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PQLI Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products

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Abstract This paper describes progress made by the Legacy Products Task Team within the ISPE Product Quality Lifecycle Implementation (PQLI) initiative. It discusses the opportunities and the required business and technical processes to justify and deliver a quality by design (QbD) project for an existing product. A process flow is included that summarizes business, technical, and regulatory considerations. A quality risk management-based approach is suggested. Relevant case studies also are presented. Comments are welcome.

Keywords Control strategy · Criticality · Critical process parameter · Critical quality attribute · Design space · Pharmaceutical target product profile · PQLI · Product and process knowledge · Quality by design · Quality risk management

Introduction and Current Position

It is clear from the scope of ICH Q9 (quality risk management (QRM), [1]) and Q10 (Pharmaceutical Quality System [2]) that they are applicable to existing products (see Glossary). These guidelines refer to processes rather than technical requirements and are optional.

ICH Q8 (R1) (Pharmaceutical Development [3]) describes the content of the P2 section of a regulatory submission for a drug product and is also optional. The P2 section can be updated during the life cycle of a product, which gives the opportunity to apply to existing products. The Annex to Q8 (R1) provides further clarification of key concepts outlined in the core guideline and also describes the principles of quality by design (QbD) (see Glossary). While ICH Q8 (R1) emphasizes new products and processes, this paper will discuss how the principles of QbD can be applied to existing products. The term QbD will generally be used when referring to the application of a science- and risk-based approach.

There is the opportunity to apply QbD principles as discussed in Q8 (R1) to existing products for the following:

- drug substances, both chemically and biotechnology-derived molecules
- individual unit operations within drug substance and drug product manufacturing processes
- complete drug substance and drug product manufacturing processes

ICH Q8 (R1) suggests that enhanced knowledge over a wider range of material attributes, processing options, and process parameters resulting from science- and risk-based approaches should be represented in an application as a design space (DS). For an existing product, this paper proposes that this higher level of understanding could be presented as DS for a whole product and/or process, or for a unit operation, or in other manners. Alternative presentations in a dossier to justify, for example, real-time release (RTR) or a reduction in post-approval stability programs could be clear justifications linking the scientific understanding to the desired opportunity.

There are key differences between existing products and new drug products. For existing products:

- There is an established data and knowledge base.
  - Manufacturing and commercial experience provides a database of information from which to draw.

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- The business environment is established.
  - There is more certainty in sales volume and supply chain requirements to support the business case for an existing product.
- There is an established regulatory history.
  - Given that the product is already approved, there must be at least one dossier, which could have been supplemented by a number of post-approval changes and/or variations in the countries or regions in which the product is approved.

Therefore, the application of QbD to existing products entails much less business uncertainty to the applicant, since the product is already approved and marketed. Furthermore, for most companies, there are more opportunities to progress a QbD project on some element of an existing product, since it is likely that there are more approved products within a company than new products, and the business case to support such a project should have more certainty of support with more obvious and immediate resulting benefits.

Given these differences between existing and new products, it is anticipated that QbD could be applied to any type of existing product, including a generic or self-medication product.

Practical Application of QbD to Existing Products

Applying QbD to an existing product requires integration of business, technical, quality, and regulatory aspects. Figure 1 shows the steps involved in applying the concepts of QbD to an existing product. The green boxes indicate the primary business and technical steps involved, including the development of an initial business case. An existing product has a known demand, cost of goods, and associated manufacturing supply chain and regulatory position from which to work. Therefore, it is appropriate for a project to begin with a business case for an existing product. The right-hand column (yellow boxes) in Figure 1 highlights some of the regulatory aspects to be considered by the company associated with different steps in the process. The left-hand column (blue boxes) denotes the QRM principles which should be applied throughout the process with the darker shade emphasizing the QRM step from Q9, which has most importance at that stage in the process.

QbD Project Business Case—Drivers for Change

The practical application of QbD concepts to existing products begins with an evaluation of the business case for making a change to a product and/or process. This evaluation will determine whether there is value in moving forward with the proposed project as well as the extent to which QbD principles will be applied.

The regulatory strategy (see Glossary) should be considered when assessing the business case and may be different when making a change using QbD principles compared with using a conventional approach. Additionally, the business case may need to be revisited throughout the process after additional knowledge and understanding is gained and QRM steps applied.

Some drivers for change include, but are not limited to the following (see also the "Benefits" section below):

- increase in technical understanding to reduce variability in supply chain performance
- reduction of supply chain cycle time
- resolution of technical problems
- reduction of complicated tests
- reduction in number of deviation investigations
- reduction in cost of quality
- improvement in yield
- introduction of real-time release
- reduction in post approval stability programs
- achievement of a company strategy, for example: to promote culture change within a company or bring employees closer to the customer
- acquire knowledge and experience internally and from interactions with regulators
- reduction in post-approval submissions

When assessing the business case for a proposed change, applying QbD principles provides increased technical understanding and added value to the company above that obtained through traditional approaches.

Confirm Pharmaceutical Target Product Profile and Critical Quality Attributes

Once the business case is supported and a regulatory strategy for the company is drafted, a review of the Pharmaceutical Target Product Profile should be performed. This review should verify the attributes of the drug product that are critical to the quality of the drug product, i.e., the critical quality attributes (CQAs), where the CQAs are typically those aspects affecting safety and efficacy, namely, product purity, strength, drug release, and stability. CQAs may include other dosage form specific aspects. Note that the same concept also can be applied to drug substance.

For an existing product, it is recognized that new clinical or safety information will not be generated and that the product profile is defined by prior knowledge and experience, including feedback from the market place and releasing product to the approved specifications. Therefore, this review will almost certainly conclude that the currently approved specification is appropriate to assure the CQAs are

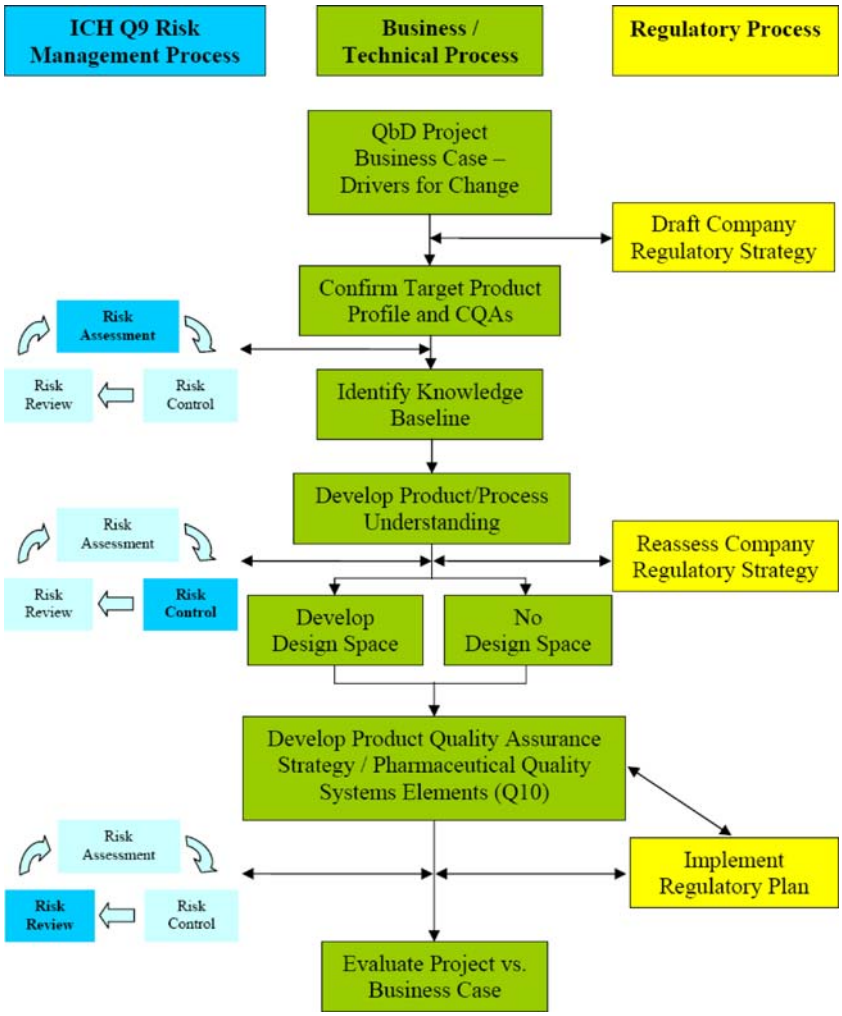

Fig. 1 Process for applying QbD to an existing product

controlled for the drug product. There may be opportunities to refine the currently approved specification, such as removing the need for a redundant attribute, revising acceptance criteria, or introducing new analytical methods.

Identify Knowledge Baseline

The next step in this process is an assessment of current product and process knowledge. In particular, this assessment evaluates the quality and manufacturing history of the product. This includes data supporting the impact of process parameters, product contact materials, and material quality attributes on the drug product CQAs. This prior knowledge may be gathered from development and manufacturing reports, annual product reviews, deviations, batch release data, stability data, product complaints, etc. Although some of these data will be empirical (e.g., that may not be from prospectively designed studies) there could be value analyzing them.

