Summary of the EMA Joint Regulators/Industry QbD workshop
(London, UK; 28-29 January 2014)

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Abstract

This paper summarises the discussions and insights gained from the key themes that emerged during the Quality by Design (QbD) Workshop held at the European Medicines Agency offices in London, UK, on 28-29 January 2014. Industry and regulators shared practical experiences from 6 case studies (5 approved small molecule products and one phase 3 biotechnological product) based on QbD submissions by 5 companies (AstraZeneca, GlaxoSmithKline, Novartis, NovoNordisk and Pfizer).

The case studies covered a range of different development, regulatory submission and post-approval aspects of QbD, and were developed through confidential discussions between the company representatives and regulators. Key themes that emerged from the workshop discussions were: 1. Presentation of Information in Submissions (Development story and the presentation of information in Marketing Authorisation Applications; Risk assessment and criticality); 2. Development Aspects (Design space; Use of models; Control strategy); and 3. Post Approval Aspects (Lifecycle management; Dossier – Quality System interactions; Handling of Deviations). Many aspects of QbD for biotechnological products are similar to small molecules, but there are some important differences highlighted in this paper.

The final section of the paper discusses some proposals for future developments to address the issues that were identified.

Keywords

Quality by Design (QbD); European Medicines Agency (EMA); Workshop London 2014; Presentation of Information; Submissions; Regulatory Dossier; Development; Risk
assessment; Criticality; Design space; Models; Control strategy; Post-Approval; Lifecycle management; Quality System; Deviations
**Lay Abstract**

This paper summarises the discussions and insights gained from the key themes that emerged during the Quality by Design (QbD) Workshop held at the European Medicines Agency offices in London, UK, on 28-29 January 2014. Industry and regulators shared practical experiences from 6 case studies (5 approved small molecule products and one phase 3 biotechnological product) based on QbD submissions by 5 companies (AstraZeneca, GlaxoSmithKline, Novartis, NovoNordisk and Pfizer).

The case studies covered a range of different development, regulatory submission and post-approval aspects of QbD, and were developed through confidential discussions between the company representatives and regulators. Key themes that emerged from the workshop discussions were: 1. Presentation of Information in Submissions (Development story and the presentation of information in Marketing Authorisation Applications; Risk assessment and criticality); 2. Development Aspects (Design space; Use of models; Control strategy); and 3. Post Approval Aspects (Lifecycle management; Dossier – Quality System interactions; Handling of Deviations). Many aspects of QbD for biotechnological products are similar to small molecules, but there are some important differences highlighted in this paper.

The final section of the paper discusses some proposals for future developments to address the issues that were identified.
**Introduction**

On 28-29 January 2014 the European Medicines Agency hosted a Quality by Design (QbD) Workshop, organized by European regulators, industry and the PDA, at its offices in London. During the workshop industry and regulators shared practical experiences from 6 case studies based on QbD submissions by 5 companies (AstraZeneca, GlaxoSmithKline, Novartis, NovoNordisk and Pfizer). Presentations from the workshop are available on the EMA website QbD page (Ref. 1) and this paper summarises the discussions and insights gained from the key themes that emerged during the workshop.

The case studies (5 approved small molecule products and one phase 3 biotechnological product) were chosen to cover a range of different development, submission and post-approval aspects of QbD, and were developed through confidential discussions between the company representatives and regulators. Many aspects of QbD for biotechnological products are similar to small molecules and this was reflected in the issues and proposals discussed during the workshop. However, there are some important differences; and those are highlighted in the paper, albeit that to date there has been limited experience in Europe with ‘QbD’ biopharmaceutical submissions.

The discussion points and recommendations from the workshop were collated into key themes and grouped into three areas, as follows:

1. Presentation of Information in Submissions
   1.1 Development story and the presentation of information in Marketing Authorisation Applications
   1.2 Risk assessment and criticality

2. Development Aspects
2.1 Design space
2.2 Use of models
2.3 Control strategy

3.  Post Approval Aspects
   3.1 Lifecycle management
   3.2 Dossier – Quality System interactions
   3.3 Handling of Deviations

The final section of the paper discusses some proposals for future developments to address the issues that were identified.

