and chelant systems. Electropolishing processes also provide passivating results. For more information, refer to the *ASME BPE International Standard*, Nonmandatory Appendix E, "Passivation Procedure Qualification."

The passive layer is mainly characterized by the chromium/iron ratio in the passive layer, which is often given as a measure of corrosion resistance; in the biopharmaceutical industry, the Cr/Fe acceptance criteria regardless of test method should be 1.0 or greater.

Rouge – Is It Acceptable, Unacceptable?

Rouge is "the" *intrinsic* phenomenon in 316L stainless steel. When visually detected, rouge may be considered unsightly, and because the alloy's qualification of being "stainless," there is the logical expectation for it not to be there at all. Consequently, it is somewhat understandable the frequent reactive, rather than proactive approach of addressing the issue of its presence in any part of a processing system, by the application of treatments that are supposed to eliminate it; unfortunately, the results are always only temporary in nature. The inescapable reality is, that considering the stainless steel composition, which includes mostly iron, the presence of rouge cannot be completely avoided in this extremely popular material; rouge will always be apparent on any product contact surface under processing conditions, and more so when operating at high temperatures.

If the presence of rouge is completely unacceptable in any process product contact surface, the alloy should be replaced by one that contains no iron or very low amounts of it.

Rouge and the Industry Opinion – A Survey

In May 2009, the ISPE Critical Utilities (CU) Community of Practice (COP) conducted a 20 question survey that revealed that although the biopharmaceutical industry has well established practices and procedures to address facilities engineering design, construction, operation, and maintenance, there is still a lot of applied scientific knowledge and disciplines interaction left to be dealt with to fully understand the behavior and utilization of materials that are a key to the functional success of these facilities. Some of the most interesting responses/opinions provided by the participating 200 biopharmaceutical professionals (engineering, Q&A, maintenance, operations) included:

- *Which rouge classification requires priority attention*; the response was somewhat equally divided into, "all rouge is unacceptable regardless of Class" (39.4%), and "rouge regardless of its classification does not require priority attention" (37.1%).
- *For the most part, rouge has not caused product failure, agency citations, or equipment failures*; the response was that rouge had not caused either a product failure, an agency citation, or equipment failures (74.6%).
- *Can rouge management be improved*; the responses were quite revealing and included, "rouge management can be improved by a better understanding of the phenomenon" (59.6%), and "by standardized industry practices" (41.4%); some additional overlapping opinions included, "with on-line detection instrumentation" (7.6%), or "all of the above" (30.3%).
- *Rouge management…*;"is a growing concern and strategies are being generated" (31.2%), "we are aware of issues, but with no plans to change practices" (30.2%), "we are waiting for guidance to be published" (25.7%), "we are aggressively and actively managing it" (24.8%), and "rouge management is not a concern" (6.9%).

Based on these survey results, some clear messages emerge; most facility engineering personnel, including those that find the presence of rouge unacceptable in their operating systems, have not had product or equipment failures, or more critically, any regulatory agency citation; in contrast, there is the expressed opinion that better understanding of system management is strongly needed, together with industry stan-

dardization of methods and means, including detection and analytical problem solving rather than random approaches for elimination of a phenomenon that cannot be separated from the nature of the material widely utilized in the construction of drug products/devices manufacturing systems.

Rouge and Regulatory Stances

Although the presence of rouge on any biopharmaceutical manufacturing system and its possible impact on surface finishes/cleanability in high purity water, pure/clean steam and other process systems fabricated with 316L stainless steel, has been known to be questioned by regulators during numerous facility inspections, there are no existing governmental guidelines or regulations dealing with its existence or the need or frequency to eliminate it when detected. At the writing of this article, the known stances of existing regulatory agencies are:

- The US Food and Drug Administration (FDA) has no written position specifically addressing rouge, its existence, prevention, or remediation methods. Their criterion is to meet established standards of quality for those systems, 21CFR, Chapter I, Part 211, Subpart D, Sections 211.65(a) equipment construction, and 211.67(a) equipment cleaning and maintenance.
- The United States Pharmacopeia (USP) covers the quality of pharmaceutical waters that are used, not the systems that deliver them; rouge is a matter that relates to material selection for those systems.

  Owner/user should decide if the water quality obtained from a system that shows rouge is still compliant with the USP as well as with internal requirements for the process.
- The European Pharmacopoeia (EP) monographs do not address rouge or give any guidance in the matter; however, the European Medicines Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), offers a document that can be applied as a guide for risk assessment on heavy metals in product streams, the "Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents" – February 2008.

Systems Inspections and Repercussions

Routine internal system inspections performed by owner/user or other related personnel trained in the assessment of rouge, frequently may classify its presence, albeit only in those locations where visual inspection is possible, by color and adherence to the surface, by physical traits such as pitting, or by analytical laboratory testing.

Regulatory facility inspections rely in part on owner/user generated documentation that may, in some instances, address rouge identification, quantity, and remediation/removal – a.k.a. "*derouging*" – treatments applied to whole systems or specific system components such as vessels, etc. Regulatory bodies, as previously stated do not have specific stances regarding rouge, but their representatives may question the need, purpose, or practicality of any procedure that owner/user may have instituted and formalized in those inspection documents. As a result of the previous statements, a rather significant question arises. Is it possible during a regulatory facility inspection to satisfactorily explain to officials why an issue where they do not offer any related specific set of rules or mandates, is being addressed with complex, non standardized, risky remediation treatments, particularly when there may not be any known negative effects to the quality, identity, safety, or purity of the flowing process product?

Remediation/removal treatments do not provide a permanent solution to the presence of rouge, and they may be potentially detrimental to exposed base metal surfaces when applied with the most aggressive chemicals and the presence of variations in rouge deposits, thus increasing the chances of surface etching and/or erosion. Chemical removal of rouge requires for a system to have the passive layer restored or enhanced with an additional corresponding passivation treatment, commonly referred to as "*re-passivation*" that may involve increased systems downtime and mounting economic concerns. Some critical points to remember: identification, prevention, and remediation treatments of rouge are subjective and not standardized at all.

Rouge Detection and Monitoring

There are various means to detect the existence and/or presence of rouge in a process system; they include highly limited visual examination of product contact surfaces, instrumentation measuring devices for various physical conditions, and analytical methods of process fluid and product contact surfaces. The presence of rouge in a process system cannot be detected using methods involving temperature, flow, pressure, conductivity, or Total Organic Carbon (TOC) measurements.

Let us now look at each one of those detection means:

- *Visual*. It is well known that there are no systems or techniques that would allow complete visual examination of all product contact surfaces in any process system. Since rouge is not corrosion, but the observed evidence of it, we are left facing an almost impossible technical conundrum, not being able to offer proof positive of any active corrosion site that may be the originator of the detected rouge, except where visual inspection may be possible (e.g., interior of vessels, pump impellers, diaphragm valves, etc.) - *Figures 2 and 3*. The fact of not being able to positively identify active corrosion sites becomes the common denominator for all existing detection methods.
- *Instrumentation*. There are various commercially available instruments that monitor rouge presence and rates. They use diverse equipment to either, visually measure the reflection rate of the stainless steel surface and provide alarms when the reflection changes; measure in real time the rouge rate and accumulation (metal loss) over time[2] or by measuring very low corrosion rates in the high resistivity of ultrapure water.
- *Analytical*. The focus on detection and monitoring, however, must be directed to analytical methods which provide specific information that will help support the effort to estimate risk of negative events or potential failures for

Figure 2. Sanitary pump casing and impeller.

a particular process/product; the analysis and estimation of results requires knowledge and experience in the field of material science and should be performed only by a trained expert. Analytical detection techniques establish the barrier properties of the passive layer and identify the presence of rouging through:

- *Process fluid analysis (non-invasive techniques)* which provides identification of mobile constituents [normally, concentration of heavy metals (Fe, Cr, Ni, Mo, etc.) and other possible inorganic particulates] within a subject system and represents the current quality status of the media, and the result of rouging. Fluid analyses require the periodic collection of representative samples from various major locations throughout a given system.
- *Solid product contact surface analysis (invasive techniques)* which provides information on the nature, microstructure, and composition of surface layers and may represent the future status of the media, and the possible threat of rouging to the media quality. Surface analyses require the periodic removal of a representative fixed surface medium (such as a sacrificial spool or test coupon) for visual and destructive analysis of the surface.

Figure 3. Vessel interior showing also a spray ball (Note differences in colors/rouge).

The methods described above may help detect and analyze rouge; however, they only provide information about the rouge itself, and cannot help to make the decision of whether any remediation treatment may be required. For example, an electron microscope picture of rouge may show a very detailed surface with rouge on it, but does not answer questions about product quality or whether rouge could be deleterious to the flowing product and by association, if it may be a threat to human or animal life. Surface analysis may provide a better understanding of what is happening, but the liquid analysis provides more valuable information about product quality.

Owner/user should establish a unique baseline level of acceptance for particulates and metal oxides, based on a risk assessment analyses that should include:

- Potential damage to the individual process/product
- Consideration of remediation procedures based on an observed and quantified escalating level of particulates and surface accumulation of those oxides
- The event (e.g., particles of rouge may end up in the final product)
- The effect of failure (e.g., negative effects of rouge particles on patients are to be expected).

Risk Control should describe actions to be taken and/or risk reduction strategies (e.g., calculate the amount of rouge from process media that can contaminate the final product and compare with limits set for heavy metals such as Fe, Cr, Ni, Mo, etc.).

Rouge – Is Removal a Solution?

Rouge presence may be slight and uniformly distributed or more concentrated or localized; in both cases its appearance is normally judged to be not esthetically pleasing on any product contact surface that it is supposed to be stain free (clean/shiny) as the name of this family of alloys indicate. As stated previously in this article, there is a common, visually influenced, reactive approach that ends-up utilizing treatments that are supposed to eliminate rouge although only temporarily.

A few questions are commonly asked when referring to the previous situation. The most notable, is it necessary to eliminate rouge every time it shows up in a process system? The answer is a clear and concise "no." The common belief is that rouge may create long term damage to the stainless steel that could result in catastrophic system failures if not remediated; the author of this article does not have supporting or contradicting evidence regarding this belief, but after spending more than 30 years of her professional life dealing with technical issues regarding biopharmaceutical facilities, she has never heard about or witnessed any such drastic failure.

With one major question answered, more questions of no lesser importance require appropriate thought and practical responses; some of these questions and answers may have already been discussed throughout this article, and they may include:

- What if it has been established that the presence of rouge is absolutely unacceptable on any stainless steel product contact surface? In this case, and without hesitation, the alloy should be replaced by one that contains no iron or very, very low amounts of it.
- Is rouge actual corrosion? No, rouge is not corrosion, but rather an observed evidence of its existence.
- Can rouge be removed from product contact surfaces? Yes. Although remediation methods do not provide a permanent solution to the presence of rouge, there are multiple available methods to remove specific rouge (Classes I, II, and III) from the process contact surface of the various biopharmaceutical process systems; they are designed to accomplish their mission by removing iron oxide and other surface constituents of rouge.
- Does rouge remediation treat the cause or source of rouge? No, rouge remediation treatments normally deal with the symptoms and not the cause or source, and should only be considered as part of a well designed monitoring system that should include individual process fluid and product contact surface analysis.
- Can rouge indicate the type of corrosion that may have originated it, its amount, or location of origin? No. In most cases, rouge does neither provide a clue to the type of corrosion that may have originated it, nor its amount or point of origin.
- Do removal processes guarantee that rouge will not re-occur? The answer is a resounding no. There is no chemical or mechanical procedure that can guarantee that rouge after its removal from a product contact surface, will not reappear.
- Can the presence of rouge be minimized? Yes, rouge presence can be minimized, but only with one critical caveat, it will sooner or later reappear if exposed to similar pre-existing conditions.
- Are there any specific stainless steel product contact surfaces where rouge may not appear? No, rouge will always appear on any stainless steel product contact surface under processing conditions, particularly, when operating at high temperatures.
- Are there industry or governmental standards/regulations addressing rouge removal? No, rouge remediation/removal treatments are subjective and not regulated or standardized at all.

Application of remediation techniques must be the result of a rigorous Quality Assurance (QA) procedure that will provide indication of significant impact on the quality or safety of the flowing product. Once rouge has been found, it is difficult and expensive to remove it; its progress may be temporarily slowed or perceptively eliminated by the application of "derouging" processes, but because the major element found in 316L stainless steel, iron, it will always reappear.

Rouge Management, the Rational Solution

The preeminent concern of the biopharmaceutical industry regarding the rational solution to rouge, should be to adopt sensible management processes of this unavoidable phenomenon, rather than to continue with the indiscriminate application of remediation treatments that may utilize subjective and sometimes confusing procedures with less than uniform and reassuring results. Corrosion (cause) is not a good thing, and as we have already seen, rouge (result) is the observed evidence of it; however, the pinpoint localization of active corrosion sites in any system becomes a rather futile enterprise because of the inherent difficulty of visually examining every single product contact surface in a system. Remediation should not be considered a forbidden treatment, but rather a sensibly applied solution, when and if, localized corrosion sites are positively identified in a process system. Find the cause, and the result would become a lot easier to deal with.

There is an increasing need for the global biopharmaceutical industry to respond with analytical approaches to the challenging subject of rouge management. To help accomplish this end, ISPE has just published a valuable source of positive information and technical suggestions (not regulations, standards, or regulatory guideline documents) contained in Chapter 10 – *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 4 – Water and Steam Systems, Second Edition, December 2011*. Some of the information provided includes:

- Analytical methods for identification of mobile constituents of rouge and surface layers composition, including type of tests, tests descriptions, and pros/cons test criteria.
- An example for a risk-based approach to rouge and its remediation measures.
- Risk analysis of possible events, and effects of failure and risk control actions for risk reduction strategies.
- Rouge remediation methodology including examples of available chemicals to conduct remediation treatment on the different rouge Classes.

Additionally, and thanks to the solid cooperation and coordination of volunteers closely associated with both ISPE and ASME, additional and/or complementary technical information has been provided; this information is contained in the 2009 Revision of the *ASME BPE International Standard*, Nonmandatory Appendices D, E, and F.

Rouge Remediation – When Needed

Rouge remediation may in some instances be necessary, but only after careful weighing of acceptable options that may include:

- Upon discovery of rouge on any process system, proper analysis and categorization should take place, and based on evidence of potential active corrosion sites where base metal may have been compromised, then perhaps consider the application of localized remediation/removal treatments, despite knowing that rouge will soon reappear if the product contact surface is exposed to similar pre-existing conditions.
- With the understanding that usually, different chemical solutions as utilized in remediation treatments, may react

quite differently in contact with potentially diverse factors, such as the various classes of rouge that may be encountered in any given system; the status of product contact surfaces throughout a system; the different composition/quality of materials that may have been used for each component; the length of time those various system components may have been in service, etc., the application of remediation treatments to large or small process systems, should always first consider conducting a thorough risk-based analysis of both, flowing products and corresponding product contact surfaces.

- Rouge should be preferably monitored and then if proven to have a negative influence on the product quality, consider using an alternate metallic or polymeric material.
- As the last and hopefully the most acceptable alternative, consider "learn to live with it safely" by establishing a program of internal monitoring and analysis of individual critical systems, and only when deviating from scientifically and unique proprietarily established baselines, both in process fluid analysis of mobile constituents and/or solid surface analysis (see Rouge Detection), consider the application of a pertinent remediation treatment to manage its presence. For more information on methods to remediate the presence of rouge in a system, refer to the *ASME BPE International Standard*, Nonmandatory Appendix D, "Rouge and Stainless Steel."