The knowledge assessment establishes whether the current data are sufficient for identifying those parameters and material attributes that are critical and noncritical to achieve the product CQAs. The PQLI paper, *PQLI Definition of Criticality* [4], gives guidance on determining criticality. Often existing controls on process parameters and input material quality attributes use narrow ranges such that the effects of varying these parameters and attributes on a drug product CQA are not discernable. In these cases and where the other data sources are insufficient, the gaps and associated risks are identified and assessed.

A risk assessment should be performed using tools such as failure mode, effects, and criticality analysis (FMECA) and a plan established to obtain the required knowledge and to mitigate or eliminate the identified risks.

Develop Product and Process Understanding

The knowledge gaps and their associated risks can be addressed through further studies and experiments using tools such as design of experiments (DoE) and multivariate analysis, factors to study being identified from the risk-based review of historical information and other prior

knowledge. These further studies and experiments could and probably should be performed at small scale for reasons of cost, experiment turnround time, and equipment and material availability. If these studies are performed at scales different to production scale, justifications should be developed to support that conclusions from these studies are applicable at production scale. Based on the new knowledge gained through these experiments, a risk control strategy can be developed to confirm that all gaps and risks will be sufficiently reduced, eliminated, or accepted with a suitable control strategy. The additional product and process understanding gained during this step also may necessitate reassessing the original regulatory strategy for this project.

Develop Design Space

If using a DS approach, the DS can be established using the prior knowledge and process understanding obtained through experiments, and using QRM. The PQLI paper, *PQLI Design Space* [5], provides guidance on developing a DS and should be referred to for additional details.

Ideally, the DS boundaries should include the entire space of multivariate combinations of process parameters and material attributes that result in product CQAs that will meet their acceptance criteria at release and through to expiry. It may not be necessary or even practical to develop a full DS for all unit operations for a process or for a single operation. Benefits may be gained by considering one or a few, ideally linked, unit operations.

In case study no. 1, a design space was proposed for a unit operation.

No Design Space

It is not necessary to develop a DS when applying QbD principles, especially to existing drug products. For example, in case study no. 2, each unit operation of the manufacturing process was reassessed, and it was determined that a specific operation could be eliminated. Prior knowledge was assessed, product and process understanding were gained, and risk management tools were applied to achieve the desired goal. Developing a DS was not applicable in this case.

Similarly for case study no. 3, a real-time release scheme was approved based on enhanced understanding linked to QRM steps without proposing a DS.

Develop Product Quality Assurance Strategy/ Pharmaceutical Quality Systems Elements (Q10)

Once the product and process understanding is obtained, and if applicable, a DS is established, the product quality assurance strategy or pharmaceutical quality system elements are reviewed. This review depends on the outcome of the increased technical understanding, the link to the proposed regulatory strategy, and may require proposing changes to the company's quality monitoring, corrective action and preventive action (CAPA), or change management systems. One part of this review will be a potential revision to the control strategy needed to assure process performance and product quality. Control strategy is discussed further in a separate PQLI paper, *PQLI Control Strategy Model and Concepts* [6]. One element of control strategy to note here, however, is the use of real-time release. The knowledge obtained by applying QbD principles, including parameter and CQA relationships, is essential to the use of real-time release strategies.

Pharmaceutical quality system elements, such as continual improvement, are fundamental to any manufacturing process. However, these elements should be reassessed with application of QbD. Questions that need to be considered when reassessing Pharmaceutical Quality Systems in light of QbD include:

- Is there a mechanism in place to review and monitor events to address risk management (i.e., risk review)?
- Does the manufacturing site's standard operating procedures allow for the QbD approach?
- Does the site's documentation fully support the application of QbD to the specific product in the event of an inspection (e.g., statistical reports, manufacturing, and validation reports)?

Implement Regulatory Plan

Once the knowledge and information are gathered and the appropriate regulatory strategy is confirmed, including revision to the control strategy, the regulatory submission can be created. Considerations at this point are how much of this information will be included in the QbD submission, what data will be available for inspection, and how much of the QRM processes to include. It should be the goal for companies to make proposals in the application which are clearly justified to facilitate review and inspection.

During the review and inspection processes, there will be interactions with regulatory agencies which should lead to greater mutual understanding and could lead to changes to parts of the filing and recommendations for the company's pharmaceutical quality system.

Evaluate Project vs. Business Case

Following approval of the regulatory submission and implementation of the change, it is appropriate to evaluate the final outcome of the project against the business case.

Did the project meet the original objectives? An assessment of key lessons from the project is worthwhile, especially as both industry and regulatory agencies continue to develop an understanding of the application of QbD and associated expectations.

Benefits

For an existing product, there are opportunities for a company to enhance the knowledge of product and/or process performance which could have many benefits. This greater technical understanding will underpin a company's ability to manufacture routinely and make its supply chain efficient. Such greater understanding may not always lead to a regulatory submission, but on many occasions, however, there may be a need for a regulatory submission.

Benefits from performing this additional work post-approval are summarized below under the following headings:

- improving manufacturing efficiency
- proposing regulatory flexibility
- business strategy

A project may be justified by one or more factors.

Improving Manufacturing Efficiency

Opportunities for improving manufacturing efficiency are many and were used to justify the ICH Q10 topic [7]. These include the following:

- reducing variability of a process and increasing predictability for the supply chain
- resolution of technical problems
- yield improvement
- reduction in cost of quality
- reduction in amount and complexity of analytical testing
- reduction in post-approval stability programs
- introduction of real-time release

Traditional pharmaceutical manufacturing and associated regulatory submissions have been based on the concept of a fixed process, which can lead to high output variability, resulting in processes that are only of the order of 2.5 to 4.5 sigma capable [8]. In contrast, manufacturing processes developed with a QbD approach establish a manufacturing environment where the relationships between material attributes, process variables, and quality attributes are well understood. Based on this process understanding, the process may be adjusted to respond to input variability and variability of process parameters ultimately to provide for reduced variability of output resulting in processes approaching or achieving six sigma capability. Movement toward these reduced levels of variability leads to significantly improved and predictable supply chain performance with reductions in inventory levels and the cost of supply.

Additionally, there are many other associated benefits such as shorter cycle times and increased yields, fewer investigations, more successful root cause analysis, and an overall reduction in the costs of internal failures (i.e., rejects, reworks, reprocessing, extra setups, emergency purchases of materials, and investigations). More efficient manufacturing should optimize use of management time, use of equipment, and size and use of facilities.

Other potential benefits from increased product understanding are in reduction and simplification of analytical testing and potential reduction in post-approval stability programs.

Increased understanding could lead to real-time process control of some unit operations and to real-time release for all or some attributes in a specification.

Proposing Regulatory Flexibility

Regulatory flexibility may be proposed through applying QbD principles to an existing product. This flexibility may be realized through proposing a DS as described in ICH Q8 (R1) or by making specific proposals in a regulatory submission. Whether using the DS approach or making specific proposals, the objective is for a company to have fewer post-approval changes or perhaps less stringent regulatory filings for specific changes (e.g., annual report versus prior approval supplement in the US).

Applying QbD to an existing product does result in a change from the more traditional regulatory submissions to more science- and risk-based submissions. The type of information and summarized data required for a QbD post-approval submission is likely to take more time to compile, and because of the complexity of the increased technical understanding and mechanisms of presentation of information, there may be more interactions with regulators during the learning phases.

However, the objective is that the investment in technical work and regulatory dossier compilation and submission will lead to reduced regulatory burden associated with subsequent manufacturing and/or analytical testing improvements. One of the drivers for a company to reduce the number of post-approval submissions and have more internal control is to have more control of timing of introduction of further improvements. This resulting situation has obvious benefits to both the company and the workload of regulators

There appears to be general acknowledgement and encouraging recognition among regulators toward the application of QbD for an existing product, and many regulatory authorities are prepared to accept QbD-oriented

post-approval submissions for existing products. They are also accepting the need to rethink and revise current guidance and legislation as seen by the FDA announcing that the post-approval regulations are being revised (21 CFR 314.70) and in EU recognition of the need to change their variations and changes regulation [9].

Business Strategy

As an alternative or additional to the business strategy of improving the supply chain for a product, there is other flexibility that a company may wish to achieve, such as introducing the ability more easily to move processes between sites, to change scales to meet demand, and/or to operate processes using a variety of equipment. Some companies also have used the increased technical certainty of success of an existing product project to promote internal company learning and introduce a change in culture. Some companies have considered that such projects allow technical and manufacturing employees to understand better the needs of their "customers." Additionally, such projects have been used by companies to understand better regulatory agency implementation of new guidance and to improve a company's interactions with regulators.

Environment

The cost pressures on the pharmaceutical industry and the regulatory agencies mean that they need to do what is necessary to ensure that marketed products are manufactured and regulated as efficiently as possible. The result has been that both industry and regulators express a real desire for changes. From industry, there is a need to reduce costs by ensuring processes are as efficient and robust as possible, and for some companies, to move processes to lower cost manufacturing bases, while maintaining or improving quality.