This paper was developed from summaries of the different themes prepared by teams of industry workshop participants with contributions from the regulatory agency participants listed in the Acknowledgements section. The success of the workshop was the result of hard work and enthusiastic contributions by Organisers, Case Study Developers, Presenters and Attendees.

1. **Presentation of Information in Submissions**

1.1 The Development Story and Presentation of Information in Marketing

**Authorisation Applications**

One of the major issues with science-rich CMC submissions has been the effective communication of the important aspects of a development program in a way that appropriately differentiates the critical aspects from the mass of supporting data. Industry and regulators share a common interest in concise, focussed submissions that facilitate efficient
assessment and support optimised lifecycle management after approval. Particular aspects of the presentation of information explored during the workshop included:

- How can the development story in QbD submissions be presented to facilitate assessment?
- What details are necessary for review of risk assessments, design of experiments (DoEs), Process Analytical Technology (PAT) tools, etc. and how would this vary depending on the use of the information in the finished product design, manufacturing process and control strategy?
- Is the Common Technical Document (CTD) format adequate to support presentation and review of ‘enhanced development’ submissions? Is separation of ‘registered detail’ from supportive information in the CTD format clear?
- How and where should the control strategy (including any proposed Design Space) and its development be described in the submission?
- When assessors are considering requests for operational flexibility would it be helpful to describe elements of the Quality System in the Application file to aid understanding of how changes are foreseen to be managed during the lifecycle?

**Recommendations**

Information presented in a dossier will vary according to the product type and complexity, the nature of the challenges overcome during development and the knowledge gained - it is not ‘one-size-fits-all’. ICH terminology should be used and non-ICH terminology such as “key”, “major” or “minor” should be avoided as the lack of agreed definition can create confusion.
Assessment is facilitated by summarising the control strategy that assures delivery of the critical quality attributes (CQAs) and explicitly stating the extent of flexibility proposed by the applicant. The CTD structure is not optimal for provision of this overall perspective to the assessor, but experience of the workshop participants suggests that the limitations can be overcome. Sections S.2.6 and P.2 have been used successfully for providing summary information. This control strategy summary would also be useful for the inspector. Tabular formats are recommended to present important elements of the Control Strategy, linking the quality target product profile (QTPP), to CQAs of drug product and drug substance and to critical process parameters (CPPs) (and material inputs) of the process.

The presentation of ‘enhanced’ or QbD aspects should include sufficient detail or rationale to explain the derivation of CQAs and CPPs, and the tabular format can link/reference detailed sections of the CTD where further detail can be found.

The depth and/or extent of information presented on risk assessments, DoEs, mathematical models etc. should depend upon their purpose or use in assuring the quality of the product and associated disposition decisions. For example, if a DoE was used for screening purposes, summary information could be sufficient. By contrast, a DoE used to establish a design space employed as part of the control strategy would need considerably more detail. This might include the rationale for the DoE approach, tables of inputs (including batch size, ranges studied, factors kept constant during the DoE) and results, data interpretation, statistical significance of parameters studied, scale-dependence, and so on. It may be helpful to consider the degree to which commitments in the manufacturing process and control strategy could be thought of as ‘non-traditional’ because it is likely that more understanding (science and risk / criticality based) would be expected in such cases e.g. if a flexible manufacturing process
and/or a “RTRt-like” control strategy is applied, more understanding is expected to be presented under development. It was agreed that Pareto plots and Ishikawa / fishbone diagrams are useful tools for communicating some risk assessments. If a design space is proposed, its development should be clearly described in the relevant development sections (e.g. S.2.6 / P.2.3), and it should be explicitly defined (e.g. by equation, tables and/or visual representations) in the manufacturing process description sections of the dossier (e.g. S.2.2 / P.3.3).