Conclusion

Concern should always be focused on whether the presence of rouge may be detrimental to the pharmaceutical water systems or the drug products to such extent that it may pose dangerous or even fatal results in humans and animals, rather than the repercussions it may present on capital equipment protection. Health and life of patients must be preeminent in all considerations that apply to the fabrication, erection, and maintenance of facilities dedicated to the biopharmaceutical industry. Rouge may not be esthetically pleasing, but it is a reality resulting from the utilization of a material that not only has iron as its main and "intrinsic" element, but that also is never chemically identical in all its forms, and it is exposed to a very complex set of processes and chemical, mechanical, and electromechanical influences.

It is suggested, that in addition to improved facilities planning, engineering design, and utilization of materials, a potential avenue for resolution of concerns presented by rouge in the life sciences industry facilities, should be the close and permanent association of owner/user's QA personnel in their Research & Development (R&D) divisions, and the QA personnel in their engineering production and facility maintenance groups. The first group would provide the scientific data regarding possible deleterious effects of rouge or any other oxide or metallic trace material (iron, chromium, nickel, molybdenum, etc.) on the safety of the flowing products; the second group should concentrate in the selection of appropriate construction materials and methods to ensure that parameters for the safe production of drug products is maintained at all times.

We must endeavor to improve our understanding of the rouge phenomenon and establish standards and practices that would simplify the various approaches and perceived solutions for addressing the rather controversial presence of rouge in process/utilities systems utilized in the biopharmaceutical industry.

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Applying a Synergetic Approach to Improve Equipment Uptime

by Kevin Pait and Preston Ingalls

This article presents an effective approach of using cross-functional teams to identify and reduce recurring failures through a systematic approach called Total Process Reliability (ToPR) netting a 90% costs savings for the plant.

The Company

Grifols Therapeutics Inc (formerly known as Talecris Biotherapeutics, Inc.) is a wholly-owned subsidiary of Grifols Inc, a subsidiary of Grifols S.A., a Spanish company based in Barcelona, Spain. Grifols S.A. is a global healthcare company and leading producer of life-saving plasma protein therapies. Grifols Therapeutics manufacturing facility is located in Clayton, North Carolina. This is a case study of a reliability improvement process put into effect at the Clayton facility with a focus on the centrifuges used in Grifols' fractionation process.

Addressing Maintenance Costs: Initial Steps

In late 2006, driven by the need to reduce high maintenance costs and increase machinery uptime, senior management at the Clayton plant decided to implement Total Process Reliability (ToPR). ToPR is a reliability process centered on proactive maintenance rather than reactive maintenance with the goal of reducing operating costs and increasing productivity of machines.

The success of ToPR, pronounced "topper" by the Clayton team, is dependent on the commitment of senior management, and so the initial ToPR program implementation began with the education of those key individuals. In addition to providing ToPR training, primary steps included baseline studies, which provided solid evidence for improvement opportunities. In order to attack high maintenance costs, Grifols also needed to identify critical equipment and problems associated with critical equipment. Through this critical equipment analysis, the centrifuges were identified as the highest cost area in the plant, averaging more than one million dollars a year for repair and maintenance. The centrifuges separate plasma into fractions that are then used in a variety of biotherapeutic products, and therefore, the equipment failure poses a threat to production rates.

Equipment Improvement Teams and M.O.R.E.

Once the centrifuges were identified as critical equipment, Grifols could develop a ToPR plan focused on improvement. According to Kevin Pait, Director of Plant Engineering and Maintenance, "we started out forming cross functional teams," referred to in the ToPR program as Equipment Improvement Teams (EITs). Composed of employees from maintenance, engineering, and production, the EITs took a centrifuge apart and then put it back together with the goal of fully understanding the machine's assembly and functionality. Senior Manufacturing Supervisor of Fractionation, Joey Hamer, said this step "taught his crew how the machine ran from top to bottom." While the initial EIT effort was important because, according to Pait, "it helped employees appreciate each other's roles and responsibilities at work," Grifols did not see desired results with the EIT approach. After rethinking their approach, management decided to form another team that would still be cross functional, but with a stronger technical base. "We had different groups all working independently trying to make a difference," said Kirk Parish, Manager of Maintenance Systems. "All these efforts existed as silos. We put all these silos together." The new team was named after the different departments represented: Maintenance, Operations, Reliability, and Engineering (M.O.R.E). The M.O.R.E. team discussed current challenges and brought forth improvement methodologies in hopes of

achieving the team's goal to cut 20% from the previous year's maintenance cost.

Identifying Root Causes

The M.O.R.E. team acknowledged that some critical variables in the machines were not known or understood, which made it difficult to identify true causes of maintenance and operation problems. Ingrained individual opinions about what leads to a centrifuge failure and a lack of data to support assertions further complicated the problem. Mike Cook, Manager of Maintenance and Reliability, said the predicament "just went around in a circle." Grifols needed to identify the root causes of failures and quantify these causes with engineering studies.

In order to objectively identify the sources of centrifuge breakdown, employees developed a cause map, which is a root cause analysis tool that starts with an event and works backward to uncover the causes of that event. "This makes you think sequentially," explained Pait, and allows for the removal of opinion through testing for true root causes. Each possible cause of failure was tested, enabling true causes to be validated with plant studies, extensive experiments, and vibration analysis. According to Hamer, vibration was the issue leading to breakdown, and so, using precision lasers, the Grifols team established a baseline vibration measurement of when the machines were functioning correctly. During the vibration analysis, the team also induced a variety of problems identified by the cause map. This allowed for vibration measurement, providing empirical proof of what led to failure. Internal bowl vibration creates additional bushing wear, spindle wear, and ultimately leads to failure as illustrated in Figure 1.

During the ToPR efforts, the team also utilized the Pareto Principle, which states, simply, that most problems are caused by a few key factors. According to this principle, if Grifols could identify these few key problem-causing factors, they should be able to eliminate (or at least drastically reduce) the rate of centrifuge failure. With this in mind, the ToPR team lined up all the factors that contributed to failure in order to identify items of "high probability and high consequence."

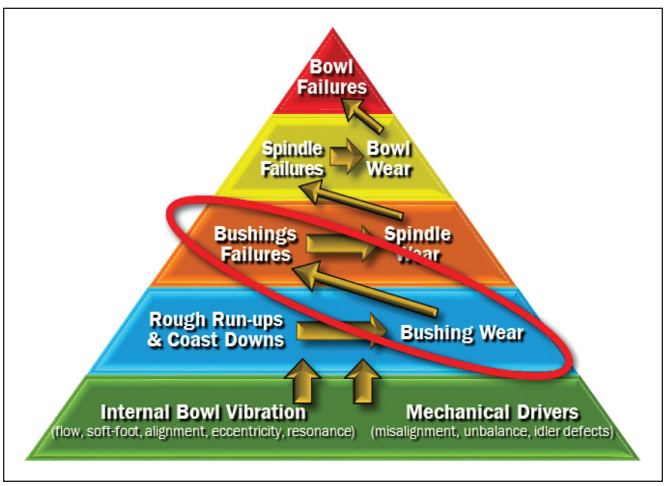

Figure 1.Failure mode progression.

One problem of "high probability and high consequence" identified by the Pareto analysis pertained to the clearance between a centrifuge's boss and bushing. As parts wear down, this clearance becomes larger and the vibrations of the machine increase. "If you get off center at the bottom," Hamer explained, "it translates into a lot of whip up top and will cause the spindle to break, leading to a dramatic crash."

> "We had different groups all working independently trying to make a difference..."

Another high risk item for the centrifuges is an improper soft foot, which often results from multiple failures that shake the machines' bases. Soft foot is a condition whereby inadequate surface contact is made between the underside of the centrifuge housing support legs and the foundation baseplate. Soft foot that is off by even a fraction of an inch can increase vibration, leading to machine failure. Correcting this high risk issue through precision maintenance was important to decreasing the number of centrifuge failures. As shown in Figure 2, the majority of the problems were due to bushing wear and soft foot.

One of the main parts of a centrifuge is the bowl where the plasma products collect during fractionation. High costs for bowl repairs contributed to the high cost of maintaining the centrifuges. In response to this issue, the maintenance department initiated an in-house bowl repair program. Prior to this initiative, bowls were always sent to the supplier for repair, but the maintenance department realized many of the bowls could be repaired at the Clayton facility. The team also discovered the bowls have a tolerance range, and as long as

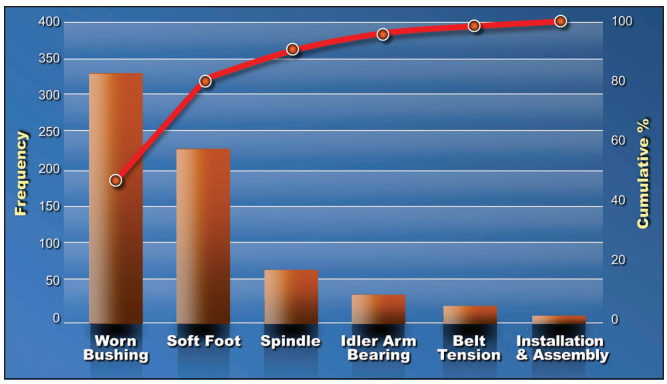

Figure 2. Pareto analysis.

the bowls fell within this tolerance range, the machines could still function. Only when the bowls exceeded this tolerance range, did they need to be completely replaced.

The cause map and Pareto analysis also identified the centrifuge's idler arm as an item of high consequence whose malfunction can lead to failure. The idler arm is a tensioning device that applies force to the belt section running from the centrifuge to the motor. This helps to ensure the centrifuge runs smoothly without belt slippage when rotating. According to Cook, if the idler has a bearing defect or if the bearing becomes egg-shaped, that is a problem starter. The centrifuge bowl then begins to shake, putting excess stress on the spindle, eventually leading to failure.

> "...builds a bridge with maintenance, operations, and engineering."

Proactive Solutions

By isolating a list of high risk occurrences that result in centrifuge breakdown, and focusing on these problems, rather than low risk issues, Grifols was able to come up with proactive solutions. A key ingredient to the ToPR program is predictive and preventative maintenance rather than reactive maintenance. The goal is to find a problem before it's too late. With this in mind, Grifols implemented the use of a go/no go gauge on the centrifuges in order to address the bushing clearance issue. Using the go/no go gauge, operators can measure the wear on the inner diameter of the bushing. When the gauge sinks too far into the bushing, it is time for the bushing to be replaced. By replacing the bushing before the clearance between the boss and the bushing becomes too high, Grifols greatly decreased the failure rates. Another predictive maintenance initiative focuses on the idler arms. With routine checks of the idler arms' tension, more failures were prevented. As mentioned above in regard to the bowl repairs, the Grifols team also created "documented tolerances." A part that drops below its documented tolerance is likely to start a problem, so the goal is to remove any parts before they drop below these measurements. In addition to the in-house bowl refurbishment program, maintenance also developed a Centrifuge Failure Tracking Book. Maintenance uses this manual tracking method in conjunction with computerized maintenance management software to trend repeat failures. The identification of failure trends helped to greatly lower failure reoccurrences. With fewer multiple failures and the use of predictive maintenance, the issue of improper soft foot dramatically decreased as well.

In order for ToPR to succeed, team members need to put forth a consistent effort toward the end goal. To establish a consistency in maintenance, Grifols developed best practices for centrifuge assembly and disassembly as well as job aids. Job aids are uniform checklists that ensure everyone is maintaining the centrifuges in the same way. Pait refers to these job aids as "enabling tools for employees" because with the job aids, as Pait explains, "you are setting people up for success."

Two additional solutions that resulted from the ToPR effort were the introduction of a spindle nut torque wrench and a Centrifuge Process Manual. Of the centrifuges, Hamer says, "We had some improper couplings and un-couplings. We needed a torque value to make sure the coupling is done correctly." The introduction of the torque wrench eliminated potential for operator-induced failures. The Centrifuge Process Manual was created by a ToPR focus group to help employees learn, in depth, about the centrifuges. An instructor's version of the manual allows trainers to guide employees through the learning process. Employee technical training is a key element in the ToPR program.

Through use of the ToPR program, the cross-departmental team was able to systematically identify the root cause of each failure. These failures were mitigated with enhancement of the technical training program, implementation of various operational and maintenance tasks, and implementation of additional preventative maintenance tasks. The ToPR program results are summarized in Table A.

Symptom	Root Cause	Solution	Cost Reduction
Excessive Vibration and Spindle Wear	Worn Bushing	Operations PM	81%
	Soft foot	Maintenance PM	
	Idler Arm Bearing	Maintenance PM	
Vibration	Belt Tension	Maintenance PM	5%
Premature Bushing Failures	Installation and Assembly	Employee Technical Training and Job Aids	4%

Table A. ToPR program results.

Conclusion

The final results of the Grifols' ToPR journey can be declared a great success. Financially, as illustrated in Figure 3, the company saw a 90% reduction in centrifuge maintenance costs, thus diminishing what had been the highest maintenance cost in the Clayton facility. By proactively managing high risk issues, the team increased machine uptime, thereby increasing plant productivity. And finally, the ToPR efforts led to a development of partnerships across plant departments. As a major driving force behind ToPR, Hamer said the effort "builds a bridge with maintenance, operations, and engineering."

Kevin Pait summarized the accomplishments. "We have come a long way over the last four years in increasing reliability and we are moving from good to great. We were able to solve a rather multifaceted and complex issue. By applying

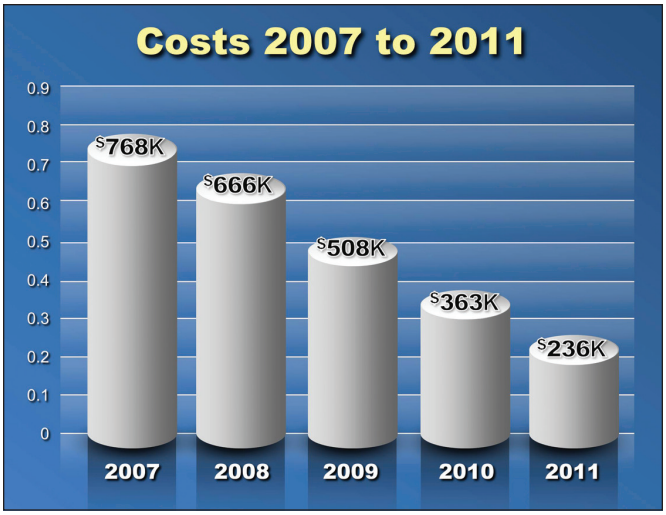

Figure 3. Historical maintenance costs.

the focused team approach of total process reliability, issues that have plagued this equipment for years were resolved. Simply put, if two heads are better than one, we proved more is better than two."

About the Authors

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Overcoming the Challenge of Poor Drug Solubility

by Mitali Kakran, Professor Lin Li, and Professor Dr. Rainer H. Müller

Problem

Recent drug discovery has led to an increasing number of new drugs with low water solubility and hence poor bioavailability, especially via oral administration.[1] The number of such drug candidates has increased enormously and almost 70% of the new drug candidates have shown poor aqueous solubility in the recent years.[2] Since approximately 65% of the human body is made up of water, a drug must have certain water solubility and possess an acceptable bioavailability level. Poorly water soluble drugs tend to be eliminated from the gastrointestinal tract before they get the opportunity to fully dissolve and be absorbed into the blood circulation. This results in low bioavailability and poor dose proportionality, which greatly hinders their clinical translations.[3] In such cases, dose augmentation would be necessary to ensure that the drug attains the therapeutic concentration range in blood. After oral administration, this dose augmentation at times causes topical toxicity in the gastrointestinal tract and such toxicity results in a decline in patient compliance.[4] On the other hand, consuming a large amount of Active Pharmaceutical Ingredient (API) would raise the manufacturing cost of developing and manufacturing the drug product. In short, these poorly water soluble drugs show a number of negative clinical effects including potentially serious issues of inter-patient variability, higher patient costs, inefficient treatment, and more importantly, increased risks of toxicity or even death.