There is also a change in the technological environment, which supports use of QbD. There is increased availability of more user friendly "point and click" software packages for use in design of experiment (DOE) studies and the development and understanding of multivariate models of processes provides the ability to realistically push forward science- and risk-based approaches. The new technical environment may help to overcome resistance that has been encountered with some scientists when asked to consider multivariate over univariate approaches in product development and process improvement for existing products.

Although there are strong drivers that support a move to a more science- and risk-based approach, it is also worth considering the barriers to such change. At the recent ISPE meeting in Copenhagen (April 2008), the following were identified as potential barriers to change in this area:

- perceptions that the effort to make such a change would outweigh the benefits
- a reluctance of industry in general to bring changes to regulators
- a reluctance to make changes to processes that are operating "satisfactorily"

All these barriers might be summarized by the saying "if it ain't broke, don't fix it."

While it is true that there are very few "broken" pharmaceutical manufacturing processes, it is also the case that although the vast majority is "satisfactory," very few meet the outstanding process quality criteria demanded in other industries. However, the changing economic environment means that pharmaceutical manufacturing is turning to the "lean" manufacturing organizations for insight in their own search for manufacturing excellence.

Therefore, there is a strong case for the move to a more science- and risk-based approach for existing products. Pressures on industry will drive change such as the development of more economic, robust, and efficient processes, and the movement of production to low cost manufacturing sites.

Some companies have already had success and delivered considerable benefits through moving to a more science- and risk-based approach for existing products as discussed, for example, in the case studies. It is the belief of the authors that the current environment supports a further and increasing move in that direction.

Conclusion

This paper has discussed the opportunities and potential benefits that a company may gain from applying science- and risk-based approach to enhance the understanding of an existing product.

Ultimately, it is up to each company to decide when to apply the principals of ICH Q8 (R1) to an existing product based on the business considerations described in this paper.

Comments are welcome regarding practical application and especially on the process flow diagram that summarizes business, technical, and regulatory considerations.

Glossary

Existing (Legacy) Product

An already-approved drug product which was developed originally using science applicable at that time within a

company and which was approved using regulations relevant to that time. It is likely that the process is largely fixed or has many univariate process parameters and unlikely that formal risk-based approaches were used either during development or in the submission.

Quality by Design

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and QRM (ICH Q8 (R1), Step 4).

Company Regulatory Strategy

A strategy in which a company considers proposed type of filing, information, and data to be included in the filing, and complementary pharmaceutical quality system elements, e.g., internal company change management system and compliance implications (ICH Q10, Section 3.2).

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Case Study no. 1

Summary

This case study from Wyeth Pharmaceuticals concerns two variations for an oral solid dosage form presented as encapsulated spheroids which have a controlled release coating. The work formed part of a continual improvement program for the product and QbD/process analytical technology (PAT) principles and tools were utilized during the project. The variations were submitted as part of the pilot phase of the EMEA worksharing exercise for quality variations [10].

The first variation proposed a variable quantity of water for granulation to produce a wet mass for extrusion–spheronization. A DS was developed from small-scale studies and an at-line analyzer used with a process model to adjust the quantity of water to optimize the yield of uncoated spheroids.

The second variation proposed elimination of redundant in-process testing of coated spheroids because statistical analyses showed that assay and dissolution results could be predicted from the results of upstream testing when applied to a statistical model.

A pre-submission meeting with the Rapporteurs selected for the EMEA worksharing exercise was very helpful in discussing scientific and procedural aspects of the submissions. The submissions included discussions of prior knowledge, development of DS and Control Strategy, and summaries of risk assessments. Flexible regulatory approaches included submission without prior stability studies because of product and process understanding, and in the case of the first variation, a proposal for validation by means of continuous quality verification rather than "three batch" validation.

The variations were submitted and collated questions from the Rapporteurs, other National Competent Authorities (NCAs), and EMEA PAT team were received at day 60. A pre-approval inspection of GMP aspects at the manufacturing facility was then completed by a team from one of the Rapporteurs. Positive assessment reports from the Rapporteurs and the majority of approvals from NCAs have now been received.

Background

The existing product concerned in this case study is an oral solid dosage form presented as encapsulated spheroids which have a controlled release coating. It is manufactured as shown in Fig. 2 at a number of locations around the world. A continual improvement program for the product included various projects aimed at improving yields, reducing cycle times and increasing efficiency, incorporating on-line or at-line process analyzers where appropriate, or utilizing other PAT tools. A review of this program resulted in the identification of two projects that provided opportunities to apply QbD/PAT concepts and which would result in variations to the national Marketing Authorizations that had the potential for inclusion in the pilot phase of the EMEA worksharing exercise for quality variations:

- Variation 1: variable quantity of water for the granulation to produce the wet mass for extrusion
- Variation 2: elimination of redundant in-process testing because of the ability to predict the results from upstream test results

The pilot phase of a worksharing exercise was for quality variations which introduced elements of process analytical technology (PAT) and/or a DS. The worksharing

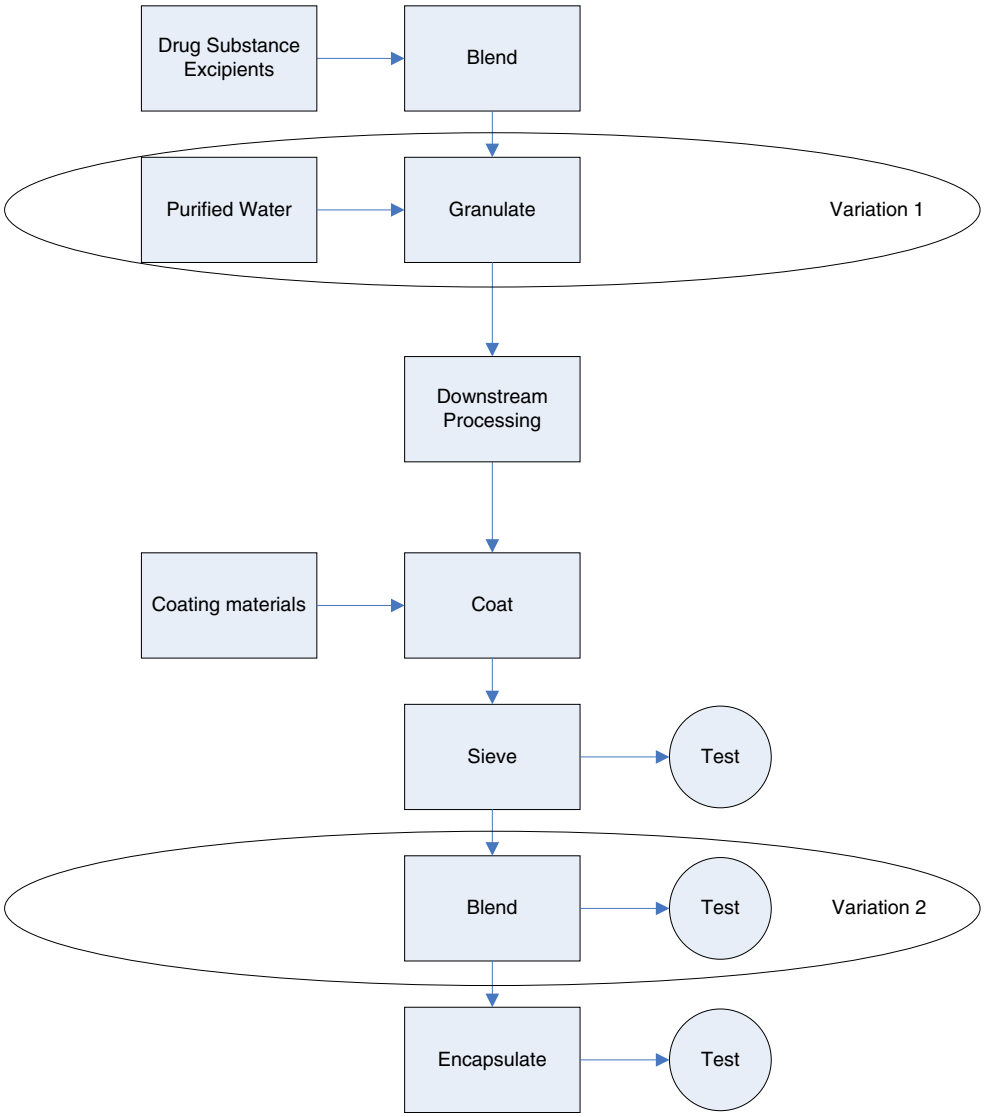

Fig. 2 Overview of manufacturing process

procedure is intended where variations to the same nationally authorized product are submitted to the different National Competent Authorities (NCAs) and is designed to produce a single outcome through a harmonized assessment (involving the EMEA PAT team) with a defined timeframe. Worksharing is a key element in the revisions to the variations proposed by the European Commission, which are intended to streamline the process for making changes to marketing authorizations, reducing the regulatory burden, and encouraging innovation [10].