1.2 Risk Assessment and Criticality

Communication of risk assessment/management in regulatory submissions presents a number of challenges, including:

- Translation of the raw Quality Risk Assessment outcomes into an appropriate summary.
- The difficulty in defining the threshold for ‘critical’ given that it is perceived as a continuum in ICH guidance (e.g. ICH Q11 Section 10.2 example 2).
- The provision of linkages between risk assessment and the development of the control strategy.
- The difficulties managing post-approval changes given the differences in the post-approval frameworks between markets (and potentially the approval of what is a CPP and non-CPP).

Furthermore, for biotechnological products additional key differences add to the challenges:

- Immunogenicity is a significant concern for biologics – and only limited knowledge exists on the relationship between quality attributes and immunogenicity.
- Complexities in biotechnological products can lead to uncertainties about the definition of CQAs and difficulties establishing linkages of process parameters to CQAs.

- CQAs may not be readily analysed in the final product and therefore consistency in the manufacturing process becomes an important part of the control strategy and consequently in-process specifications and controls are frequently set based on manufacturing capability as well as safety & efficacy.

- Even if defined as non-critical, the inclusion of non-CPPs in process descriptions for biopharmaceuticals can present a burden in lifecycle management because changes currently require prior approval before implementation.

**Recommendations**

Quality risk assessments can help to prioritise development activities and identify critical process parameters and material attributes potentially affecting product quality, guiding the establishment of the control strategy. Risk assessment is an iterative process, being repeated during development as new knowledge is gained, so that the extent to which risks have been mitigated can be assessed. For this reason the sequence or time points of the risk assessments during the development should be clearly described. The risk assessment tool used (e.g. FMEA) should be stated and, when a quantitative tool is used, scoring and thresholds used to classify the risks should be explained. Information on the Applicant’s experts who performed the risk assessment is not required in the submission and it was agreed that raw data from the risk assessment was not needed for the assessment of the Marketing Authorisation application. However, if a novel risk assessment is used, a definition of the tool and a sample output should be provided.
The differentiation of critical and non-critical parameters is generally based upon the severity of impact on the critical quality attributes of the drug product or drug substance. However, for biopharmaceutical products the impact of process parameters on process performance indicators, such as yield, can also be important to define. In general the identified CQAs are unlikely to change during the product lifecycle, although there can be some uncertainty about some potential CQAs for biopharmaceuticals. Because the definition of criticality of a parameter is based upon current knowledge, it could evolve during the development and commercial manufacturing stages of the product lifecycle as process changes are made, or as new knowledge is gained. It should therefore be subject to an ongoing process of risk assessment during the lifecycle of the product. Risk assessments can be used to support variation applications and should be available for inspection.

The use of prior knowledge of the applicant in the assessment of risk is acceptable. Risk assessment outcomes that are not aligned with existing scientific knowledge should be justified. A variety of tabular presentations of risk assessments were presented in the various case studies at the workshop. A matrix presentation of CQAs versus manufacturing process steps can be used to summarise the holistic risks and failure modes across a manufacturing process (see table below) and it was also suggested that more detailed tables presenting CQAs versus PPs and material attributes in each of the process steps could be useful:

(Table I)

A good example for presenting a risk assessment summary table is also presented in the training material of the ICH Q-IWG on the implementation of Q8/Q9/Q10. Scoring and
thresholds used to classify the risks are provided and risks discussed in the comments column in Table II:

(Table II)

The implications of criticality are explored in more detail in subsequent sections on Design Space (2.1), Role of Models (2.2) & Control Strategy (2.3).

2. Development Aspects

2.1 Design Space

Although the design space concept from the ICH Q8, Q9, Q10 guidelines has been incorporated into the European regulatory framework including the EU Guideline on Variations categories, the value of the concept is not being fully realised through the product lifecycle. From a global perspective, depending on the regulatory framework in place, the review outcome and lifecycle management of a product submitted with a design space can have substantially different outcomes.

Aspects that were raised for discussion included:

- Purpose of the design space and role in the control strategy.
- Clarity in the definition of design space in the dossier and the operational flexibility being requested by the applicant, including
  - The outcome of multivariate experimentation and the description of processes by design space compared with Proven Acceptable Ranges (PARs);
  - Consequences for regulatory changes when non-Critical Process Parameters (non-CPPs) are included in the design space: a potential interpretation of the EU Guideline on Variations categories is that all changes to a design space are
classified as high risk changes (Type II variations). Can changes to non-CPPs be managed differently to CPPs?