In the drug discovery stage, a number of *in-vitro* assays are conducted to evaluate several biological properties such as efficacy, membrane permeation properties, and genotoxicity. The performance of such poorly water soluble new drug candidates also might be affected in these *in-vitro* cell culture assays because the solubility constraint or precipitation of the drug in the test medium may give inaccurate data regarding the drug properties. In preclinical development, the data quality of the *in-vivo* toxicity assessments also could be degraded since toxicological studies usually require higher exposure than that in pharmacological or pharmacokinetic studies to assure its safety. Overall, the poor bioavailability of a drug substance might result in limited therapeutic potential for clinical use, thereby leading to insufficient clinical outcomes. Therefore, poor water solubility of many drugs is one of the major obstacles in the development of highly potent pharmaceutics.

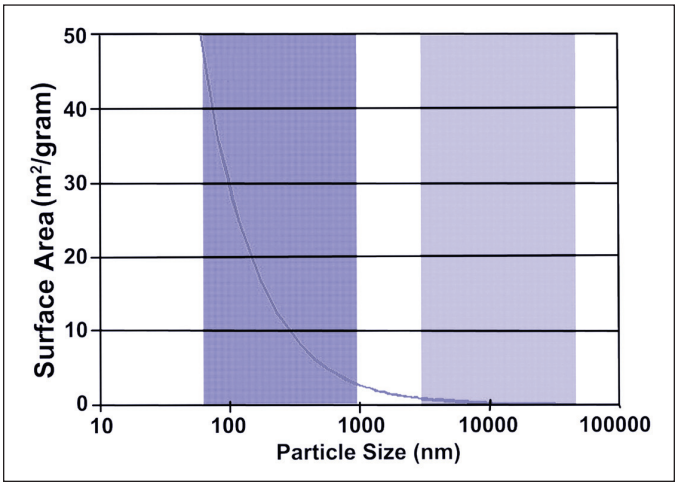

Figure 1. Reducing the particle size leads to an exponential increase in surface area.

Possible Solutions

In contrast to developing completely new drugs, introducing upgraded or advanced formulations greatly reduces the risk, time, and capital invested in drug development. Many approaches have been developed to enhance the dissolution rate as well as bioavailability of poorly water soluble drugs, including both

modifications to the drug substance itself and the creation of specific formulations. Physical modifications often aim to increase the surface area, solubility, and wettability of the drug particles and typically focus on particle size reduction[5,6] or generation of amorphous particle states.[7,8]

Drug Nanoparticles

A classical formulation approach for such poorly soluble drugs is nanonization that means producing drug nanoparticles with mean particle size below 1 µm.[9] The principle is to increase the dissolution velocity by enlarging the surface area of the drug powder. Consideration of the Noyes-Whitney equation provides the insight as to how the dissolution rate of poorly soluble compounds might improve:[10]

$$\frac{dm}{dt} = \frac{DA}{h}(C_s - C_{bulk})$$

where dm/dt is the dissolution rate of drug, D is the diffusion coefficient of drug, A is the surface area of drug, C_s is the saturation concentration of drug, C_{bulk} is the concentration of drug in the bulk, and h is the thickness of the hydrodynamic boundary layer. As shown in Figure 1, the surface area per gram of the drug increases as the size of the drug particles is decreased from bulk to a micro to a nano scale. The very small particle size results in a large surface area (A) and thus in an increased dissolution rate according to the Noyes Whitney equation. Therefore, drug particles in the nanometer size range will dissolve more rapidly than a conventional formulation and result in increased flux across the gut lumen and to the blood.

Nanoparticles exhibit some interesting surface properties due to their very small size. They are able to deliver Active Pharmaceutical Ingredients (APIs) across a number of biological barriers, i.e., the Blood Brain Barrier (BBB), different types of mucosa and epithelia, and cell membranes for transfection applications. They also show excellent adhesion to biological surfaces, such as the epithelial gut wall[11,12] and this bioadhesion increases with decreasing particle size as shown in Figure 2. The adhesive nature of nanoparticles due to increased van der Waals interactions (due to increased contact areas made available by nanoscale particles' surfaces) with the biological membrane/gut wall[9], not only facilitates permeation, but also assists in reducing food effects hence, leading to enhanced bioavailability.[13] In addition, utilization of the dense, solid state confers an additional advantage of higher mass per volume loading. This is crucial when high dosing is required. Fast dissolution of nanoparticles facilitates its use for API where the absorption window is quite narrow, as the drug will dissolve quickly and in doing so avoid unsuitable environment for API absorption or stability. Other related positive factors include dosing and patient-related factors, namely possible dose reduction or escalation; improved dose proportionality and reproducibility; and enhanced dose tolerance, compliance and reduction in food effects and hence improved efficacy and safety.[13] However, as the van der Waals forces become dominant at nano-scale, they cause the drug nanoparticles to agglomerate.

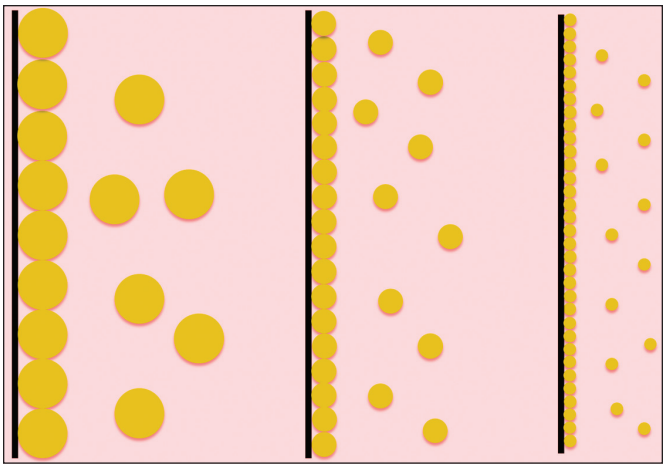

Figure 2. Reducing the particle size leads to greater adhesion to biological surfaces.

Solid Dispersions

Solid dispersions may be defined as the dispersion of one or more active ingredients in molecular and amorphous forms in an inert carrier or matrix in the solid state.[14,15] Dispersing drug nanoparticles in a carrier matrix can prevent aggregation and a fine dispersion will increase the available surface so that wetting and dissolution can occur more rapidly. For formulations targeting dissolution and bioavailability enhancement, solid dispersions often take the form of "solid solutions," where the drug is molecularly dispersed in a hydrophilic polymer. Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size should be reduced to its absolute minimum viz. the molecular dimensions so that the dissolution rate of the drug is determined by the dissolution rate of the carrier. In addition to that, hydrophilic carriers allow a more extensive wetting of the drug particles resulting in the higher solubility and dissolution rate of poorly water soluble drugs. Furthermore, combining the drug with an amorphous carrier can change the degree of crystallinity of the drug. In most cases, the drug is not in the crystalline form, but in the amorphous state and such different solid forms can influence the dissolution, bioavailability, stability, and other drug properties.[16] An amorphous form allows higher solubility and faster dissolution of the drug in comparison to its corresponding crystalline form because of its higher internal energy and greater molecular mobility. Poorly water soluble crystalline drugs, when in the amorphous state, tend to have higher solubility because no energy is required to break up the crystal lattice during the dissolution process. However, as the amorphous phase is metastable compared to the crystalline state, there is some risk that phase transformation (i.e., crystallization) may occur upon storage, limiting their use in pharmaceutical dosage forms. Judicious selection of a carrier to improve the dispersion of drug can lead to stable amorphous formulations.

Present Study

This study focuses on improving the dissolution rate of extremely hydrophobic quercetin (3, 3', 4', 5, 7-pentahydroxyflavone), which is a polyphenolic flavonoid and one of the most prominent dietary antioxidants. Quercetin also has been proven to possess potent chemopreventive and antiproliferative effect and has demonstrated strong inhibition of breast, colon, lung, and ovarian cancer cell growth.[17,18] In spite of this wide spectrum of pharmacological properties, its use in the pharmaceutical field is limited by its low water solubility. Bioavailability of quercetin is shown to be poor and its pharmacological effect is restricted by its poor solubility and fast metabolism. Reducing particle size and creating amorphous states provide a solution to this problem. It is observed from Figure 3a that the original quercetin used in our study exhibited lack of uniformity in size and particles were in the range of 30 to 35 µm. Therefore, efforts have been made to enhance the dissolution rate of quercetin by fabricating its nanoparticles and solid dispersions. There are two main approaches for nanoparticle preparation: top down (break big particles down to nanoscale) and the bottom up (build the nanoparticle from molecular scale building blocks). In the present study, quercetin nanoparticles have been fabricated using the top-down techniques of bead milling and high pressure homogenization; and bottom-up technique of evaporative precipitation of nanosuspension, also has been used to prepare the solid dispersions of quercetin.

Bead Milling

A bead mill consists of a rotating vessel which is partly filled with beads (milling media). The attrition and shear forces generated due to the impaction of the beads with the drug generate sufficiently high energy input to break the drug microparticles into nanoparticles. Aqueous nanosuspensions of quercetin were fabricated by agitating bead mill Bühler PML-2 (Bühler AG, Uzwil, Switzerland) in a continuous mode using yttrium stabilized zirconia milling beads of size 0.4 to 0.6 mm. The smallest average particle size of quercetin nanoparticles obtained after milling the suspension of quercetin containing 5% (w/w) quercetin stabilized with Tween 80 (1% w/w) for 60 minutes was 319 nm[19] as shown in Figure 3b. According to the theory, with a reduction in the size of milling media in a mill, the number of contact points is increased exponentially, resulting in improved grinding and dispersing action and hence, leading to smaller particles. However, in our study, no major difference was observed in the particle size of the quercetin nanosuspensions fabricated using 0.2 mm and 0.4-0.6 mm sized milling beads. Since it is easier to separate the 0.4 to 0.6 mm sized milling beads from the product than the 0.2 mm ones, the 0.4 to 0.6 mm size milling beads were found to be efficient. The market leading technology for the production of drug nanoparticles by wet milling is Elan Corporation's NanoCrystal® technology, which was first developed by Liversidge et al.[20] In 2000, the US FDA approved the first drug Rapamune (sirolimus) that specifically uses nanotechnology to increase solubility.

High Pressure Homogenization

Nanosuspensions of quercetin (5% w/w) in Milli-Q water with Tween 80 as a stabilizer (1% w/w) were produced by LAB 40 (APV Deutschland GmbH, Unna, Germany) using a high pressure piston gap homogenizer. Prior to high pressure homogenization at 1500 bar (20 cycles), the coarse quercetin suspension was pre-milled at increasing pressures (2 cycles at 300 bar, 2 cycles at 500 bar, 1 cycle at 1000 bar) to diminute very large particles in order to prevent blocking of the homogenization gap. In APV LAB 40, the drug suspension, contained in a cylinder of diameter about 3 cm, passes through a very small homogenization gap in the homogenizer having a width of 25 µm under a high pressure (100-2000 bar), which leads to a high streaming velocity. According to the Bernoulli's law, in a closed system, the flow volume of liquid per cross-section is constant, which implies that the reduction in the diameter leads to a tremendous increase in the dynamic pressure (i.e., also streaming velocity), and simultaneously a decrease in the static pressure when the suspension is in the homogenizer gap. When the static pressure falls below the vapor pressure of the water, it starts to boil at room temperature and gas bubbles form, which implode when the suspension leaves the gap and comes under the normal pressure conditions again (cavitation). The formation of gas bubbles and their implosion causes shock waves, whose enormous power along with the turbulent flow and shear forces leads to the diminution of particles of the suspension.[9] The quercetin particle size decreases with increasing number of homogenization cycles. The number of homogenization cycles required is mainly influenced by the hardness of the drug, the finesse of the starting material and the requirements of the application route or the final dosage form.[9] In the case of quercetin nanoparticles, 20 cycles were found to be optimum and the smallest average size obtained for quercetin was 338 nm[19] as seen from Figure 3c. The technology based on high pressure piston gap homogenization of particles in pure water was developed by Müller et al.[21] and later acquired by SkyePharma and has the trade name of DissoCubes™. However, there are no marketed products based on this technology at present.

Evaporative Precipitation of Nanosuspension (EPN)

Quercetin was dissolved in a solvent (ethanol) and then a nanosuspension was formed by quickly adding an antisolvent (hexane). Drug nanoparticles in the nanosuspension were obtained by quick evaporation of the solvent and antisolvent using a rotary evaporator, followed by vacuum drying. The type of antisolvent, drug concentration, and solvent to antisolvent ratio were optimized in order to yield the smallest particles. The morphology and size of the particles changed with the type of antisolvent used. With water as an antisolvent, the particles were big, irregular, and flake type.[22] However, with hexane, the particle morphology was more needle-like with smaller particle size. It was observed that increasing the solvent to antisolvent ratio and decreasing the drug concentration in solvent resulted in lower particle sizes. Drug concentration of 5 mg/ml and the solvent to antisolvent ratio of 1:25 (v/v)

resulted in the smallest particles of size 739 nm[22] as shown in Figure 3d. It should be noted that the amount of the residual solvents (ethanol and hexane) in the samples prepared by EPN was below the acceptable level for residual solvents in pharmaceuticals as determined by FDA for the safety of the patient. Hexane is a Class 2 solvent, whose amount should be limited (290 ppm) and ethanol is a Class 3 solvent, with low toxic potential and minimum amount of 5,000 ppm.[18] For the EPN prepared samples, the amount of hexane was below 125 ppm and ethanol was below 20 ppm as determined by gas chromatography, hence satisfying the FDA criteria. Precipitation techniques are not being used at present to fabricate drug nanoparticles at industrial scale. However, evaporative precipitation of nanosuspension is a simple and cost effective method and can be developed further for large scale production.