Business Case

For the manufacturing facility, the business drivers for the projects were:

- increased yield of uncoated spheroids by reducing variability arising from the process
- reduced cycle time through the elimination of redundant in-process testing

In addition to the specific benefits from the changes in the unit operations noted above, we recognized that participation in the pilot worksharing program could realize other benefits:

- faster implementation of changes because of the defined timetable in the worksharing procedure
- lower compliance burden because of the single outcome from the worksharing procedure, i.e., harmonized marketing authorizations
- improved understanding of the preparation, submission, and assessment of quality by design (QbD) and PAT-related applications within Europe

However, there were some risks associated with participation in the worksharing pilot, including the

possibility that a single outcome would not be achieved because the procedure was voluntary—the NCAs are not legally bound to accept the decision reached during Worksharing. Typically, a manufacturing site supplying European markets also will supply other markets outside of Europe so a successful outcome from the Worksharing procedure would still need approval of the change in these other markets for the manufacturing facility to avoid the increased complexity resulting from operating multiple versions of manufacturing process. Therefore, our planning included approaches to mitigate the risks associated with these potential problems.

Confirm Target Product Profile and Critical Quality Attributes

The nature of the in-process changes being considered were such that there was no change in the Target Product Profile, and consequently the Finished Product Specification. The critical quality attributes (CQAs) for the finished product that were of primary interest were the dissolution and drug content—assay and content uniformity. Other CQAs were not impacted by the changes proposed.

Identify Knowledge Baseline

The product was developed in the late 1980s/early 1990s using good scientific principles and subsequently extensive successful manufacturing experience had been gained. The manufacture of spheroids using extrusion–spheronization is a widely used and proven technology. A considerable body of scientific literature exists for this technology and Wyeth had also employed external experts on a number of occasions. Knowledge gained from the development studies, commercial experience, and commercial-phase process optimization studies on this product also was supplemented by the knowledge gained from related products manufactured by Wyeth.

Develop Process Understanding

An outline of the manufacturing process is shown in Fig. 2. Granulations are produced to give a wet mass suitable for extrusion and spheronization. The resulting spheroids are combined to give a load for the coater where the controlled release coating is applied. The coated spheroids form a sub-batch and may be combined in multiple sub-batches to give a batch for encapsulation. The individual sub-batches must meet the specifications before being combined to give the encapsulation blend—the blending process is not a technique for bringing "failing" sub-batches into specification—and the coated spheroids are tested at various points in the process to ensure satisfactory dissolution and assay of the encapsulated product.

Variation 1: Variable quantity of water for the granulation to produce the wet mass for extrusion

A fixed quantity of water was specified in the description of the granulation process employed to produce a wet mass suitable for extrusion and subsequent spheronization. The fixed quantity of water formed part of the compliance details for the registered manufacturing process; therefore, it could not be changed without prior regulatory approval. During routine manufacturing operations, it was found that variability in a major excipient caused some variability in the size distribution of the spheroids. Although this was controlled by downstream processing prior to the coating operation to ensure consistent input into the coating step, variation in the yield of uncoated spheroids presented an opportunity for improvement. The relationship between the yield of uncoated spheroids and the characteristics of this excipient, as reported on the certificates of analysis, was investigated, but a correlation could not be established. Further investigation and discussions with the supplier suggested that other material attributes might be important, but the relationship was complex and poorly understood. Furthermore, based on current knowledge, it was impractical to control variability by modifications to the specification of the excipient. Since the relationship between the excipient physico-chemical characteristics and quantity of water required to give a suitable wet mass is imperfectly understood, it is not yet possible to predict the quantity of water required. So instead, the variation proposed to vary the quantity of water as necessary to produce a wet mass giving the maximum yield of spheroids of the correct size.

A design of experiments approach was used to study the granulation step at small scale. Initially, a screening study was used to identify the most significant variables. A second study employed a response surface design to understand the multivariate relationship, including any potential interactions, between the most significant variables. Data from a number of commercial-scale batches showed that the quantity of water could be varied without affecting the finished product CQAs of interest.

Because the understanding of the effect of variability of the excipient on the granulation process is incomplete, efforts are continuing to develop this understanding through further experimental work, as well as material and process monitoring and trending.

Variation 2: Elimination of redundant in-process testing because of the ability to predict the results from upstream test results

This variation proposed the elimination of testing of coated spheroids carried out after blending because it was

considered redundant. In the registered process, the coated spheroids are tested at three points as shown in Fig. 2: after the coating operation (as a sub-batch), after blending several of the sub-batches of coated spheroids into a larger single batch for encapsulation, and after encapsulation. It was proposed to eliminate testing at the second point, i.e., of the blended spheroids prior to encapsulation, because the results obtained at this point could be predicted from the results obtained from the first tests on the coated spheroids (as a sub-batch), applied to a statistical model.

Graphical and statistical analyses of assay and dissolution were carried out on a random selection of recently manufactured batches. Visual comparisons of predicted and actual values were made using individual value plots, boxplots and scatterplots, and any differences identified using descriptive statistics (mean, standard deviation, etc.). After applying an Anderson-Darling test for normality, either a paired *T* test (both data sets normally distributed) or Wilcoxen test (data not normally distributed) was used to examine the hypothesis that there was no statistically significant difference between them. It was established that the assay and dissolution results of the blended spheroids could be predicted from the results of the individual sub-batches comprising the blend and that fill weights for encapsulation could be set similarly.

Define Design Space and Control Strategy

Variation 1:

Data from the small-scale response surface DoE study of the granulation was used to establish a DS for the granulation for the production of uncoated spheroids. Parameters forming the DS included the quantity of water and the rate of water addition during the granulation process and properties of the granulation. However, to simplify the translation of the DS to operational practice, some of the variables, such as the rate of water addition, were fixed at target values in the batch record and a model was developed to relate the quantity of water added to the yield of in-specification spheroids. Since all the DOE batches generated product of suitable quality, the smallest and greatest quantities of water used were translated into commercial scale quantities by applying engineering scaling factors and proposed as the range for the quantity of water in the description of the manufacturing process in the regulatory submission. This range was consistent with the commercial-scale batches that had been successfully manufactured with different quantities of water and shown to produce spheroids of suitable quality.

No attempt was made to identify the "edges of failure" for the DS, but data from one earlier study showed that the addition of insufficient water would result in a wet mass that could not be further processed successfully. This suggests that the DS could be expanded to an "edge of failure" related to downstream processability of the wet mass: provided the wet mass from the granulation can be processed then the nature of the downstream processing and controls mean that spheroids will be of suitable quality. However, for business reasons, the company will choose to operate at a region within the DS that gives the maximum yield of uncoated spheroids.

For monitoring and control of the process, data from an at-line analyzer is used, in conjunction with a model developed from the experimental work, to adjust the quantity of water to meet predefined properties of the granulation derived from the DOE studies. The aim is to give a wet mass that after extrusion and spheronization produces an optimum distribution of uncoated spheroids, and thereby maximizes the yield at this step in the process.

Since the variation concerned the optimization of yield in this process step, the control strategy remained essentially unchanged. Informal risk assessments were conducted when developing the data and considering potential impact of the change on the entire product CQAs. A formal risk assessment of the impact of the change was made in which various failure modes were identified and the impact on the product evaluated. It was concluded that no new controls were needed if a variable quantity of water was used in the granulation and that product quality would be unaffected.

Variation 2:

A DS was not formally established for this change, but the variation clearly involved a modification to the control strategy for the product. An informal risk assessment was made of the likely impact of removal of the testing of the coated spheroids. Once the statistical analyses had been completed, a formal risk assessment was conducted to evaluate the impact of the proposed change on product quality. As with the risk assessment for the first variation, various failure modes were identified and the impact on product quality considered. The conclusions from this risk assessment were that the proposed change provided an equivalent control strategy and that product quality would not be affected.

Regulatory Strategy, Review, and Approval

Although the EMEA has published a reflection paper [11] that suggests information to be included in dossiers when PAT is employed, we requested an informal pre-submission meeting with the Rapporteurs and EMEA because of the nature of the variations and the novelty of the Worksharing procedure. We were able to discuss various scientific

aspects of the variations, the presentation of information, and agree on certain procedural aspects of the submissions. This proved to be very helpful in confirming the validity of some approaches we proposed and clarifying procedural issues for this pilot program.

When preparing the variations, summaries of the formal risk assessments were included, and appropriate citations and references were made to the prior knowledge (as discussed above) to support the approaches and conclusions presented. The development of the DS and the at-line analyzer was described in the first variation and the statistical analyses presented in the second variation. Control strategy was discussed in both variations in relation to the current controls and impact of the changes on product quality.

A number of areas were identified where "flexible regulatory approaches" might be possible. For example, for both variations, data from specific prior stability studies were not submitted. Arguments were presented to demonstrate that such studies were inappropriate and/or unnecessary because of the prior knowledge and product and process understanding. For variation 1, the variable quantity of water for the granulation, arguments were presented to explain why the conventional "three-batch" validation approach was inappropriate. Instead, a continuous quality verification (continuous process verification) approach has been proposed for implementation of this change.