- Impact of scale on design spaces developed using small-scale experiments and verification of design space at commercial scale.

**Recommendations**

Companies should consider the need to develop a design space and the way it will be applied in the manufacture of the drug product or drug substance. Enhanced development (QbD) does not require the development of a design space: this is optional. At present is seems that design space can be most usefully used to support the registration of, for example, adaptive processes (that is, adjusting CPPs based on upstream attributes) and for application of real time release testing (RTRt) based on soft sensors (e.g. dissolution) where description of the interactions of material attributes and process parameters are important in defining how the process and product quality is controlled.

Depending on how the design space is derived, it may include both CPPs and non-CPPs, but in some cases a design space description in a dossier may include only CPPs and material attributes impacting CQAs. Nevertheless, a sufficiently detailed description of the manufacturing process is required in the dossier and this could also include non-CPPs. Operational flexibility associated with the design space should be described by the applicant, and it may be beneficial for the applicant to propose how changes associated with the design space would be managed. For example, a table for quality attributes and process parameters defining the design space with the corresponding ranges, together with a table for quality attributes and process parameters not included in the design space with their target values or ranges could be used. Target settings or operating ranges could also be included to indicate
the initial region where it is intended to operate the commercial process. However, it should be stressed that movement within an approved design space is a deliberate, validated adjustment to the process to make it operate optimally within approved limits and hence does not require a variation application.

Design space verification has been discussed in recent guidance from the EMA-FDA pilot program for parallel assessment of QbD applications (Q&A published 4 November 2013). Verification of the whole design space at commercial scale prior to commercialisation is not necessary. Verification of a more restricted region, for example the operating ranges, may be performed initially. This should be accompanied by a design space verification protocol, which should justify and describe, applying a risk-based approach, how the applicant will conduct the design space verification studies. Where the design space has been established using small-scale experiments and models, the impact of scale must be considered by the applicant, and any scale-independence justified. These justifications can be based on first-principles understanding and/or empirical correlations.

It was confirmed that it is possible to release batches based on compliance with the design space, if this has been approved by the competent authority. Soft-sensor models used for RTRt decisions may be supported by multivariate data analysis (MVDA) and statistical process control (SPC).

2.2 Role of Models

Process modelling is an integral part of the QbD framework. Models can be derived to assist in process development, process understanding, design space determination, on-going process verification, as well as Process Control (feedback or feed-forward) thereby making modelling
part of the product lifecycle. The increasing use of modelling and inclusion of model-related information in dossiers has highlighted several areas where common understanding has not been achieved, including:

1. Operational flexibility associated with the use of models

2. Terminology and implications related to some empirical models – concepts like Out-Of-Trend (OOT) and Out-Of-Specification (OOS)

3. Terminology related to PAT models

Recommendations

Discussions during the workshop confirmed agreement that the level of detail about the model to include in the dossier should be related to the impact of the model i.e. High, Medium, Low risk models as per the guidance in the ICH Q-IWG ‘Points to Consider’ document. For example, if a Multivariate Statistical Process Control (MSPC) model is used for monitoring only and not for control purposes, then it can be regarded as a low or medium impact/risk model. However, if an MSPC model is used as part of a RTRt strategy then it could be considered a high impact model.

When models are used in the control strategy the following aspects should be described in order to provide clarity for assessment of the dossier:

- Is a design space model used as a basis for RTRt?
- Is a PAT tool utilized for release, or for in-process monitoring?
- When used for process monitoring, is the model used for continuous improvement, or as an alternative approach to validation?
- Are calibration samples and validation samples for spectral calibrations clearly defined?
• What model maintenance plans are in place? Since a model is always provisional, its validity should be confirmed by regular review, and updates made as needed. This process should be incorporated in the company’s Pharmaceutical Quality System and is subject to inspection.

Assumptions and limitations of any models should be explained and justified, as appropriate. The type of justification for theoretical models (based on first principles) and empirical models could be different. When statistical indices are used their meaning (and any assumptions) should be explained.