Quercetin Solid Dispersions

Solid dispersion of quercetin in polyvinylpyrrolidone (PVP) and Pluronic F127 (F127) also were prepared by evaporative precipitation of nanosuspension. Both quercetin and the carriers were dissolved in ethanol and later the common antisolvent (hexane) was added, followed by quick evaporation and vacuum drying. Quercetin to carrier ratio used was 1:1 (w/w). The 5 mg/ml quercetin concentration in ethanol an ethanol to hexane ratio of 1:25 were used.[22] X-ray diffraction (XRD) was used to study the nature of drug in solid dispersions. The complete absence of any diffraction peak corresponding to the crystalline drug indicates that the drug is no longer present in the crystalline form, but exists in the amorphous state. As seen from Figure 4, the original quercetin have several diffraction peaks suggesting its crystalline nature. PVP is amorphous as indicated by its diffraction spectrum without any prominent peak. On the other hand, F127 is semi-crystalline and exhibits two sharp diffraction peaks at 2θ =19.12° and 23.27° as seen from Figure 4. It can be clearly observed that the quercetin peaks were absent in its dispersion in PVP and F127.[22] In addition to the fact that the drug is present in an amorphous form, the results also suggest that the drug is dispersed at molecular level in the polymer matrix. The presence of a

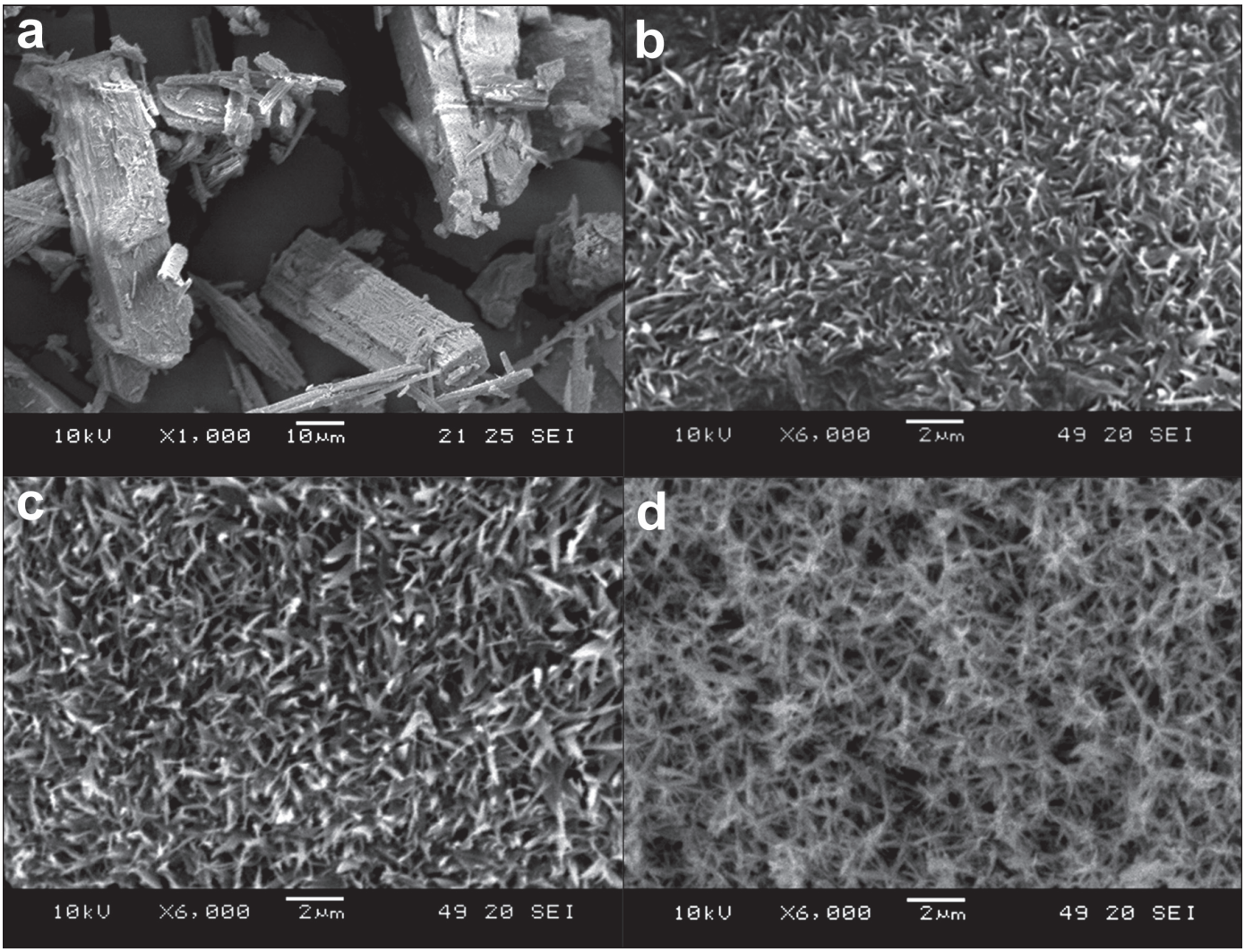

Figure 3. Scanning electron microscopic photographs indicating clear reduction in particle size of quercetin by many folds, (a) original quercetin; and quercetin nanoparticles produced by (b) bead milling, (c) high pressure homogenization and (d) evaporative precipitation of nanosuspension.

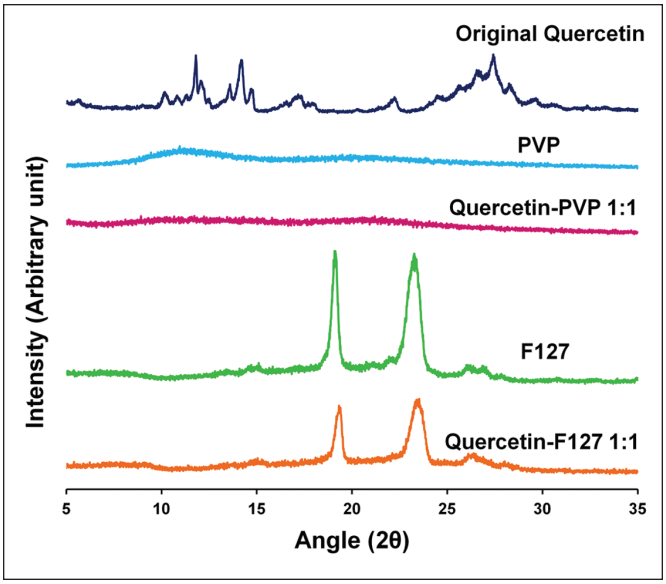

Figure 4. X-ray diffractograms for original quercetin, PVP, F127, quercetin-PVP and quercetin-F127 dispersion at 1:1 ratio.

polymer or polymeric additive has been shown to possess an inhibitory effect on the precipitation and hence, the reduced crystallinity of the resulting drug.

Research on new solid dispersions and the related fabrication processes have been widely reported in the literature during the past several decades. Today a number of solid dispersion products are marketed including: Kaletra® and Norvir® (Abbott), Nimotop® (Bayer), Gris-PEG® (Pedinol), Cesamet® (Meda Pharms), Intelence® (Tibotec), Certican® or Zortress® (Novartis), Isoptin SR-E® (Abbott), Crestor® (Astrazeneca), Nivadil® and Prograf® (Astellas Pharma, Inc.), Rezulin® (Pfizer), Sporanox® (Janssen Pharmaceutic), and Toramat®, Vociflon®, Montelukast®, Palibone®, Iasibon®, Razilan® and Ostiral® all from Pharmathen S.A.

Dissolution Study

The dissolution test was performed using a USP II rotating paddle apparatus with a Pharmatest PTW SIII (Pharma Test, Germany) at 37°C and a rotating speed of 100 rpm in 900 ml of DI water. Quercetin samples containing an equivalent of 5 mg of quercetin were dispersed in the dissolution medium. At certain time points, samples were withdrawn from the dissolution chamber and then filtered and analyzed using high performance liquid chromatography. The dissolution test for each sample was performed in triplicate and the dissolution data was averaged. As seen from the dissolution profile in Figure 5, only about 8% of the original quercetin dissolved within 60 minutes, showing a very poor dissolution rate. On the other hand, all the formulations prepared showed the drastic increase in the dissolution rate. The greatest increase in the dissolution rate is exhibited by the solid dispersion systems. The possible explanation is the reduction in the particle size to molecular level or the generation of an amorphous state (as shown earlier by XRD study). The quercetin nanoparticles presented increasing the order of dissolution rate with decreasing particle size as: evaporative precipitation of nanosuspension < high pressure homogenization ≤ bead milling although there was no significant difference in the dissolution profile of quercetin nanoparticles prepared by high pressure homogenization and bead milling. To sum up, nanosizing and amorphization of quercetin tremendously enhanced its dissolution rate. As a result, the quercetin nanoparticles and solid dispersions prepared are expected to demonstrate a better bioavailability than the original drug powder.

Conclusion

Looking at the average particle size, bead milling produced the smallest particle size, followed by high pressure homogenization, and then evaporative precipitation of nanosuspension. Comparison of the three methods of fabrication showed that each technique had its own advantages and disadvantages. Bead milling has the disadvantage of increased time and costs associated with the separation procedure of the milling material from the drug nanosuspension and the potential erosion from the milling material leading to product contamination. High pressure homogenization is an energy intensive process and the application of such high pressures can affect the large-scale pharmaceutical production. Moreover, when a suspension is produced from these methods an additional drying process is required to obtain the powder form for oral administration. But they have the advantage that the drugs that are poorly water soluble in both aqueous as well as organic media can be easily formulated into nanoparticulate suspensions. On the other hand, evaporative precipitation of nanosuspension is comparatively a cost effective, low energy, and simple process, and no post processing is required, but the drug compound should be soluble in an organic solvent, which should be miscible with an antisolvent. Solid dispersions of quercetin in PVP and F127 also were produced by evaporative precipitation of nanosuspension. Solid dispersions are an excellent alternative and have shown the positive results,

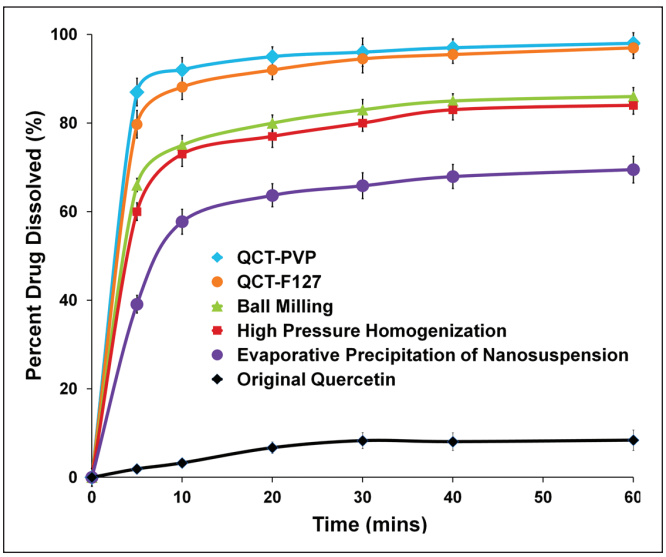

Figure 5. Dissolution profile of original quercetin; quercetin nanoparticles prepared by bead milling, high pressure homogenization and evaporative precipitation of nanosuspension; and quercetin-PVP and quercetin-F127 dispersion at 1:1 ratio.

but there are issues related with the long term stability of the formulations.

In the future there is a lot of potential for the development of the bottom up precipitation techniques for large scale production of drug nanoparticles and further improvement of the milling and homogenization techniques. Solid dispersion is a promising approach, which is already very prevalent. Surfactants can be added to a carrier matrix, thus, forming a ternary dispersion, for superior stability of the formulations and better dispersion of drug in the carrier.

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Revision of the Guideline on Process Validation

Presented by Dick Bonner, Vice Chairman and Director Regulatory Affairs ECA, Advisory Board Member European QP Association

European requirements with regard to Process Validation are in motion with the availability of the new EMA Draft Guideline on Process Validation. The European Compliance Academy (ECA) conducted a survey in September 2011 to evaluate how the European industry views Process Validation. The results were mailed to the EU Commission and the EMA. This editorial summarizes the survey results.

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On 25 February 2010, the Committee for Medicinal Products for Human Use (CHMP) and Committee for Medicinal Products for Veterinary Use (CVMP) published a Concept Paper on the Revision of the Guideline on Process Validation. This revision's goal is to implement modern aspects ("enhanced approach") to move toward a "continuous process verification." The deadline for comments ended on 31 May 2010.

In the meantime, the US FDA finalized a Guidance for Industry Process Validation: General Principles and Practices in January 2011. This Guidance was intensively discussed in the industry.

However, the European requirements with regard to Process Validation are in motion. On the one hand, it seems to be obvious that a new understanding with regard to process validation on the basis of process understanding is "state of the art" today. On the other hand, the current requirements defined in Annex 15 to the EU GMP Guide and in the current version of the Note for Guidance on Process Validation do not yet reflect this approach.

Therefore, the ECA and the European QP Association initiated a survey to evaluate the view of the European industry with regard to Process Validation. The following presents the results of the survey.

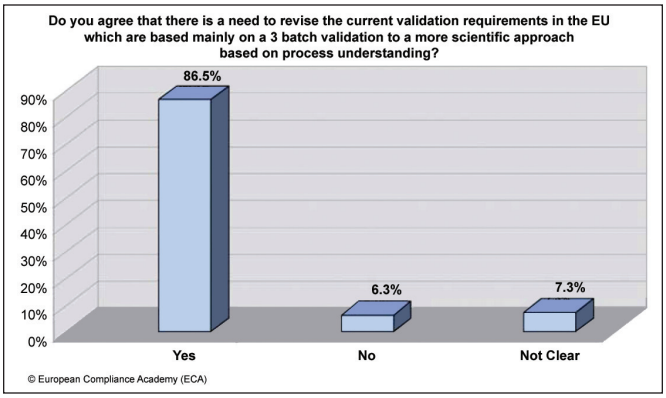
Summary

To understand the current practice and the view of the European industry, a survey was conducted in September 2011. More than 500 professionals provided their input to the survey – single questions were skipped by some of the respondents.

The result relative to the first question asking for the respondents' background showed that the large majority came from medicinal products manufacturers (more than 50%), followed by respondents from API manufacturers and companies manufacturing both medicinal products and APIs (each 25%). Some additional respondents – not fitting into these categories – came from medical device manufacturers, consultants, vaccine manufacturers, or food manufacturers. These "Others" only represent a single digit percentage. Three of those answering further came from the regulatory area.

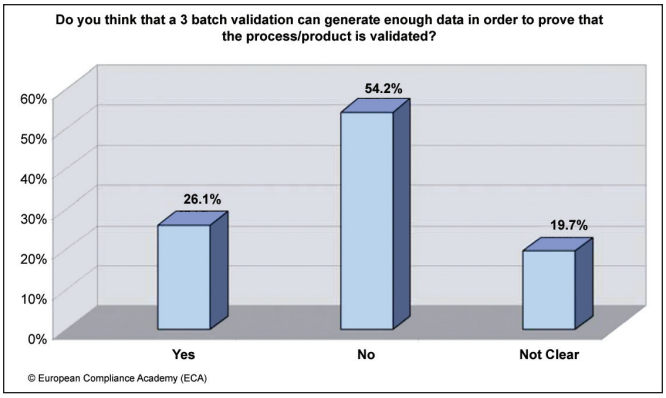
Details

Many respondents (86,5%) agree with the statement that it would be necessary to modify the current validation requirements – which are mainly based on the three batch model – to a more scientific approach and process understanding. A clear "No" was expressed by only 6.3%.



The opinions with regard to "Data Quantity" provided by the three batch validation varied a bit more. Merely a little more than a quarter (26%) of those questioned believe that this approach generates enough data to show the process/product's validity and therefore value it as efficient. However, more than half of the respondents (54.2%) do not agree with this estimation. Noticeable is the group of undecided respondents (20% "not clear").

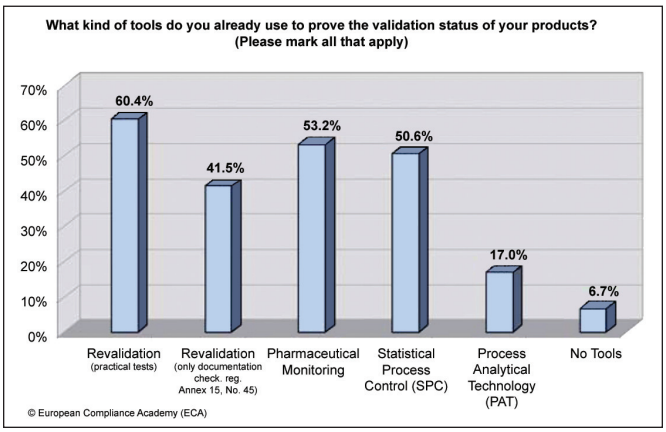
Asked for their estimation of the new FDA Guidance for Process Validation as a basis for a modern approach, almost 57% believe that the Guidance of the US authority would provide a good foundation. Close to 40% have not decided



yet, and merely a small part of respondents – 3.4% – thinks that the FDA Guidance would rather not be a good basis. However, only a few from this group specified their opinion: "No clear / Too broad expectations" probably summarizes the single comments the best. Only two participants mentioned "growing expenses" as main reasons for their criticism.