An interesting outcome of the risk assessment and preparation of the first variation was the conclusion that an existing in-process control that was not registered should be registered. This was because this control assumed greater importance as part of the overall control strategy when varying the quantity of water for the granulation.

The worksharing procedure envisages the possibility of pre-approval inspection of the GMP aspects of such variations. For the proposed variations, a pre-approval inspection of the manufacturing facility was completed by a team (i.e., representatives for both assessment and inspection) from one of the Rapporteurs after the clock stop at day 60. Discussions during the inspection proved helpful in clarifying certain details included in the submission and in the questions received from the Rapporteurs, other NCAs, and the EMEA PAT team.

Because these were variations of a nationally registered (rather than centrally registered) product, with various strengths, and there also were associated variations needed to ensure harmonized marketing authorizations across multiple EU markets, this project finally involved Wyeth submitting more than 100 variations to NCAs as part of the Worksharing procedure. Positive assessment reports were received for both variations after responses to the questions at day 60 were submitted and reviewed by the Rapporteurs, and at the time of writing, the majority of approvals from the National Competent Authorities have been received.

Resources and Timescales

A multifunctional team was established to complete any additional work on the improvement projects and prepare the variations. Because the Worksharing procedure and some QbD/PAT concepts were new, some additional effort was required to prepare the variations. However, resource requirements to complete these projects were probably comparable to similar variations for a centrally registered product, and overall, the resources needed were probably lower than would have been required if the same variations had been submitted without using the Worksharing procedure.

Conclusions

These two projects demonstrated that QbD/PAT principles and tools could be successfully applied to continual improvement efforts on a product and realize significant business benefits for the manufacturing facility.

Although these were relatively simple, the process of developing and preparing the two variations was valuable in helping to develop our understanding of how the concepts described in ICH Q8, Q9 and Q10, and the FDA PAT guidance [12] could be applied to an existing product and successfully communicated to regulatory agencies. The worksharing procedure enabled a single outcome from the variations in a defined timetable and facilitated harmonized marketing authorizations to be maintained.

Milestone	Timing
EMEA worksharing pilot announced	June 2006
Wyeth proposed variations accepted into pilot	December 2006
Pre-submission meeting with Rapporteurs	April 2007
Variations submitted	June–July 2007
Day 0	August 2007
Day 60 clock stop: questions and inspection of manufacturing facility	October 2007
Day 90: positive assessment report for each variation	Q1 2008
Approvals by NCAs	Q2 2008 ongoing

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Case Study no. 2

Summary

This case study discusses a project to redesign the manufacturing process for an existing drug product. The objective of the project was to assess each unit operation utilizing the principles of quality by design (QbD) and refine the current manufacturing process through the concept of continual improvement. The focus of this case study is specifically on the autoclaving unit operation of the manufacturing process for a single-dose liquid intranasal dosage form with registered acceptance criteria for the microbial limit test attribute. It was not considered necessary to develop a DS for this project since the benefits could be obtained using a more conventional application of increased product and process understanding supported by a more appropriate and justified control strategy.

Business Case—Drivers for Change

This project was driven by the desire of the company to apply QbD principles to an existing drug product, to drive cultural change within the manufacturing operations, and to gain experience with the regulators in applying science- and risk-based approaches to existing manufacturing processes. The drug product discussed herein was chosen based on the substantial database of information and knowledge gained through 9 years of manufacturing experience.

Confirm Target Product Profile and Critical Quality Attributes

Each unit operation was assessed for a more fundamental understanding of its impact on product quality and the regulatory specification approved in the regulatory dossier. Due to the substantial commercial and patient experience with this existing product, it was assumed the currently approved specification was considered the critical quality attributes (CQAs).

Identify Knowledge Baseline

The release of each batch of product is based on compliance with acceptance criteria for the attributes from the regulatory specification listed in the first column of Fig. 3. The effect of each unit operation on the attributes for the drug product was investigated with the aim of building quality into the process rather than verifying it at the end of batch manufacturing. The outcome of this review resulted in the conclusion that the autoclaving unit operation had a potential to impact the attributes indicated with a check mark below.

Impurities

A more fundamental understanding of the effect of autoclaving on the impurity levels in the drug product was obtained. An evaluation of 14 commercial batches manufactured during a 6-month production period confirmed that the temperature cycles used during autoclaving contribute to the impurity levels (see Fig. 4).

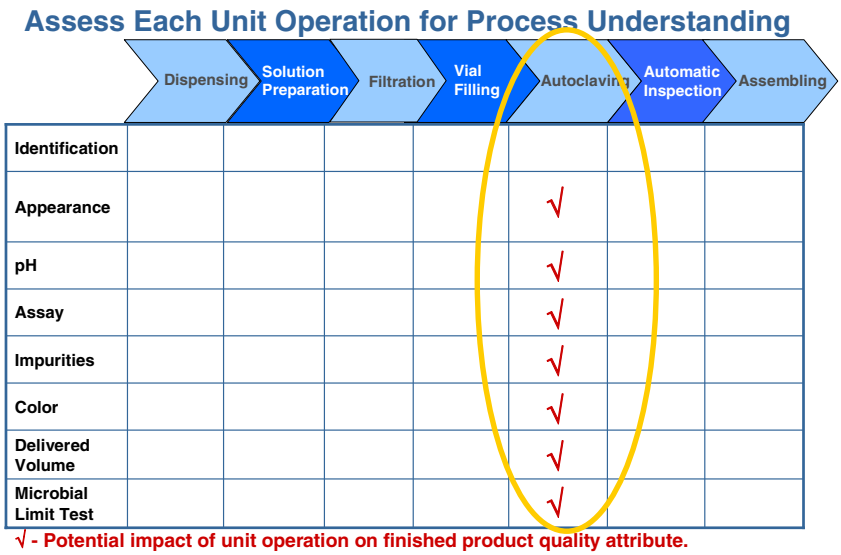


Fig. 3 Assess each unit operation for process understanding

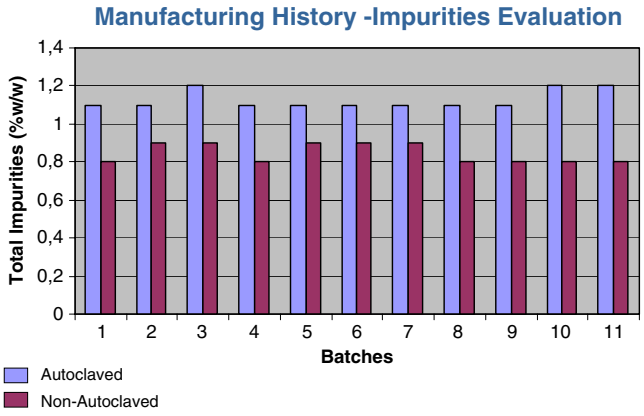


Fig. 4 Manufacturing history-impurities evaluation

Microbiological Controls

The microbial map (Fig. 5) depicts the microbial assurance and control systems applied during the current manufacturing process. The microbial assurance system is comprised of multiple elements, such as filtering each batch through a 0.2-µm filter and performing critical operations, such as vial filling, under laminar air flow (ISO 5). Microbial controls in the current process consist of environmental monitoring as well as bioburden testing of the bulk solution and filled vials prior to autoclaving.

The bioburden for the drug product prior to autoclaving is well controlled as demonstrated by the results for 50 commercial batches manufactured during the 5-year interval from 2001 to 2006. A result of <1 CFU/mL was obtained for all batches, which is well below the final drug product acceptance criteria of ≤100 CFU/mL for the microbial limit tests.

Product Knowledge

Studies performed in accordance with USP General Chapter <51> *Antimicrobial Effectiveness Testing* demonstrate that the formulation for the drug product, which does not contain preservatives, is inherently bactericidal and fungistatic. For the bacterial and yeast challenge organisms, a minimum of a 3-log reduction was observed. No increase was observed in the total count for the mold test organism (see Fig. 6).

Based on the evaluation of manufacturing history, current controls, and product knowledge, the working hypothesis was that autoclaving could be eliminated from the process while still meeting the registered acceptance criteria.