2.3 Control Strategy

A control strategy derived using a systematic science- and risk-based approach is a key output of an enhanced approach to development, linking process understanding, product and process complexity and the applicant’s manufacturing commitments. Agreeing the control strategy as a central output of enhanced development would lead to optimal consideration of the following key questions by all parties:

• Are critical quality attributes of the product sufficiently assured by the proposed control strategy? If not, what additional controls / commitments (or justification) should be provided?

• Does risk assessment information need to be described in more detail to justify any ‘enhanced’ (reduced) elements of manufacturing process commitments or controls?

• Does the experimentation conducted support the applicant’s proposed manufacturing commitments and controls (e.g. design space, RTRt, flexible processing)? Is potential risk from development of process at small-scale mitigated by the control strategy applied?
• Does the control strategy assure quality across the lifecycle? If not, what additional controls or change management commitments should be considered? (e.g. design space verification; non-routine tests etc.)

Recommendations

Product release against specification alone does not necessarily assure product quality, an appropriate control strategy is necessary. The control strategy proposed should provide assurance of all CQAs and should come from process understanding guided by risk assessment. A control strategy can utilise end-product tests, input and intermediate material controls, and process and in-process controls from various types of analytical methodologies. GMP provides an underlying support to the product-specific elements of the control strategy. As product and process understanding increases it may impact the control strategy implemented:

• A product with enhanced understanding can employ a different approach to controls and manufacturing commitments compared to a product for which less understanding exists (where a more traditional control strategy, probably including full end product testing, may be expected).

• Enhanced knowledge can lead to a control strategy providing enhanced assurance of quality with reduced end product testing and increased operational flexibility.

• The effect of scale should be considered for control strategies developed from small-scale experiments, although a control strategy can be developed that operates independently of scale or location in the ‘manufacturing operating space’.
It is important to show how the applicant has control over what the patient needs. Using product and process understanding may enable applicants to balance the level of detail provided about the process in relation to the level of detail provided about associated tests.

- When a CQA is controlled by end product testing, the process elements that provide the CQAs should still be described. The description of these process elements can be at a level of detail that assures regulatory oversight of significant changes balanced with the risk associated to the unit operation, and with the importance of the output(s) from this unit operation (e.g. consider criticality of QA(s) affected by that unit operation). In the workshop an example was presented in a case study where the description of the type of mill to be used for the API was sufficient in the context of the proposed control strategy for particle size distribution, and additional details of milling conditions were not needed.

- When a CQA is controlled in process, it should still be discussed in the tabular summary of control strategy, even though it may not appear on the final product specification. The omission of any CQA from the specification should be rationalised.

Because acceptance criteria are linked to process operating conditions, a change requested to an acceptance criterion of an attribute can change the acceptable range of manufacturing parameter(s). Process boundaries should not be overly constrained (for example, by requesting ranges to be tightened on the basis of limited batch data showing good process consistency) as this could have a negative impact on process capability. Conversely, broad operating ranges not supported by development work, batch analysis data and/or scientific rationale should not be proposed.
When considering changes to manufacturing processes the impact on the control strategy should be assessed as well as evaluating the risk to product quality. The introduction of control strategies derived from enhanced approaches, such as RTRt, may necessitate some changes – usually relatively minor - to existing Pharmaceutical Quality Systems.

3. **Post Approval Aspects**

3.1 **Lifecycle Management**

One of the major opportunities for industry and regulators is to define how the understanding of product and process can be used to support risk-based decisions to manage changes in a product-specific manner during the product lifecycle. An applicant that has developed enhanced product and process understanding and applied it through the control strategy should be able to achieve different lifecycle management conditions (for example, lower categories of variations for certain changes) than an applicant without such enhanced understanding. There is a perception that enhanced development approaches are not yet resulting in benefits for industry and regulators in a reduction in the burden of post-approval regulatory changes. Furthermore it is becoming clear that differences in the post-approval frameworks globally make it difficult to interpret how to manage changes associated with a design space (for example, see the discussion above on the inclusion of non-CPPs in a design space).