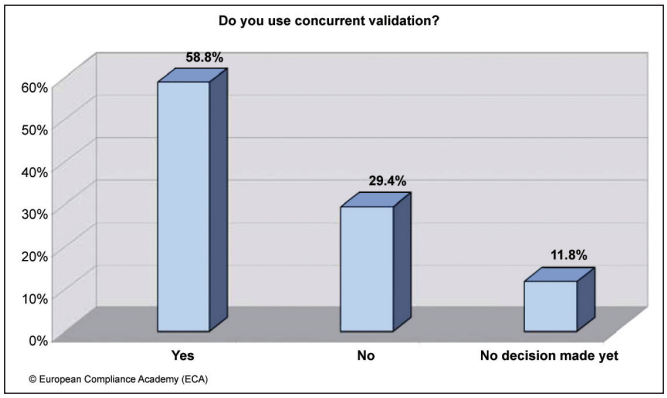
"Do you think that the approach for new products should be different to legacy/existing products?" Exactly 68% answered with "Yes" to this question, 19% negated it. Almost 13% have not decided yet. Among those considering different approaches as necessary, nearly 75% think that legacy/existing products should be verified through statistical data (e.g., Cp, Cpk). For almost 27%, legacy products should not be subject to new requirements. Further comments with regard to optional requirements for legacy products were quite heterogeneous. Five comments can be summarized with the intention to use the APR/PQR as a means for evaluation of legacy products, three respondents recommend the use of SPC for these products. Further, five persons providing input also plan (re-)validations for large process changes with regard to the manufacture of legacy products.

For the question "What kind of 'Tools' do you already use to prove the validation status of your products," respondents could choose between the answers Revalidation (Practical Tests), Revalidation (Documentation Check), Pharmaceutical Monitoring, SPC, PAT, and No Tools with the option to mark all applying answers.

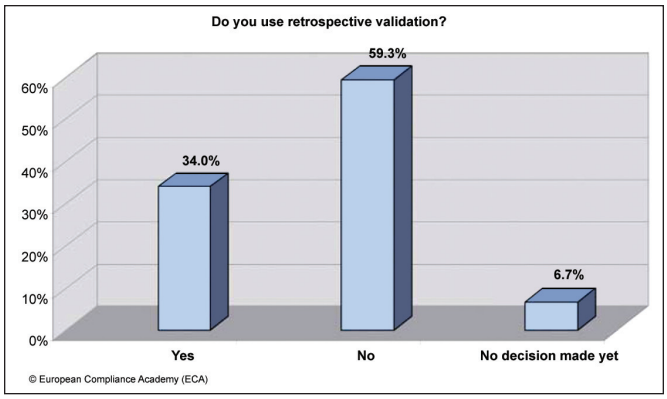


The feedback clearly showed that the pharmaceutical industry likes to take advantage of the width of possibilities. A little more than 50% conduct SPC (50.6%) and pharmaceutical monitoring (53.2%). Some 41% use document check and 60.4% still perform practical revalidation tests. PAT is used by 17%, and 6.7% do not use any tools. These answers were substantiated by 33 additional comments. A large majority (20 comments) recommends APR/PQR. Three respondents mentioned trend analysis.

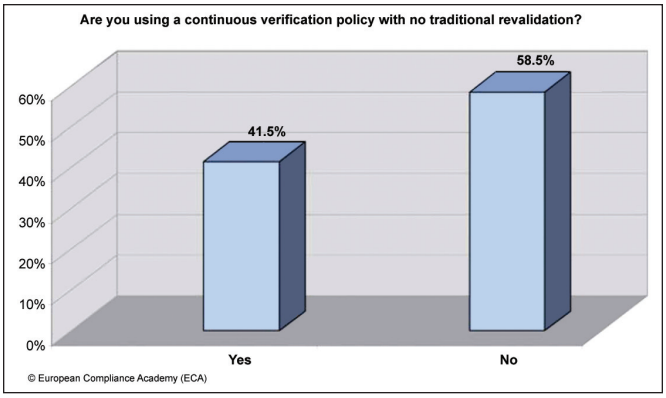
Quite surprising were the results with regard to the question "Do you use concurrent validation?" Nearly 60% answered "Yes." Close to 30% (29,4) do not, and almost 12% remained undecided. The number of comments received to the additional question "Why do you use concurrent validation" for those affirming was also surprising (205 comments). This means that 40% of all survey respondents did also provide a comment to this question. A quarter of those (53) noted that they use concurrent validation for small batches or product volumes. Further, 17% (34) use it after slight changes, for 15% (39) "cost and time savings" are the reason for concurrent validation. Finally, seven respondents blame market pressure for this approach.



Answers to the question "Do you use retrospective validation?" resulted in 34% answering "Yes." Almost 60% said "No," and 6.7% were undecided. As for the question before, the number of comments (116 comments) from those affirming the additional question "Why do you use retrospective validation" did surprise the survey designers. After all, that is close to 23% of all participating in the survey. Almost half of those (45%) use the retrospective validation for legacy products. Nearly 20% mentioned to use it for verifying the process, and only four respondents do actually use it in the meaning of a revalidation.



Close to 84% noted that they do have a revalidation policy, a little more than 16% do not. Less than half of the respondents (41.4%) further use a "continuous verification policy" without traditional revalidation, the majority (58.5%) does not.



Conclusion

The survey yielded some surprises. For instance, the noticeable high number of participants (and also the number of comments). 509 persons providing input truly shows that validation is a topic that bothers the industry. Amazingly clear is also that the industry knows that the "three batch model" should be modified toward a more scientific approach and process understanding although a quarter of all respondents still believe that three batches can generate sufficient data to show the validity of a process. Vice versa, more than 50% do not believe this. With regard to this specific question, 20% were undecided – which also shows some uncertainty.

Whether the new FDA Process Validation Guidance provides a good basis for the new direction for a new validation approach in Europe was evaluated quite differently. 57% believe the new direction can be based on the US authority's Guidance, but nearly 40% have not made up their mind. Almost 70% would like to see different regulations with regard to new and legacy products – whereas nearly ¾ recommend statistical data as a tool for the validation of legacy products.

Interesting were the comments with regard to methods for showing the validation status of products. With some 50% SPC and pharmaceutical monitoring were represented equally often. A little more than 60% (60.4%) conduct practical revalidation tests and 40.5% perform document checks.

Statements with regard to the use of concurrent and retrospective validation were particularly interesting. Both are validation types that should rather be an exception. Still, almost 60% noted to validate concurrently, and 34% use the retrospective validation. However, the use is mostly regulation compliant. 25% apply concurrent validation for small batches and/or small product volumes, respectively 17% after (slight) changes. The retrospective validation is mainly used for legacy products (45% of the answers). Moreover, somewhat surprising are the statements by 15% of the respondents who either mentioned to use concurrent validation as a means for cost and time savings or due to market pressure. A revalidation policy seems to exist in most of the companies (more than 80%), and more than 40% even have established a "continuous verification policy" – and thus already move toward a modern validation approach.

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How ISPE is Answering the Battle Cry for Unwavering Quality

ISPE President and CEO Nancy S. Berg discusses how the Society will lead the industry's movement toward a culture of quality.

by Nancy S. Berg

What would you do if you weren't afraid?

I have had the opportunity and privilege to meet many business and political leaders throughout my career. Perhaps the most memorable meeting was with one of the world's most recognized United States statesmen, retired four-star general in the United States Army, General Colin Powell. Powell's career and accomplishments go far beyond what we can cover in *Pharmaceutical Engineering Magazine* and frankly, his background is less important than his call to leadership.

When I first met Powell, his public speeches and presentations were centered on conviction, doing what is necessary and what is right, and he never failed to make it a point to emphasize the relationship between leadership and making the tough call in support of long-term results. He always appreciated getting the full picture, understanding root causes, and that doing the right thing was almost always the most difficult. He challenged audiences to have courage in their decisions and convictions, often ending his talks with this intriguing question *"what would you do if you weren't afraid?"*

Powell encouraged his audiences to face up to difficult situations, to find compromise if possible and if not, to make right even the most difficult of circumstances. He encouraged leaders to demand excellence and to model behaviors that bred uncompromising commitment, the very highest expectations and unwavering integrity. My impression is that Powell believes that people morally desire the best in all situations, much like we morally desire uncompromising quality in the production of safe medicines.

Are we doing everything we can in the relentless quest for unwavering quality?

I have been impressed that *unwavering quality* is our industry's battle cry. That makes patients feel safe. What also strikes me is while there is a relentless quality commitment, in many companies, "quality, quality leadership, and quality management" are still viewed as assignments, job titles, or company functions. Even more startling is that some companies define quality as "what regulators expect" rather than making quality the predominant leadership philosophy that drives their organizational culture and decision-making.

Our industry goes above and beyond to ensure the safety of our patients; it invests billions in R&D and production to bring forward the most innovative products, and it is working diligently toward common best practices and harmonization to improve quality on all fronts. As a leader, I still wonder how we could all do more. What would we do if we weren't afraid (of cost, of time, of saying yes or no, of challenging a process, an inspector, or being bold about getting the right answers)?

There is much to be done to move industry to the next level – where quality is our culture and more than just a goal or a function. In conversations with company and regulatory leaders, ISPE is being asked to lead industry toward greater awareness, knowledge, and application of enterprise-wide quality management systems. Leaders also agree that the industry

needs stronger commitments to leading change; removing stop-gaps and short-term responses to quality concerns. They desire to better understand how to cut costs and reduce risks, and to discontinue the practice of rewarding short-term gains without a complete understanding of the long term effects on quality and the patient.

ISPE to Lead Quality Management Systems, QbD, and Supply Chain Education, Discussions

Breaking down silos and barriers is certainly difficult, especially in pharma where there are massively complex supply chain and regulatory relationships. Complex yes, but impossible, no. Over the next year, ISPE will be forming groups and leading special discussion meetings, where members and industry will open up dialog with regulatory agencies to begin the critical tasks of identifying and resolving issues to remove barriers that one way or another penalize our product standards, technological innovation, and our industry's integrity. In other words, issues that prevent faster and more effective implementation of quality management systems, including QbD, as well as specific areas within supply chains that present the greatest obstacles, cost constraints, and patient risk.

As part of our expanded mission, ISPE will be engaging the entire product lifecycle in discussions around design and integration issues and our regulatory colleagues will be at the table with us, much like they were during our recent CGMP Conference cosponsored by the FDA (4-5 June, Baltimore). It was at this meeting that industry agreed that our biggest obstacle might be ourselves.

During this Conference, ISPE's distinguished keynote presenters from companies and regulatory agencies echoed the need for the industry to step up to better decision-making, particularly when challenged to reduce costs and in managing challenging global supply chains. FDA leader Janet Woodcock told the audience that "industry must get beyond the fear associated with meeting regulatory standards and drive their companies toward producing safe, high quality medicines."

To build on Powell's question, what *could* we do if we weren't afraid? I suggest that to achieve more reliable outcomes, we must remove the roadblocks and barriers and stop suggesting we need to do something and just do it. What are your suggestions? How would you like to lead or be involved with ISPE in advancing industry? I want to hear from you.

Mission Possible

So there we have it. Industry and regulators aligned. ISPE leading a plan to focus industry on its core purpose; let's bypass distractions and do what is necessary to achieve our desired future. I think our future is bright and our mission is possible. Won't you join us in our pursuit?

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International

Chinese SFDA Chief of Discipline Inspection Group Signs Memorandum of Understanding[1] with the Netherlands Healthcare Inspectorate

On 19 April 2012, Yu Xiancheng, Chief of Discipline Inspection Group of the State Food and Drug Administration, signed the Memorandum of Understanding between the State Food and Drug Administration of the People's Republic of China and the Healthcare Inspectorate of the Kingdom of the Netherlands with Gerrit van der wal, Inspector-General of the Netherlands Healthcare Inspectorate in The Hague, Netherlands. Both parties will strengthen cooperation in the field of drug and medical device supervision.

British and Japanese Regulatory Agencies Meet[2]

A delegation from Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom, headed by Professor Sir Kent Woods, Chief Executive of MHRA, visited PMDA for the first Japan- UK bilateral meeting. In the meeting, participants from MHRA, Ministry of Health, Labour, and Welfare (MHLW) and PMDA discussed wide-ranging topics, including promotion of clinical trials, GMP inspections, and future direction of global collaboration.

Chinese SFDA Commissioner Yin Li Meets the Delegation of Ministry of Industry, Trade, and Labor of Israel[3]

On 29 May 2012, Yin Li, Commissioner of the State Food and Drug Administration (SFDA) met with the delegation led by Shalom Simhon, Minister of Industry, Trade, and Labor of Israel. Both sides exchanged opinions on relevant issues related to medical devices. Main directors of SFDA's Department of International Cooperation, Department of Medical Device Supervision, and Center for Medical Device Evaluation attended the meeting.

Chinese SFDA Commissioner Yin Li meets Deputy Head of the State Administration of Ukraine on Medicinal Products[4]

On 17 May 2012, Yin Li, Commissioner of the State Food and Drug Administration (SFDA), met with the visiting Andrii Zakharash, Deputy Head of the State Administration of Ukraine on Medicinal Products. Both sides signed a memorandum of understanding on bilateral cooperation, and exchanged views on strengthening cooperation in the future. Main director of SFDA's Department of International Cooperation and relevant directors of Department of Drug Safety and Inspection, Department of Drug Registration attended the meeting.

Chinese SFDA Deputy Commissioner Wu Zhen Meets the Delegation of Iran's Ministry of Health and Medical Education[5]

On 15 May 2012, Wu Zhen, Deputy Commissioner of the State Food and Drug Administration (SFDA), met with the delegation led by Marzieh Vahid Dastjerdi, Minister of Health and Medical Education of Iran. Both parties exchanged views on enhancing exchange and cooperation in the supervision of traditional medicines.

ICH

Additional E14 Q&As Available on the ICH Website[6]

In April 2012, the ICH E14 Implementation Working Group (IWG) finalized under Step 4 of the ICH Process four additional questions and answers addressing sex differences, incorporating new existing topics finalized by the E14 IWG in June 2008; the Q&A document was renamed R1. The updated E14 Q&A document is available for download from the E14 Section on the Efficacy Guideline page at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.

PIC/S

Korea Applies for PIC/S Membership[7]

On 10 April 2012, the Korea Food and Drug Administration (KFDA) applied for PIC/S membership. The Rapporteurs were expected to be appointed at the PIC/S Committee Meeting on 7 to 8 May 2012 in Geneva.

Japan Applies for PIC/S Membership[8]

On 9 March 2012, Japan's Ministry of Health, Labour, and Welfare applied in its name as well as on behalf of the Pharmaceuticals and Medical Devices Agency and the Japanese Prefectures for PIC/S membership. The Rapporteurs were expected to be appointed at the next PIC/S Committee Meeting on 7 to 8 May 2012 in Geneva.

PIC/S Aide-Memoire on Assessment of Quality Risk Management Implementation[9]

The purpose of this document is to assist GMP inspectors in the assessment of QRM implementation in industry during regulatory inspections. Parts of this Aide-Memoire also may be useful (with suitable modification) during other GXP inspections where similar principles of QRM also apply. This Aide-Memoire also should contribute to a harmonized approach for inspection of QRM in industry between the different PIC/S members.

Asia/Pacific Rim

Australia

Dr. John Skerritt Appointed New Head of Australian TGA[10]

The Commonwealth Department of Health and Ageing (DoHA) has appointed Dr. John Skerritt as the new National Manager of the Therapeutic Goods Administration (TGA), which is responsible for regulating therapeutic goods, including medicines, medical devices, blood and blood products.

In making the announcement, the Secretary of the DoHA, Professor Jane Halton, said Dr. John Skerritt, who has a PhD in pharmacology and is an adjunct Professor at the University of Queensland, is currently the Deputy Secretary of the Department of Primary Industries in the Victorian Government and comes to the TGA with extensive experience in medical, agricultural and environmental policy, regulation, research, research management, technology application, and commercialization.