Develop Product and Process Understanding

A risk analysis was conducted to determine the risks of eliminating the autoclaving step from the manufacturing process. Based on the recommendations in ICH Q9 QRM,

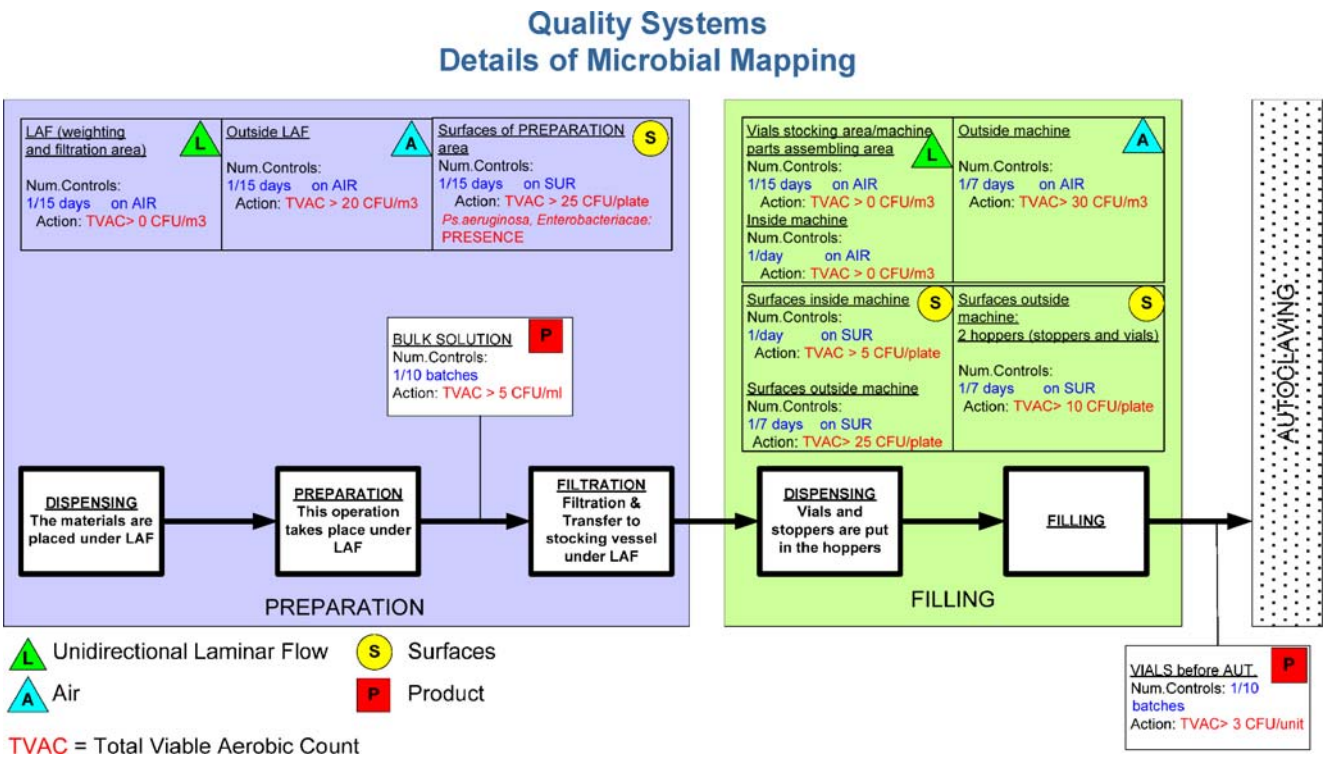


Fig. 5 Microbial Map

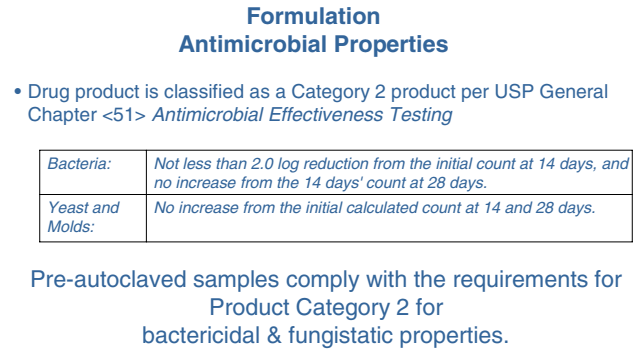


Fig. 6 Formulation antimicrobial properties

the project team selected Failure Mode, Effects and Criticality Analysis (FMECA) as the risk management tool.

FMECA is appropriate for evaluating potential failure modes within a manufacturing process and their associated risks. This tool requires a thorough investigation of the failure modes with respect to their degree of severity, their probability of occurrence, and the detectability of their consequences (Fig. 7).

The team developed a customized scoring grid to address the question of whether eliminating autoclaving from the manufacturing process results in an acceptable risk (see Table 1). The aspects of risk outlined in the grid are defined as follows:

- Severity is the estimation of the impact of a failure mode.
- Occurrence is the estimation of how often a failure mode may occur based on the last 5 years of production data.
- Detectability is the estimation of the ability to detect or prevent a failure.

Numerical ratings were assigned to the various levels of risk associated with each aspect so that a risk priority number can be calculated for each failure mode.

A risk control range also was defined to assess whether the risk priority number associated with a given failure mode is acceptable or if further action is needed to mitigate the risk (Fig. 8).

Figure 9 illustrates the application of FMECA to the vial filling step and the conclusions that were reached based on the current microbial assurance and control systems that are in place. The conclusions were the following:

- If the drug product is autoclaved, there is no adverse effect on microbial quality as autoclaving significantly reduces the risk of contamination.
- If the drug product is not autoclaved, potentially contaminated vials and stoppers can contaminate the drug product.

Based on the scoring table provided previously, the risk priority number (RPN) is 21 when the drug product is autoclaved, and 105 if the autoclaving step is eliminated.

Based on the predefined risk control range outlined above, a risk priority number=105 is considered a potential risk to the patient requiring the development of a risk control strategy to mitigate the risks in order to justify the elimination of autoclaving.

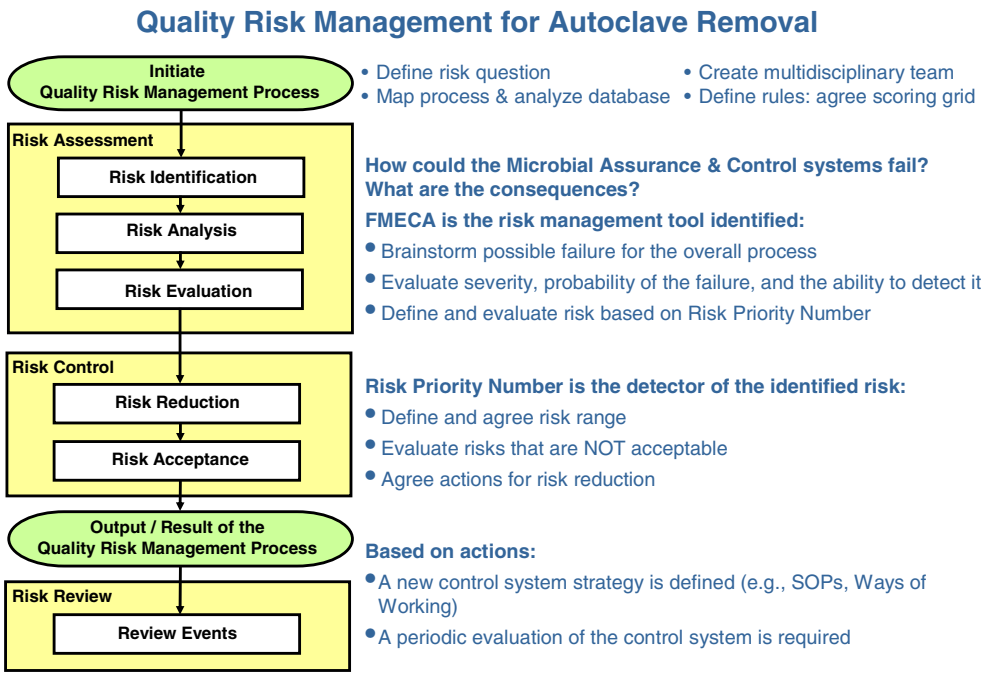


Fig. 7 Quality risk management for autoclave removal

Table 1 Initiate quality risk management define the rules

Scoring table

Rate	Severity		Occurrence		Detectability	
1	No effect	None	<1 Occurrence in 5 years	Very rare	All the applicable controls are in place	Always detectable
3	No patient impact Process performance decreasing (MLT<10 cfu/ml)	Low	1 Occurrence in 1 to 3 years	Rare	Most of the applicable controls are in place	High probability of detection
5	No patient impact Process performance decreasing (MLT<100 cfu/ml)	Medium	1 Occurrence in 6 to 12 months	Sometimes	Some of the applicable controls are in place	Moderate probability of non-detection
7	Potential patient impact Batch not rejected (MLT>100 cfu/ml and objectionable microorganisms absent)	High	1 Occurrence in 1 month	Frequent/No Information	Few of the applicable controls are in place	Remote probability of detection
10	Potential patient impact Batch rejected (MLT>100 cfu/ml and objectionable microorganisms absent)	Very high	>1 Occurrence per day	Very frequent	None of the applicable controls are in place	Not detectable

For the example of vial filling, the corrective actions that were identified (Fig. 10) will reduce the occurrence and increase the detectability of the identified failure modes associated with each risk category. Consequently, implementation of these corrective actions lowers the risk priority number from 105 to 25 for the vial filling operation without subsequent autoclaving. This risk priority number correlates to a very low risk which is acceptable to the product, patient, and the business.

Develop Product Quality Assurance Strategy/ Pharmaceutical Quality System Elements

The actions agreed upon to reduce the risk associated with the removal of autoclaving include modifying production equipment design, tightening microbiological specifications for components, and revising standard operating procedures to improve the microbiological control of operations performed in the manufacturing area. Bioburden testing also will be performed on every batch rather than the current practice of one out of ten batches.