Moving towards an approach to post-approval change management that would enhance lifecycle management (e.g. reduce period for implementation of innovations, reduce the resources associated with the management of post-approval changes) would be a common benefit for industry and regulators. This may require understanding of how the applicant’s quality management system can support management of quality and management of change,
and, in consequence, need some consideration of how assessor and inspectors work together to bring the full value from the application and from the quality system, without having to include detailed elements of the quality system in the application file.

**Recommendations**

As noted earlier, the recommendations concerning the presentation of information in dossier are linked with, and could support, the optimisation of change management through the product lifecycle.

A comprehensive, robust control strategy could facilitate management of certain changes if the control(s) are independent of the change (e.g. change of scale, if the controls applied are independent of scale; note that at the time of the Workshop changes in batch size of active substances or finished products are subject to Variation submission).

The potential impact of a change could be influenced by the control strategy applied. For example, a change of a manufacturing operating parameter may have a lower risk if it is complemented by additional controls that provide an orthogonal view of the consistency and reliability of the output post change. This is analogous to redundancy engineering approaches (i.e. duplication of components or system elements to increase reliability) and could enable adjustments in the approach to regulatory oversight for such changes.

Management of some changes is accepted as being solely within the company quality system (subject to regulatory oversight through inspection), while others should not be subject to ‘prior approval’ but could be ‘do and tell’ with the dossier content being updated through e.g. an annual reporting mechanism. It was noted that in some regions, including Europe, certain
prospective changes can be managed by utilisation of Post-Approval Change Management Plans or Protocols (PACMP) which are expected to lead to faster and more predictable implementation of the changes post-approval since the strategy and test to verify the effect of the change on product quality is agreed upfront with Regulatory Authorities. At the time of the workshop the experience with PACMPs in Europe was still relatively limited.

Where products developed by both traditional and enhanced approaches are manufactured in the same facility, the same change management process and Quality Management System will be used to assess changes and potential effect on quality. Where there is good product and process understanding (e.g. knowledge gained from an enhanced development approach), the risk associated with a certain change may be perceived as being lower than an equivalent change where there is less knowledge of the potential impact of that change on product quality.

3.2 Dossier - Quality System Interactions

The manufacture of a drug substance and drug product must be conducted as described in the approved submission and according to current Good Manufacturing Practices. The relationship between the submission and the quality system, and the corresponding interaction by assessors and inspectors to provide regulatory oversight, is therefore of considerable importance. This is even more relevant when enhanced and/or non-traditional controls or manufacturing commitments are approved and this was exemplified in the discussion points arising from several of the case studies:
• Would closer interactions between assessors and inspectors (and R&D and Manufacturing) be beneficial for “enhanced development” submissions, and if so, how can this be achieved in practice?

• Should certain elements of the Pharmaceutical Quality System (PQS) be summarised in the application file to provide context for the commitments that are approved, and if so, what should be included?
  ▪ The ICH Q-IWG Q&A (approved April 2009) on this aspect was noted:
    Q3: Is it necessary to describe the PQS in a regulatory submission?
    A3: No, however, relevant elements of the PQS (such as quality monitoring system, change control, and deviation management) can be referenced as part of the control strategy as supporting information.

• Despite the IWG Q&A noted above, many companies are concerned that inclusion of any PQS information in the registration dossier will lead to the PQS/Quality Management System information being considered as registered detail or ‘regulatory commitments’ and therefore subject to regulatory post-approval variations.

• Implementation of ICH Q10 was intended to complement or enhance GMPs by achieving product realisation, establishing and maintaining a state of control, and facilitating continuous improvement, and consequently regulatory procedures should facilitate these processes in a streamlined and efficient way.

Recommendations

A stronger reliance on the PQS to exercise the required control could facilitate certain types of change management, deviation control, or selection of starting materials. The possibility of filing ‘do and tell’ variations was noted as a positive aspect of the European regulatory system. Examples in some other regulatory systems outside of Europe were also noted. These
include the ability to negotiate additional commitments (subject to routine inspections) as part of the approval process with the US FDA that are subsequently handled by the Annual Reporting process and do not require prior approval. In Japan, PMDA processes allow for changes to certain operating conditions to be managed within the company quality system at the discretion and under the oversight of the Quality-Responsible Person.