Australia Publishes Risk-Based Regulatory Framework[11]

In recent years, there has been an increasing demand for more openness and transparency in Government from a well-educated and computer-literate society. This affects all areas, but is espe-

cially important for the TGA because its work has a direct impact on the health and wellbeing of millions of Australians. The new risk-based approach can be found at http://www.tga.gov.au/about/tga-regulatory-framework.htm.

Hong Kong

Regulation of Health Claims of Orally Consumed Products Now in Effect[12]

Provisions related to the control of health claims of orally consumed products under the Undesirable Medical Advertisements (Amendment) Ordinance 2005 came into force 1 June 2012. The advertising of six groups of health claims of orally consumed products, except those customarily consumed as food or drink, will be prohibited/restricted.

India

Probe Finds Collusion Between India's Drug Regulator, Pharma Firms[13]

Officials of India's drug regulator have been colluding with pharmaceutical firms to speed up approval procedures, allowing some drugs that are not permitted in other countries to go on sale, according to an 18-month investigation by lawmakers.

Japan

Japanese PMDA Publishes PMDA-Vision: Its Current Situation and Aim for the Future[14]

PMDA published a presentation outlining important information, including: organizational updates, approval review, safety measures, regulatory science, and PMDA international vision. The presentation can be found at http://www.pmda.go.jp/english/presentations/pdf/presentations_20120327-28-1.pdf.

Europe

European Union

European Medicines Agency Publishes New Document on Regulatory Procedural Advice on Similar Biological Medicines[15]

The guidance brings together in a single place a number of regulatory and procedural questions already published on the Agency's website in existing regulatory documents. It complements existing guidance documents on innovative products and should be read in conjunction with the Agency's scientific guidelines on biosimilars.

Chairman of Top EU Drugs Committee Resigns[16]

The Chairman of the European Medicines Agency's main committee for approving new drugs resigned suddenly in a move a spokesman said was related to his position at the French healthcare regulator, AFSSAPS.

European Medicines Agency Boosts EU Transparency with Online Publication of Suspected Side Effect Reports[17]

The European Medicines Agency has begun publishing suspected side effect reports for medicines authorized in the European Economic Area (EEA) on a new public website: www.adrreports.eu. The reports come directly from the European Union (EU) medicines safety database EudraVigilance, and are one of the many types of data used by regulators to monitor the benefits and risks of a medicine once authorized. The launch of the new website is part of the Agency's continuing efforts to ensure EU regulatory processes are transparent and open and is a key step in the implementation of the EudraVigilance access policy.

Estonia

Estonian State Agency of Medicines Launches New Website[18]

The new website (http://www.sam.ee/en), which is based on Drupal, preserved all the information that was available on the old website – everything can be found in the same place it used to be. In addition to the new website, you also can visit the Client Portal (http://www.sam.ee/en/welcome-client-portal) and the Registry of Activity licenses (http://www.sam.ee/en/registry-activity-licences-english). Both are available in English.

France

France Creates New Agency to Replace French Food Safety Agency of Health Products[19]

The National Security Agency of Medicines and Health Products (MSNA) was officially created. The publication of the decree concerning the governance of MSNA, the Official Journal of 29 April 2012, allows the implementation of one of the main measures in the Act of 29 December 2011 on strengthening the safety of the drug and health products. This measure will be effective from 1 May 2012. The new agency replaces the French Food Safety Agency of Health Products (AFSSAPS), which takes the tasks, rights and obligations.

North America/ South America

Canada

Health Canada Issues "Quality System Framework for the Inspectorate Quality Management System (QM-0001) – 2012"[21]

The purpose of the Quality System Framework is to outline and communicate the Quality Objective and Quality Policy for the national Inspectorate compliance and enforcement program. The QSF also ensures that the requirements of the applicable International Standard are applied uniformly and consistently throughout the Inspectorate's core and related functions.

Health Canada Publishes "Guidance on Classification of Observations for Inspection of Cells, Tissues, and Organs Establishments (GUI-0101)"[22]

This document is an administrative tool and is intended to: assist in the classification of observations made during inspection of Cells, Tissues and Organs (CTO) establishments, promote uniformity in the assignment of ratings to individual observations, and to overall inspection ratings of the CTO establishments; and provide examples of situations of non-compliance with the Safety of Human Cells, Tissues, and Organs for Transplantation Regulations.

USA

US CDER Publishes Strategic Plan for Regulatory Science and Research 2012 to 2016[23]

The CBER Strategic Plan for Regulatory Science and Research provides an overview of CBER's regulatory environment

addressing the challenges of regulating biologics, the researcher-reviewer model used in CBER, and a description of the CBER's Research Management program. This information will provide an explanation and context for understanding CBER's research strategic goals, objectives, and strategies.

US FDA Commissioner Addresses Topic of Innovation[24]

In remarks given at the NEHI Conference on Bridging the Innovation Gap, the US FDA Commisioner Margaret Hamburg addressed the topic of innovation, and the role the FDA plays in bringing innovative products to market. The speech can be found at http://www.fda.gov/NewsEvents/Speeches/ucm302037.htm.

US FDA Strengthens International Collaboration to Ensure Quality, Safety of Imported Products[25]

Commissioner Margaret A. Hamburg, M.D. released the Agency's "Global Engagement Report," detailing the many activities and strategies the FDA is using to transform from a domestic to a global public health agency. The report describes the steps the Agency is taking to ensure that imported food, drugs, medical devices, and other regulated products meet the same rigorous standards for safety and quality as those manufactured domestically. "As our world transforms and becomes increasingly globalized, we must come together in new, unprecedented, even unexpected, ways to build a public health safety net for consumers around the world," said Hamburg.

US FDA Blogs About Global Engagement[26]

In a blog post, Mary Lou Valdez, FDA's Associate Commissioner for International Programs, announced a new global initiative web page, which can be found at http://www.fda.gov/AboutFDA/GlobalInitiative/default.htm. She also discussed the Global Engagement Report, (http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm298576.htm) which chronicles global activities, organized by seven key strategic areas, including:

1. Establishing foreign posts
2. Strengthening regulatory systems capacity
3. Harmonizing science-based standards
4. Leveraging knowledge and resources
5. Conducting risk-based monitoring and inspections
6. Preparing and responding to public health crises
7. Advancing regulatory science

US FDA Says Focused on Tracking Drugs After Approval[27]

The US Food and Drug Administration reported that it spends as much effort and resources on monitoring a drug after it is approved as it does in the pre-approval process.

US Top Court Rules for Generic Drugmaker on Patent[28]

The US Supreme Court ruled in favor of a generic drug maker in a case over how companies can fight brand-name rivals in an effort to get their cheaper medicines to market. The high court unanimously ruled that the generics company, Caraco Pharmaceuticals, could sue a brand-name drug maker to get it to narrow its patent description with the Food and Drug Administration.

US FDA Creates New Standard for Cargo Theft[29]

The purpose of this Standard Operating Procedure (SOP) is to provide a general procedure for determining the FDA's regulatory response when a cargo theft involving an FDA-regulated product has occurred. When followed in conjunction with the established procedures for product removal from the market, public notice, and handling medical product shortages, if applicable, the procedures described in this document will ensure that FDA's regulatory response to cargo thefts is consistent and effective.

The FDA is very concerned about the increase in cargo and warehouse thefts of FDA regulated products, including prescription and over-the-counter medicines, vaccines, medical devices, and infant formula. These crimes threaten the public health because product that has left the legitimate supply chain poses potential safety risks to consumers. There have been several cases where patients experienced adverse reactions from stolen drugs, reactions that were most likely due to improper storage and handling. We do not want to see this increase in thefts continue. This procedure outlines the steps that the FDA may take in addressing cargo thefts that are reported to the Agency to minimize the public health risks associated with the stolen products.

US Institute of Medicine Issues Report: Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad[30]

Many low- and middle-income nations do not have technologically advanced regulatory systems, which limits their oversight of food and drug safety, says a new report from the Institute of Medicine. The discovery of a counterfeit version of the cancer drug Avastin earlier this year underscores the challenges for US regulators as imports increasingly dominate the American market.The report recommends 13 steps that the US Food and Drug Administration and other organizations can take over the next three to five years to bolster the safety systems in developing nations. Partners in this effort include other federal agencies, international organizations, the regulated industries, and regulators in developing countries. Recommended steps include encouraging the development of low-cost technologies to prevent fraud and assessing whether the pilot Secure Supply Chain program can be expanded. The report also urges the regulatory agencies in developed nations and industry associations to devise ways to share inspection results and emphasizes the importance of donor investment in developing countries' regulatory systems.

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ILF Engage with Asian Regulators in Japan and China

by Robert Tribe, ISPE Asia Pacific Regulatory Affairs Advisor

The International Leadership Forum (ILF), which usually meets in the USA or Europe at least twice a year, held meetings in Asia for the first time in April 2012. The meetings were chaired by Lou Schmukler, President Global Manufacturing and Supply, Bristol Myers Squibb Co.

The ILF met in Hiroshima, Japan on 13 April 2012 in conjunction with the annual ISPE Japan Conference which was the 10th Anniversary of the Japan Affiliate. It also met in Beijing, China on 15 April 2012 in conjunction with the annual ISPE China Conference.

Senior regulators from MHLW (Japan), PMDA (Japan), SFDA (China), Shanghai FDA, Beijing FDA, Zhejiang FDA, Shandong FDA, PIC/S, and MHRA (UK) attended the meetings to discuss top industry concerns, participate in frank panel discussions, and provide input to the finalization of the ILF Global Positioning Strategy (GPS) document.

The GPS document was well received by the regulators and valuable input was shared to help facilitate the finalization of the document. The final draft of the GPS document is available for review and comment at: http://www.ispe.org/index.php/ci_id/36256/la_id/1.htm

The main discussions concerning regulatory issues that arose during the ILF meetings were as follows:

Japan Regulatory Issues:

- On 9 March 2012, the MHLW applied for PIC/S membership in its name as well as on behalf of the PMDA and the Japanese Prefectures.

- There were essentially 48 GMP Inspectorates in Japan (one central Inspectorate and 47 Prefecture Inspectorates).

- All 48 Inspectorates will work to the same single Quality Management System in order to help ensure a uniform and consistent approach to the inspection and authorization of manufacturers of pharmaceutical products in Japan.

- Regular training seminars are held for the inspectors of all 48 Inspectorates in order to help ensure uniform interpretation of the Japan GMP requirements.

China Regulatory Issues:

- The China GMP (2010 revision) was implemented by SFDA on 1 March 2011. It contains 14 chapters and 313 articles as basic GMP requirements, and is similar in approach and content to the EU and WHO GMP requirements (http://eng.sfda.gov.cn/WS03/CL0768/65113.html). There are currently five annexes which cover sterile products, APIs, biologicals, blood products, and Traditional Chinese Medicines (TCMs). Discussions will be held later in 2012 to include additional annexes to bring the content of the China GMP closer to the EU and PIC/S GMP Guides.

- There are two levels of GMP inspections in China; at the national level, the SFDA inspect manufacturers of higher risk pharmaceutical products (such as sterile products and biologicals), while at the local level, the provincial FDAs inspect manufacturers of other pharmaceutical products (such as non-sterile products, APIs, etc.)

- Manufacturers in China were given the following timeframes to comply with the new China GMP:

  - For higher risk pharmaceutical products: up until the end of 2013
  - For other pharmaceutical products: up until the end of 2015

- A company is required to obtain the following three documents in order to sell pharmaceutical products in China:

  1. A manufacturer authorization certificate
  2. A product licence
  3. A GMP certificate

  Manufacturers must apply for a GMP inspection after obtaining the first two documents. The manufacturer will not be allowed to produce pharmaceuticals without GMP certification from the regulatory authority (this will apply after the end of the relevant transition period of either 2013 or 2015).

- The SFDA website currently has a searchable database of medicine manufacturers that have been inspected (only in Chinese language at this stage). This database shows for each manufacturer the scope of the inspections conducted by SFDA and the history of compliance with the China GMP (2010 revision) and the previous version.

- The SFDA has commenced conducting overseas inspections as a pilot program to gather information. So far, seven manufacturers from five different countries had been inspected under this program with more inspections planned. The inspections undertaken to date have revealed some differences in China GMP requirements in comparison to other GMP requirements.

Concludes on page 2.

ILF Engage with Asian Regulators in Japan and China

Continued from page 1.

- The SFDA had participated in PIC/S meetings and training seminars over the past few years and is interested in applying for PIC/S membership sometime in the future.

PIC/S Regulatory Issues:

- PIC/S is a different kind of organization to that of ICH. While PIC/S membership comprises 40 regulatory authorities from all over the world, ICH membership comprises both regulatory and industry representatives from only three regions of the world – North America, Europe, and Japan. Because PIC/S is open only to regulatory authorities, it is most unlikely that PIC/S and ICH would merge, although they will continue to cooperate with each other.

- PIC/S is an informal cooperative arrangement between regulatory authorities and unlike an Mutual Recognition Agreement (MRA) between countries, it had no legal status or treaty status. Because of this, it is very common for PIC/S member authorities to exchange information on GMP inspections without any obligation to accept the results of inspections.

- A wide range of information is exchanged between PIC/S member authorities, including GMP inspection reports, forward inspection schedules (to avoid duplication of inspections), investigation reports, rapid alerts, drug recalls, training courses for inspections, and databases of manufacturers that are inspected and licensed, etc.

- Once a regulatory authority becomes a member of PIC/S, they are subjected to periodic reassessment to ensure that their systems, procedures, and inspection standards remain equivalent to PIC/S requirements.

- The regulatory authorities of Slovenia, USA (US FDA), and Ukraine were the most recent authorities to become members of PIC/S. The regulatory authorities of Japan and South Korea were the most recent authorities to apply for PIC/S membership with the authorities of Indonesia, Thailand, Philippines, New Zealand, Taiwan, Brazil, Iran, and UK (veterinary) currently being assessed for membership.

(Note: several weeks after the ILF meeting, PIC/S announced that the regulatory authority of Indonesia will become the 41st member of PIC/S from 1 July 2012).

Schmukler thanked the regulators and all participants for their frank and active participation in the meetings, and indicated that it was likely that the ILF would repeat the meetings in Asia in the future.

Glossary of Regulatory Authorities attending the Asia ILF Meetings

MHLW	Ministry of Health, Labour and Welfare, Tokyo, Japan
PMDA	Pharmaceuticals and Medical Devices Agency, Tokyo, Japan
SFDA	State Food and Drug Administration, Beijing, China
Shanghai FDA	Food and Drug Administration of Shanghai, China
Beijing FDA	Food and Drug Administration of Beijing, China
Zhejiang FDA	Food and Drug Administration of Zhejiang, China
Shandong FDA	Food and Drug Administration of Shandong, China
PIC/S	Pharmaceutical Inspection Cooperation Scheme, Geneva, Switzerland
MHRA	Medicines and Healthcare Products Regulatory Agency, London, UK

About the ILF

The ILF was formed 20 years ago. It is a global advisory group comprised of senior leaders from the pharmaceutical industry dedicated to:

- Providing leadership and direction on critical issues facing the pharmaceutical industry
- Aligning the pharmaceutical industry globally
- Establishing dialogue with regulators to discuss critical technical issues
- Identifying opportunities for innovation
- Promoting consistency
- Seeking worldwide harmonization where appropriate

The ILF provides direction on focus and priorities to guide the strategic plan and activities of ISPE, and to coordinate interactions with other professional societies. The ILF operate independently of ISPE although ISPE provides administrative support.