The elimination of autoclaving coupled with the implementation of the control strategy identified by the risk analysis exercise will assure adequate microbial control of the drug product. In addition, elimination of autoclaving will have the benefit of lowering the impurities in the drug product.

The quality systems and processes that will be used to ensure that the drug product continues to meet the registered quality requirements and provide periodic reporting available for confirmation by the regulators were defined. The product and process performance of the drug product is evaluated continuously through the site's periodic product review process and is compiled for or reported to respective regulatory agencies, as required.

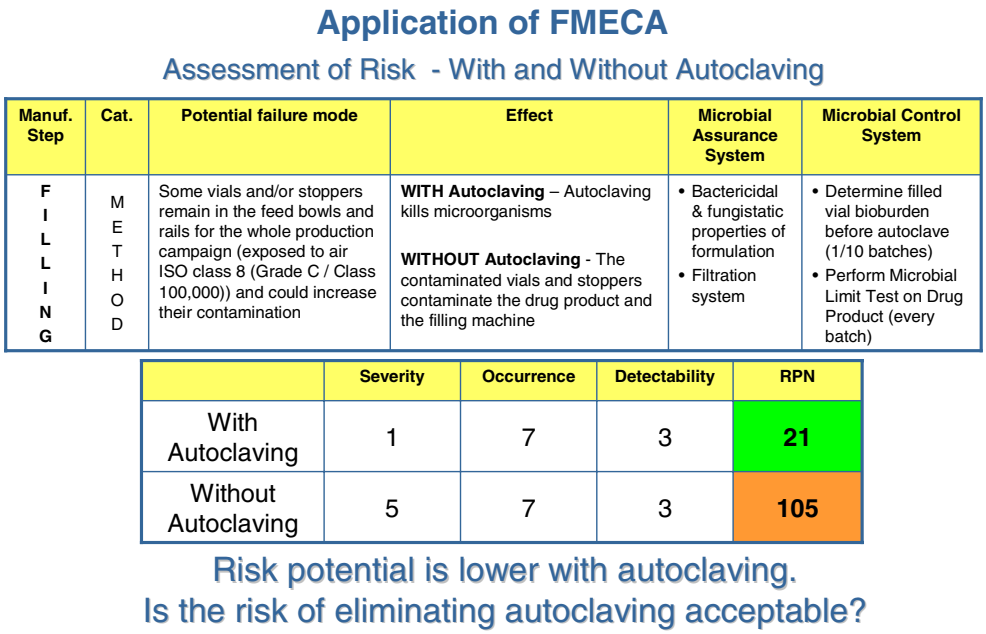
For example, in the US, the information is reported in the annual product review, as required by current good manufacturing practices (21CFR 211.180(e)). The report includes a review and trending of analytical and stability data, in-process controls, raw materials, packaging components, and changes to the process, facilities, and equipment. The output of this review provides recommendations for further process and product improvements. This evaluation process meets the objectives of ensuring that the drug product continues to meet the registered quality requirements.

Fig. 8 Risk control acceptance and reduction

Evaluate Project vs. Business Case

Re-evaluation of the manufacturing process, while applying QbD principles, led to the elimination of an entire unit operation, which ultimately led to a more time- and cost-efficient process.

Fig. 9 Application of FMECA



The main challenge of this project from a regulatory standpoint was translating site documentation (e.g., the output from the FMECA exercise) and product and process knowledge into a regulatory submission. Additionally, it was a challenge to ensure all departments were aligned with updating processes and/or systems to accommodate the QbD approach.

Post-approval submissions, which included information demonstrating product and process knowledge as well as details regarding the FMECA exercise, were submitted to and approved by US and European regulators with minimal questions. The end result of this project was not simply a revised manufacturing process, but also a knowledge base that serves as a platform for continual improvement throughout the lifecycle of the drug product.

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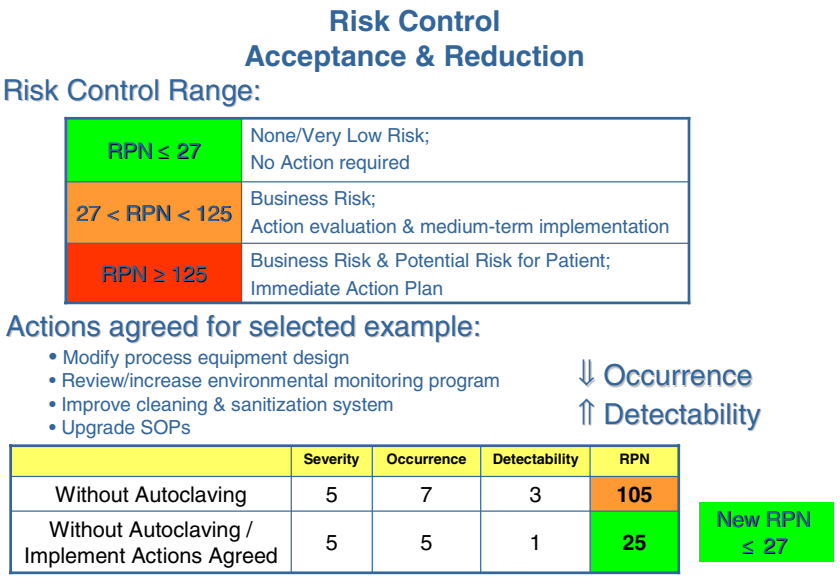
Fig. 10 Risk control
Acceptance and reduction



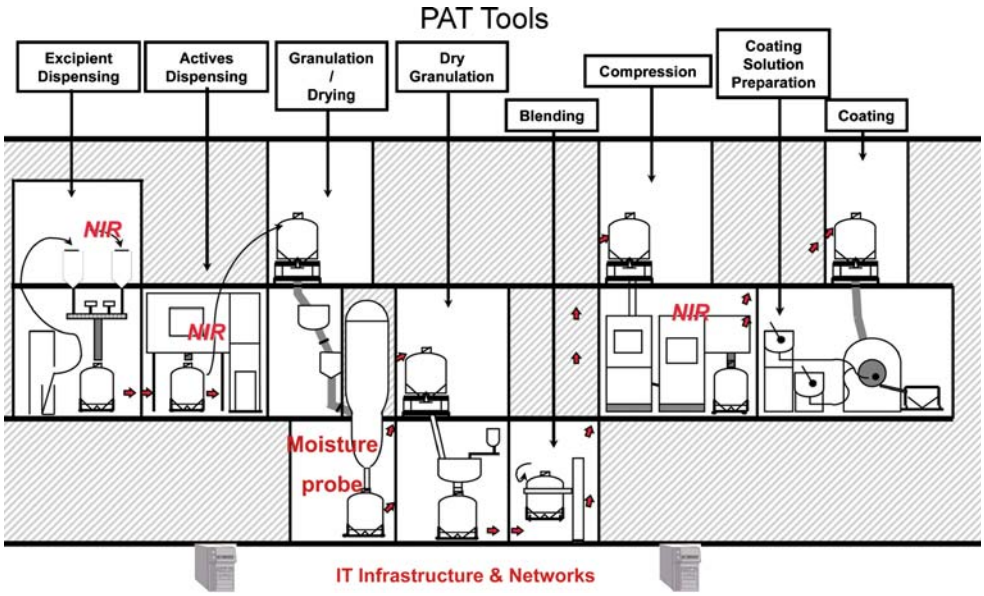


Fig. 11 PAT Tools

Case Study no. 3

Summary

This case study will discuss how AstraZeneca developed a real-time release strategy for an existing marketed oral dosage form, and summarize some of the technical and regulatory challenges, which led to satisfactory approval throughout European member states for real-time release as an operational alternative to conventional end-product testing. The post-approval variation was submitted, reviewed, and approved using the EMEA worksharing procedure [10].

Background

AstraZeneca and the original companies prior to merger in 2000 were interested in the concept of real-time release for existing marketed products, and indeed had an ambition to apply it to a product at time of first approval. Several projects were progressing, and these were labeled under various titles, such as parametric release, process analytical chemistry, and of course, process analytical technology (PAT).