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Bringing New Products to Market Faster

by Adam Fermier, Paul McKenzie, Terry Murphy, Leif Poulsen, and Gene Schaefer

This article presents ideas, concepts, and prototype experience on how to bring products faster to market through a more structured and integrated management of product, process, and analytical data based on proven industrial standards (S88/S95) and data warehouse technology.

Introduction

Large pharmaceutical organizations are currently being pressured to increase the efficiency and effectiveness of their business in terms of leveraging internal and external resources to deliver faster on design, execution, analysis, and reporting. Inconsistency and sometimes a complete lack of structure around key business processes has led to intensive allocations of resources spent on last minute efforts to complete regulatory filings and technology transfers on time. Inherent in these efforts is often a misplaced emphasis on gathering primary data rather than its transformation into information and knowledge and its subsequent analysis. Thus, these efforts are typically the result of an information "push" through the corporation as opposed to an information "pull" driven by a well-coordinated knowledge management strategy. The root cause of this push versus pull in the pharmaceutical industry is the fundamental lack of a scalable knowledge management strategy that can handle the lifecycle management of a novel medicine end to end.

Building a solid knowledge management strategy for the industry has many requirements and challenges. Fortunately, other data driven industries have tackled the knowledge management challenge by adopting industrial standards for batch execution and planning/modeling (i.e., ISA S88/S95 compliant).[1-5] However, the problem is how to assemble and contextualize the data scattered throughout many systems. Compounding this problem is that these systems are often a mix of validated and non-validated systems; therefore, it is imperative that the strategy encompasses a modular and scalable approach to the integration of information contained within these systems.

Data warehousing is a common informatics approach that can help meet the requirements set forth above where the data warehouse has a data model conforming to the standards. Bringing these two concepts of a data warehousing strategy in combination with what some have called recipe-based execution will enable the assembly of data rich systems into a common system defined here as a "Recipe data Warehouse" (RW). The RW strategy will allow the organization of data across multi-source execution systems and will drive more data rich decisions for products in a timely manner. This will ultimately lead to increasing the quality, capability, and capacity of the organization to execute our ultimate business deliverables: New Drug Application (NDA), Biologic License Application (BLA), technology transfer, and delivery of therapeutics to patients.

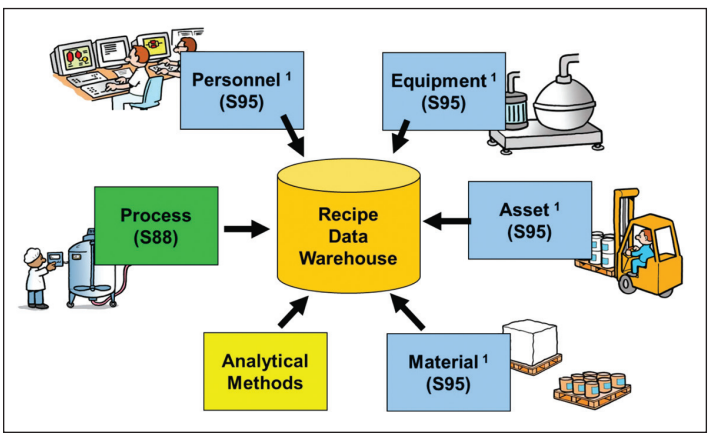

Figure 1. S88 & S95 recipe objects to be managed by recipe data warehouse.

Defining the Strategy

S88/S95 standards provide definitions around people, materials, and equipment as well as procedural models on how these are combined to make products *Figure 1*. Typically, quality monitoring methods are not well defined in these standards; however, the

associative resulting data from these methods could be easily stored. The core of the recipe data warehouse is based on a well structured and tested data model which must:

- Support the business objectives/planned system functions (S95)
- Provide modeling of recipes including specification of processes, personnel, equipment/assets, materials, and analytical methods (S88/S95)
- Align with current/best practice in pharmaceutical manufacturing, i.e., development of small and large molecule drugs
- Align with relevant S88/S95 models
- Include modeling of analytical methods/data, which is not well defined in S88/S95
- Adopt the S88/S95 object oriented thinking (use object classes and instances)
- Adopt the S88/S95 expandability/collapsibility concept (use recursive relations)
- Allow for stepwise development of a recipe based on recipe building blocks (use reference or inheritance)
- Enable ad-hoc addition of analytical measures that may initially not have been defined in the recipe
- Provide ability to capture in process or release data (discrete and continuous)

Putting all these requirements into a centralized recipe data warehouse can be daunting, but well defined strategies in data warehousing can help tremendously.[6] The strength of combining these two strategies is the common modular approach. The data warehousing strategy breaks the information management into four unit operations as outlined in Figure 2. Data source systems provide all source data for the recipe warehouse and in this strategy validation and compliance issues, including change control are addressed in these source systems. The data staging area is a complex, yet simplified manner to help conform to the S88/S95 data standard and designed to optimize data writing speeds. The data presentation area now pre-aggregates data from the data staging area designed to optimize read speeds. The data access tools provide a means to deliver standard reports as well as ad-hoc to advanced trending/analysis. Like the data source systems, the data access tools are meant to be non-system specific to provide the modularity and flexibility required.

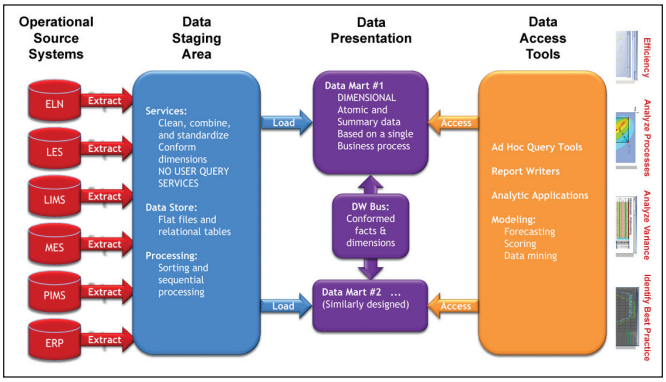

Figure 2. Overview on information management – pulling data from source systems.

It is important to note that the data structure must be applied and/or understood within these data source systems to effectively leverage this strategy. The transformation from the data source systems into the recipe data warehouse is called Extraction-Translate-Load (ETL). It arguably is the most critical portion of the strategy as it will ultimately be required to handle the diversity of data models in the source systems and conform to one common system independent model.

Recipe Development Process – Driving Standards and Flexibility

The overall business objective is to bring new products faster and more efficiently to the market. To do this, the complete development process from discovery to commercial manufacturing of new drugs must be standardized and based on common recipe data models and tools. A key driving motivator behind this strategy is presented in Figure 3 where the organization prepares in a proactive nature to perform technology transfer between each critical clinical milestone. The strategic modification enables more flexibility to the organization as a whole whereby decisions and priorities can change significantly during the products lifecycle. The recipe data warehouse must support each overall step in the development of new drugs:

- Pre-Clinical Phase
- Clinical Trials Phase I
- Clinical Trials Phase II
- Clinical Trials Phase III
- Product Launch and Manufacturing

The product development process should be managed by QbD principles and include the following steps:

- Quality Target Product Profile (QTPP) development
- Prior knowledge collection and Critical Quality Attributes (CQA) identification
- Product and process development including Critical Process Parameters (CPP) identification
- Design space development, including Design of Experiments (DoE)
- Control strategy development, including real time release testing and process validation
- Continuous improvement supported by, e.g., Process Analytical Technology (PAT)

The recipe warehouse must include the necessary data to perform each of these steps thereby encapsulating the continuum of compliant data - *Figure 3*.

S88 Recipe Objects and S95 Complementary Objects

The recipe data warehouse will be based on a common language for exchange of information about products and recipes for manufacturing of products as described in the ISA standards S88 Batch Control,[1-3] and S95 Enterprise Control System In-

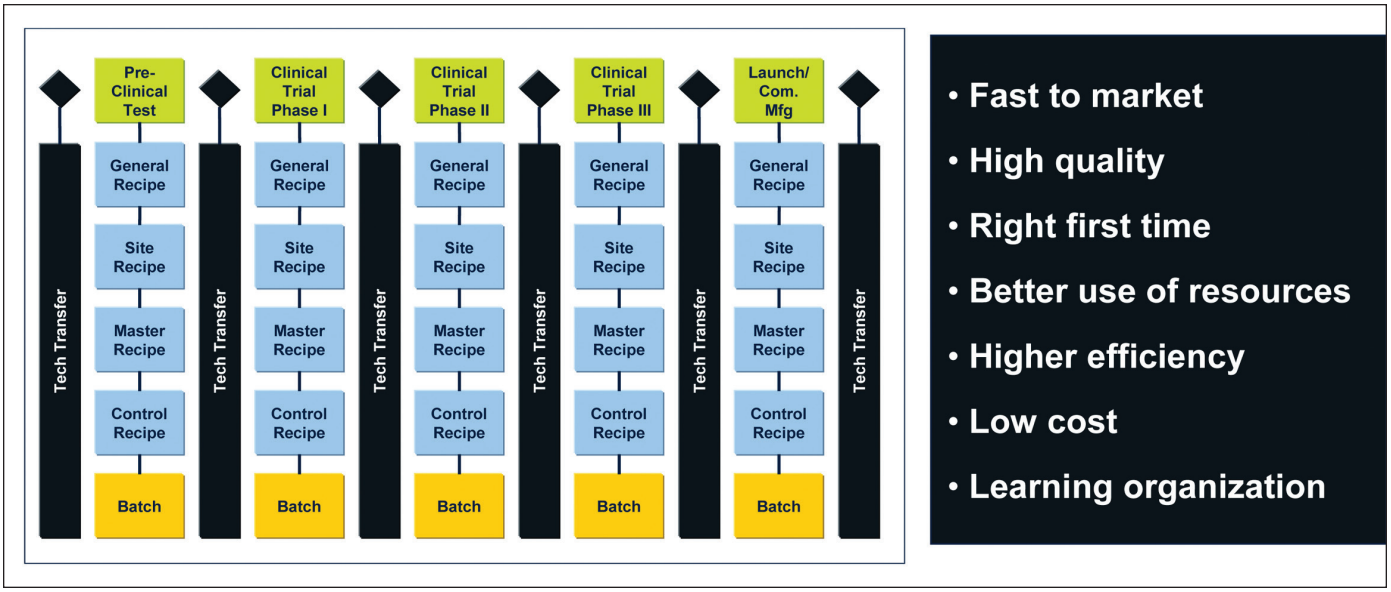

Figure 3. Recipe data warehouse must support tech transfer throughout complete development/manufacturing life cycle management.

tegration.[4-5] Alignment on these standards will help provide a common structure over the data which is maintained in multiple source systems.

Figure 4 describes the matrix of models described in S88. The horizontal slices address varying levels of repeatable units, operations, and parameters. The vertical slices then define varying levels of restrictions applied to these models which increase moving from the process model on the left side to the equipment model (physical model) on the right side. It is assumed that the equipment can be controlled by either a paper-based or a computer-based system, which get its product specific input from a recipe (equipment control). Fundamentally, it is important to note that the recipe establishes the link between the process and the equipment in this matrix format to provide for ultimate flexibility.

Implication of Vertical Slices in the Procedural Model

The evolution from a process view to an equipment/execution view is defined as procedural control which is synonymous to a control strategy. Hence, if your regulatory filings are aligned with these overall procedural models, it will help ensure you are indeed providing the most transparent process definitions to the agencies as well as providing flexibility for your commercial manufacturing. For example, a regulatory filing would outline a general recipe and include all Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) defined, and include a procedural definition as a mean to describe the products control strategy. Certainly, master and control recipes leveraged in development that helped define these CPPs and CMAs would be shared, but only to justify the overlaying general recipe for the product. In such a manner, commercial manufacturing and the agencies are provided clear definitions and processes for the control strategy.

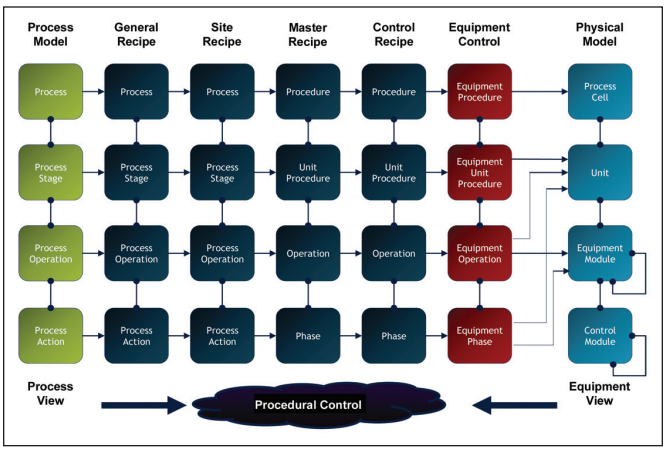

Figure 4. S88 procedural controls and model definitions.

S88 describes how process descriptions may be transformed into similar structure for a recipe. It is important to note again that the information captured in the recipe contains both the process execution as well as the quality testing methods/data. It is through this combination of information in one central location that facilitates effective definition of CPPs and CMAs.

Recipe Definitions

According to S88 Reference,[1-3] a recipe is "an entity that contains the minimum set of information that uniquely defines the manufacturing requirements for a specific product." It is used to describe products and how to produce products. In practice, you need varying degrees of information specificity for different recipients of the information in the organization. That's why S88 operates with four different recipe types as shown in Table A.

Process Models Equivalent to a Platform

Strictly speaking, process models are intended to be independent of product and materials. However, in discussions around alignment of platform definitions and recipe based definitions, we have taken the editorial liberty to enable some material definitions/classes to be defined in these process

models as well as equipment parameters and settings. This decision was made to help enforce some further standardization the corporation was looking for in the overall platform discussions.

Product Specific Recipes

Figure 4 describes the evolution from a general recipe to a control recipe. Note the clear equipment independency implied by these recipe definitions. This is important to note and follows on the conversations above around actual filing strategies/recommendations for products. The S88 standard,[1-3] defines four different recipe types:

- General recipe: a type of recipe that expresses equipment and site independent processing requirements.
- Site recipe: a type of recipe that is site specific.
- Master recipe: a type of recipe that accounts for equipment capabilities and may include process cell-specific information.
- Control recipe: a type of recipe which, through its execution, defines the manufacture of a single batch of a specific product.

Each of these recipes is further described in the S88 standard as shown in Table A.

Recipe Types
The ***General recipe*** is an enterprise level recipe that serves as the basis for lower-level recipes. It is created without specific knowledge of the process cell equipment that will be used to manufacture the product. It identifies raw materials, their relative quantities, and required processing, but without specific regard to a particular site or the equipment available at that site. The general recipe provides a means for communicating processing requirements to multiple manufacturing locations. It may be used as a basis for enterprise-wide planning and investment decisions.
The ***Site recipe*** is specific to a particular site. It is the combination of site-specific information and a general recipe. It is usually derived from a general recipe to meet the conditions found at a particular manufacturing location and provides the level of detail necessary for site-level, long-term production scheduling. However, it may also be created directly without the existence of a general recipe. There may be multiple site recipes derived from a general recipe, each covering a part of the general recipe that may be implemented at a specific site
The ***Master recipe*** is that level of recipe that is targeted to a process cell or a subset of the process cell equipment. Some characteristics of master recipes include the following: • The master recipe has to be sufficiently adapted to the properties of the process cell equipment to ensure the correct processing of the batch. • The master recipe may contain product-specific information required for detailed scheduling, such as process-input information or equipment requirements. • The master recipe level is a required recipe level, because without it no control recipes can be created and, therefore, no batch can be produced
The ***Control recipe*** starts as a copy of the master recipe and is then modified as necessary with scheduling and operational information to be specific to a single batch. It contains product-specific process information necessary to manufacture a particular batch of product. It provides the level of detail necessary to initiate and monitor equipment procedural entities in a process cell. It may have been modified to account for actual raw material qualities and actual equipment to be utilized.
Recipe Categories of Information
The ***Header*** in the recipe comprises administrative information. Typical header information may include the recipe and product identification, the version number, the originator, the issue date, approvals, status, and other administrative information.
The ***Formula*** is a category of recipe information that includes process inputs, process parameters and process outputs. A ***process input*** is the identification of a raw material or other resource required to make the product. A process parameter details information such as temperature, pressure, or time that is pertinent to the product but does not fall into the classification of input or output. A ***process output*** is the identification and quantity of a material and/or energy expected to result from one execution of the recipe. ***Equipment requirements*** constrain the choice of the equipment that will eventually be used to implement a specific part of the procedure. In general and site recipes the equipment requirements are typically described in general terms, such as allowable materials and required processing characteristics. At the master recipe level, the equipment requirements may be expressed in any manner that specifies allowable equipment in process cells. At the control recipe level, the equipment requirements are the same as the allowable equipment in the master recipe.

Table A. Glossary of recipe terms as defined in S88.[1]

Implication of Horizontal Slices in the Procedural Model

According to S88, each of these vertical slices is further matrixed to describe in a structured way by splitting the process up into process stages, process operations, and process actions - *Figure 5*. To complete the process description a set of parameters describing required materials, equipment and personnel and specifying process variables may be assigned to each process action.

According the S88 standard, [1-3] the recipes contain the following categories of information: header, formula, equipment requirements, and procedure. Each of these categories is further described in the S88 standard as shown in Table A.

Recipe Data Warehouse Development – S88/S95 Meets Kimball

Combining the S88/S95 data standards with the informatics strategy outlined by Kimball, we have called this system the "recipe data warehouse"[6] recognizing the importance of the relationship between recipes and informatics (i.e., information management) strategies. The combined data model is proposed in Figure 6 recognizing some key staging areas isolating the source systems and target systems. Source systems are exist-

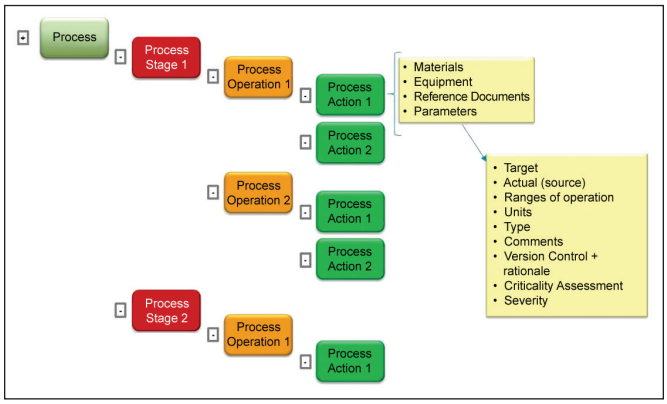

Figure 5. S88 based recipe structure.

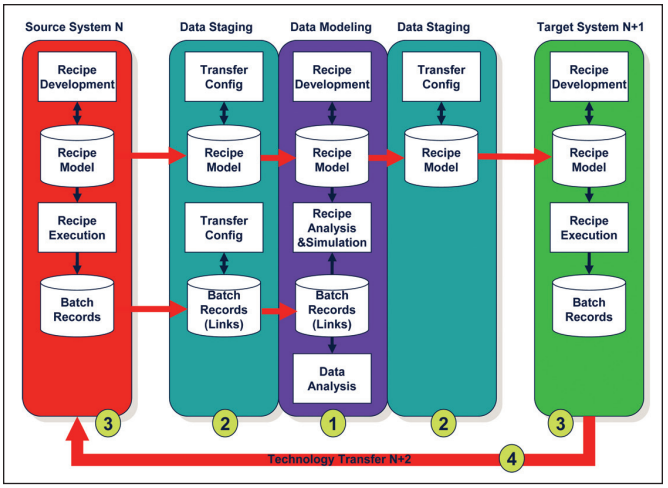

Figure 6. Recipe data warehouse conceptual system architecture.

ing systems that are used to create or modify existing product recipes in the central recipe data warehouse or to produce batches based on existing product recipes where the batch data will be used for data analysis by the central recipe data warehouse. Target systems are existing systems that use existing product recipes to produce batches (experiments, lab production, commercial production, etc.). The numbers in parenthesis below relate to Figure 6.

The conceptual architecture illustrates both the central recipe data warehouse (1) the data staging for connected systems (2), and the connected systems (3) as well as the conceptual workflows (4) related to defined business processes which creates, modifies, uses, or analyzes the recipe data (e.g., material, equipment, people and process definitions, and in process data as well as release/stability data).

It is anticipated in the generic model that all, some, or none of the current systems can act in the role of both being a source system or a target system (3).

Data staging is intended for each connected system to enable standardizing and normalizing on data structures in the central recipe data warehouse and de-coupling these structures from the native data structures used in and by the connected systems themselves.

The core of the architecture is the Central recipe data warehouse (1), which holds the following types of data:

- Standardized/normalized product recipes
- Tools for recipe development, including recipe building blocks
- Meta data for recipe analysis and simulation
- Meta data for linking to batch data in any defined source system (3)
- Tools for analyzing recipe/batch data

It is important to realize that a significant portion, if not all of our current data is stored in a manner that does not comply with recipes and sources range from excel workbooks, custom databases, emails, pdf documents, paper records, etc. So a huge value in building a unified, system independent model is that it helps to capture and contextualize this disparate data today.

The transformation or mapping from/to the specific systems of the generalized data models and structures used in the central recipe data warehouse is done by data staging.

The data staging is intended to be an integrated part or the central recipe data warehouse with centralized configuration of the transformations. This gives a good de-coupling of the connected systems from the central recipe data warehouse and it furthermore gives a robust and consistent basis for managing the data transformations.

For some of the current systems, a full and complete data transformation may not be possible or GMP and other regulations may prevent a direct storing of data into the central recipe data warehouse. In such cases, the data staging could include a user interface component for committing of the transformed data. Data staging has to cover both product recipe data and batch data transformations.

Data staging has for some of the existing systems to be bi-directional to enable business process workflows. This is illustrated by the data staging between the source systems and the data modeling for transforming data that creates or modifies existing data in the recipe data warehouse. Data subsequently leaving the warehouse would go through a similar staging environment where appropriate mapping to system specific definitions would be defined. The inbound and outbound data staging is clearly not identical and must be treated as separate transformations with specific and individual configurations for each of the connected systems.

User interface components shall be included for configuration of the data transformation and eventual data commitment functionality.

Workflows which can be for optimizing, fine tuning, and development of recipes is illustrated by the target system (N+1) which loads an existing production recipe (or recipe component) from the central recipe data warehouse. This recipe is then modified before or during recipe execution and batch data is collected during this execution.

There may now be a desire to update the production recipe to a new "version" in the central recipe data warehouse, and the "arrow" with "technology transfer N+2" indicates that this specific system used for the recipe execution now changes from being a target system to also being a source system. In this way, many of the existing systems can be used as both a source and a target system.

A special methodology which could be used for recipe development is simulation of processes. Simulation of processes is based on Process Models which can be developed based on historical batch data by use of standard software products.

Once such process models have been developed, these can be used by software engines to simulate the modeled process with a variance on inputs (recipe modifications).

In the current concept illustrated above, such simulation is intended to be included as applications in the central recipe data warehouse, but such simulations also could be seen as just another set of source and target systems. In the latter case, this may require that additional data staging components are made for batch data from the central recipe data

warehouse to the target system to enable the process model to operate (recipe execution) on real batch data. (This data staging component is not illustrated).

Other Functions

The recipe data warehouse may eventually comprise data for use in quite a number of other applications. Figure 7 shows the envisioned functions.

The core function of the recipe data warehouse is called recipe authoring. Recipe authoring is the stepwise development/refinement of the recipe from the initial idea of the product to commercial manufacturing of the product to be supplied to the patient.

The recipe authoring process will be based on selection and combination of predefined recipe building blocks kept in a library. Different kinds of building blocks will be kept for specification of processes and related resource requirements (personnel, equipment, methods, and materials). The building blocks must represent the best practice in the complete development organization.

The development of new recipes will take advantage of the object oriented approach using object classes and object instances as described in S88, e.g., you may have a class of equipment called fluid bed dryers in your library and based on that class, you may create an instance of a fluid bed dryer called fluid bed dryer 23 linked to a specific recipe operation.

The recipe authoring will be supported by a graphical front end based and recipe representations standards like Sequential Function Charts (SFC) as described in S88.

Parts and bits of a recipe may be developed outside the recipe data warehouse in one of the source systems linked to the recipe data warehouse and then transferred to the recipe data warehouse through a standard based interface (recipe upload).Based on the data kept in the recipe data warehouse, the users may perform a number of different analysis and simulations:

- Simple views/reports, based on SQL queries in the database
- Advanced statistical analysis/reporting, based on statistical analysis methods, like statistical process control, Multivariate Data Analysis (MVA), Principal Component Analysis (PCA), etc.
- Risk assessment/reporting, based on entry of experience based or theoretical risk probability and risk consequence figures
- Advanced process modeling, based on pre-defined rules/equations for material and energy balances
- Advanced what-if analysis/simulation, based on process modeling methods

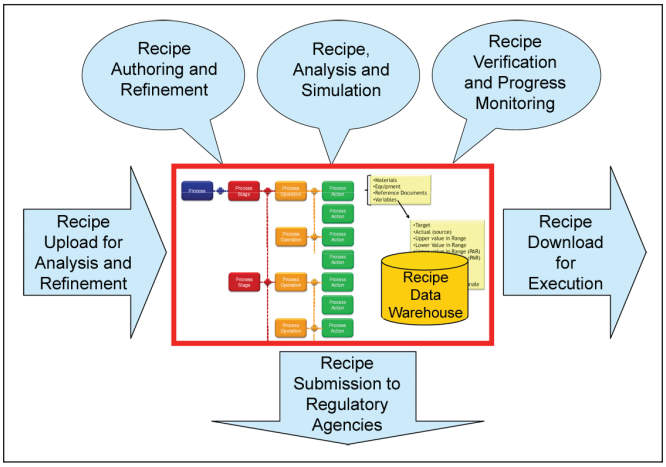

Figure 7. Recipe data warehouse – envisioned functions.

These analysis/simulation/reporting tools will be implemented by linking third party standard software packages to the recipe data warehouse. The recipe authoring process will be supported by various types of recipe verification functions:

- Automatic verification for consistency, based on recipe building rules
- Automatic verification of completeness, based on comparison with pre-defined recipes
- Automatic verification of regulatory/GxP compliance, based on check against pre-defined specification of regulatory/GxP requirements

Further, the recipe authoring process will be supported by a progress monitor describing Key Performance Indices (KPIs) for maturity and readiness for submission/approval:

- Monitor dynamically progress on recipe development
- Compare different versions of recipe and track changes

The progress monitoring tool would provide management with an excellent overview of the product development progress.

Eventually the recipe data warehouse may be used to download recipes for execution in a target system (recipe download). A target system could, for example, be a batch control system in a commercial manufacturing facility. This would require quite detailed modeling of not only the process and the related resource requirements, but also modeling of conditions for transitions and constraints for use of particular equipments.

The recipe data warehouse may store data from execution of recipes or provide on-line links to such data kept by external source systems making it possible to use historical data for the analysis and simulations described above. Historical data may exist in large amounts and may be kept in special historian databases and it may be smart to keep such data in these special databases and just establish links to the data when needed for analysis.

Eventually, the recipe data warehouse may be used for submission of files for approval by regulatory authorities like FDA. Two levels of support may be envisioned for submissions:

- Automatic provision of data for file submissions to regulatory authorities, for example:
  - Collating information over time for a given unit operation would link to S3.2.6 – process development history

  - Information for the current master recipe would link to S3.2.4 process description
  - Specific information gathered during certain instances of the control recipe would link to S3.2.5 process validation and would for the core data set for ongoing process verification, especially useful when combined with the general or site recipe definition(s) for products manufactured at multiple sites
- Manage/track changes related to submitted files

The recipe data warehouse may be used for transfer of recipe data between different systems used for:

- Modeling/specification
- Batch control/execution/reporting
- Quality control/LIMS

Transfer of data between source and target systems would require validation of the recipe data warehouse.

Current Recipe Data Warehouse Experience

A prototype of the recipe data warehouse was built based on S88 and S95 standards and consistent with the published data models.

Standard S88 recipe process models for manufacturing processing and testing thereof was undertaken to drive a common platform of definitions for solid dosage and large molecule synthesis. These process models were loaded into the recipe data warehouse and subsequently used as a framework to abstract general, site, master, and control recipes from previously collected process and analytical data.

Implementation of the concept presented here required a significant amount of data manipulation as the current structure was as diverse as the number of experiments. Thereby, a significant amount of work was undertaken to transform executed batch records and associative analytical data into the recipe structure described above. More than 300 control recipes were converted and stored in the recipe data warehouse. Once the data was loaded, some query tools were developed to help retrieve and visualize the information from the warehouse as depicted in Figure 8.

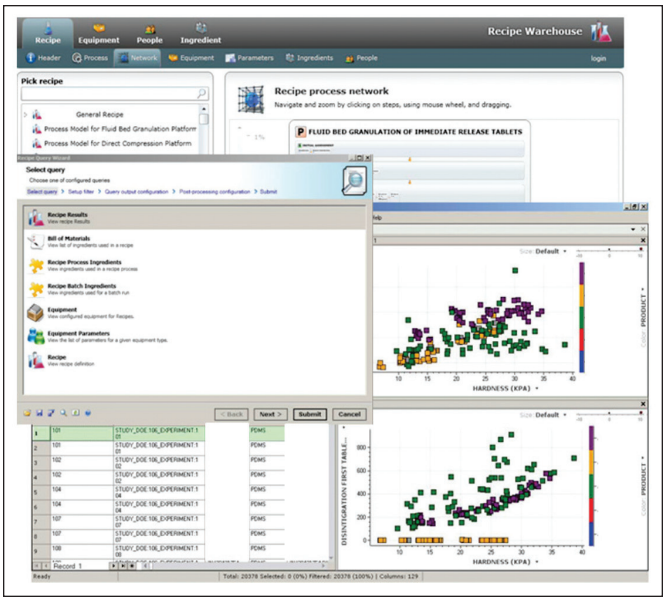

Figure 8. Recipe data warehouse – user interface.

Further Development Plans

Any data warehousing approach requires the organization to look at a continuous improvement of the data model, analysis, and reporting to help ensure learning is leveraged across the lifecycle of the product and across products. As such, the recipe data warehouse future will include expanding the data integration into quality control systems as well as business management tools. Through the combination of product knowledge and resource allocation, the acceleration goals of the organization can be reached, ultimately delivering value to the patients.

Conclusion

The pharmaceutical industry is awash with data, resultant from recipe execution. This data is generated via analytical and process recipe execution, but lacks context to support swift product lifecycle management. As such, recipe based execution requires a strategic approach toward the data management associated with said execution in order to change the current data paradigm from reactive to proactive with respect to releasing the inherent knowledge. To achieve the sustainability and ultimate vision of recipe based execution a system strategy coined "recipe data warehouse" is outlined here. The strategy leverages both external (S88/S95) and internal best practices by which a novel data warehouse was generated to address both. Through the implementation of such a system, the business benefits can be realized via the embracement of scientific and engineering methods. Empowering employees in the corporation will without doubt lead to a sustainable, scalable, and flexible environment to execute on the complex nature of commercializing new medicines for our patients.

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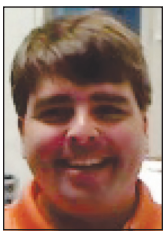

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