The example project was running before and in parallel with various regulatory initiatives, such as the US FDA guidance on PAT [12], the EMEA guideline on parametric

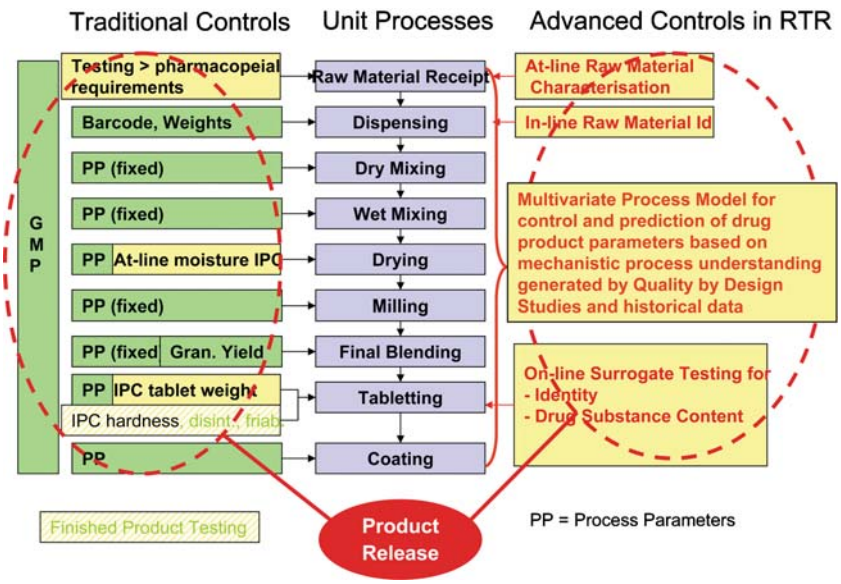


Fig. 12 Information elements to support release

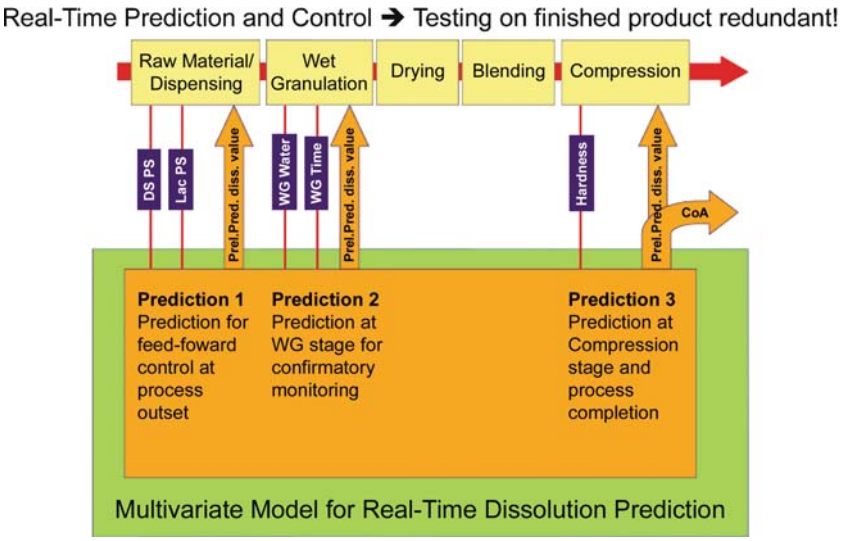


Fig. 13 Scheme to predict end-product dissolution

release [13], and the ICH guidelines Q8, Pharmaceutical Development and Q9, QRM. It is an established product, registered nationally throughout Europe, and in the rest of the world. The product is an immediate release tablet with conventional wet granulation and fluidized-bed drying, followed by compression and application of a nonfunctional film coat. In Europe, it is manufactured in two plants in one location with more than 600 batches having been manufactured successfully. The tablet contains 40% drug substance loading. The drug substance has low aqueous solubility, is lipophilic, rapidly absorbed, being Biopharmaceutical Classification System (BCS) class 2, with no degradation during processing.

Business Case

The project was to introduce real-time release (RTR) for an existing approved product, this desire not being business critical. The main objectives were business learning relating to the technical, operational, and organizational aspects of application of on-line and at-line analysis to the process, as well as to the regulatory application process, which should give dialogue with regulators. "Regulatory flexibility" was not a major driver. Review at the end of project indicated that cycle times had reduced from a typical time of about 12 days from dispensing of ingredients to availability to the market to about 4 days, QC/QA work reducing from 8 days to 8 h. This reduction in time leads to a need for less working capital, which is a major cost-saving and given the work to confirm process robustness as part of the scheme, there is additional assurance that product will pass specification, giving a more predictable supply chain.

Confirm Target Product Profile and Critical Quality Attributes

Review of the original development information and experience from more than 10 years supply to the market confirmed that the target pharmaceutical product profile and critical quality attributes (CQAs) of identity, assay, content uniformity, and dissolution remained unchanged.

Identify Knowledge Baseline

Review of original pharmaceutical development information along with manufacturing experience confirmed that it was not necessary to make any change to the formulation or the finished product specification. Further review of manufacturing information, including time series statistical analysis of production batches, also confirmed a robust manufacturing

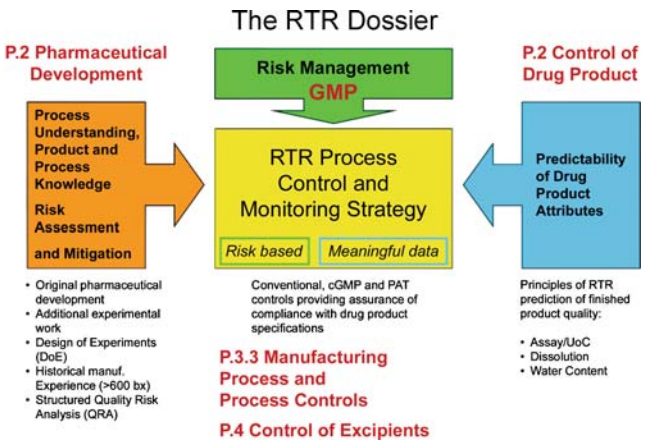


Fig. 14 The RTR Dossier

process with only weak time order-dependent manufacturing pattern. A formal quality risk assessment (QRA) using Failure Mode Effect and Criticality Analysis (FMECA) was conducted and showed that, to operate a RTR scheme, no additional parameters to those already known were required to be studied. The major input variable that has an impact on CQAs is particle size of drug substance, as expected for a BCS class 2 drug. This FMECA did conclude that there was more structured work required to understand better the interaction between drug substance particle size and other raw material input variables, and to produce values for a certificate of analysis in lieu of end-product testing, for example, to predict dissolution values for drug product. Values for other quality attributes in the finished product specification could be more easily determined from the proposed RTR scheme since at-line tests were in effect surrogates for end-product testing.

Develop Product and Process Understanding

As a consequence of the QRA described above, two design of experiment (DOE) series of studies were conducted. The first was designed to understand better the relationship between raw material properties and processing parameters and develop a process model. This process model allows calculation of dissolution values from raw material attributes and process parameters. The second series of studies supplemented information from the first series and refined the robustness of the near infrared (NIR) calibration model. Both series of studies were designed based on the initial QRA exercise and on further review of historical data so that experimental designs were optimized. Most of this DOE work was conducted at smaller scale than that used for normal production, indeed at small laboratory scale; however, some studies were conducted to justify that the conclusions from smaller scale studies are applicable at production scale, and information was given justifying the applicability of the model to production scale.

Develop Design Space, Product Quality Assurance Strategy, and Control Strategy

Based on output from these studies and review of historical information, a RTR release scheme was proposed, based on a further QRA, and this is summarized in terms of new at-line analyses involving NIR techniques in Fig. 11, and in terms of information elements to support release in Fig. 12. The scheme to predict end-product dissolution is given in Fig. 13.

As an important part of establishment of routine operation of the control strategy, considerable effort was given to establish and validate an in-house system for capturing and storing data, this aspect being one of the major challenges of the project.

Regulatory Strategy, Review, and Approval

For this example, it was decided not to develop a DS submission, although sufficient information was judged available to do so. The regulatory submission strategy was to gain approval for a novel concept (RTR for a solid dosage form) using some at-line NIR-based analytical methods supplemented by conventional data taken during production. The baseline position before this variation submission was essentially different dossiers approved in each member state, not in common technical document (CTD) format, and the intention was to move to a single harmonized dossier across all member states using the, at that time, untried EMEA worksharing procedure. An outline of the important elements of the dossier construction is given in Fig. 14. The submission was a type 2 variation to an existing approved license, and pre-meetings were held with the EMEA PAT team and quality working party to gain agreement to the principle.

Review of the dossier was more complex than normal since there was a pre-approval inspection which involved reviewers from the Rapporteur member state and questions on the submission came from reviewers and inspectors. The attendance of the reviewers at the inspection was very beneficial in reaching a shared understanding of the control strategy. EMEA rigorously followed timescales given in the worksharing procedure; however, there were a lot of questions which required time for the sponsoring company to consider and answer, resulting in the final timescale to approval being slightly longer than regulatory procedure.

The application was approved in the Rapporteur and co-Rapporteur member states and subsequently in other states indicating that RTR for a solid dosage form using in-process NIR methods is approvable in European member states. In this case, end-product testing is eliminated and replaced by a matrix of information elements from raw material and in-process testing using new at-line analytical methods in combination with conventional in-process tests. The finished product specification and method of processing remained unchanged compared with before the variation submission.

Resources and Timescales

The project in totality was in operation for approximately 5 years; however, the technical program following the first QRA took about 2 years and involved an estimated eight people full time (not the same people throughout) for that period. The regulatory submission took about 8 months to construct, review, and approve.

Conclusion

A RTR scheme as an operational alternative to conventional end-product testing was developed and successfully ap-

proved in Europe using the EMEA worksharing procedure. The project was complex and involved many disciplines from the company working in an efficient project team.

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