3.3 Handling of Deviations

Practical experience with the commercialisation of a number of products developed with enhanced approaches and utilising non-traditional control strategies has led to the identification of a number of issues around the handling of deviations, particularly in relation to non-CPPs presented in the registration dossier, and QP discretion.

- Requests from Regulators to include details such as high and low limits for non-CPPs as part of the overall process description in the registration dossier were reported in the case studies. This brings non-CPPs within the scope of registered details that must be complied with for successful batch release. As such they are effectively treated similarly to CPPs, and deviations of non-CPPs against targets or limits creates unintended investigations. It would be beneficial to clarify if the QP has the ability to determine whether those materials are acceptable for use.

- The EMA QP reflection paper allows for one-off approval of unplanned deviations, however, there is no allowance for multiple deviations of non-CPPs. Furthermore, there is often reluctance for QPs to adopt the discretion option as it has not been formally included in official guidance (EU GMP Annex 16 was being revised at the time of the workshop).

- The need to present sufficiently detailed manufacturing process descriptions (i.e. defining process parameters, their ranges or target values) in a submission should be
balanced with the consequential need to submit variations for post-approval changes, which arises from the interpretation that changes to non-CPPs are subject to Type II variations, requiring prior approval before a permanent change to the limits can be made.

Recommendations

Comments from regulators at the workshop suggested that aspects of the “QP discretion” reflection paper may be incorporated into the Annex 16 revision to formalise the approach to one-off deviations for QPs. There is a need, however, to extend the QP discretion around minor deviations where they relate specifically to parameters classified as non-CPPs in the registration document.

It was agreed that to provide assessors with an holistic and sufficiently detailed view of the manufacturing process it is necessary to provide CPP and non-CPP details in the process description. A proposal from regulators was to identify non-CPPs in the process description in the dossier and to specifically state that future post-approval changes to them would be conducted according to a Type IA or Type IB process, providing clarity and agreement at the point of approval of the dossier.

4. Proposals for Future Developments

4.1 New ICH Quality Topics

In reviewing the workshop presentations and discussions, and recommendations from the participants, it is apparent that two issues dominated:
- Presentation of information in submissions - Clarifying certain aspects of the required level of detail and presentation format to facilitate the preparation and assessment of MAA dossiers.

- Lifecycle management - Gaining value from enhanced knowledge through the commercial phase of the product lifecycle by facilitating post-approval changes.

The output from the workshop informed the contributions of the EMA regulators and Efpia industry representatives in the ICH Informal Quality Discussion Group meeting at ICH Minneapolis (June 2014). At that meeting a 5-year plan for ICH Quality topics was developed that includes the following topics:

- ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- Quality Overall Summary

The ICH Q12 concept paper includes a description of three issues to be addressed:

- Regulatory dossier (level of detail and definition of regulatory commitment)

- Pharmaceutical Quality System aspects (harmonized risk-based change management system and knowledge management system)

- Post-approval change management plans and protocols

The elaboration of Q12 is aiming to address many of the points identified during the workshop related to the lifecycle management of post-approval changes, including:
• A means of differentiation of commitments (e.g. within process descriptions) based on understanding / residual risk (not the current simple definition of criticality). All discussions on criticality are really discussions on post-approval change management.

• This differentiation should be explicitly linked to post-approval change management expectations. Variations to non-CPPs, if included in a design space or process description, should be managed as a minor change, in line with the low risk posed (e.g. managed internally within a site PQS, or as a Type IA/IB rather than Type II variation). It is agreed that all parameters do not affect a CQA equally: some have more effect than others and therefore the regulatory framework should accommodate differences between CPPs vs non-CPPs for post-approval changes. Clarification of the possibility for this within the current regulatory framework or adjustment to the framework would be appropriate and reflect a risk-based approach linked to criticality for management of changes during the commercial phase of the product lifecycle.

• Post-approval change management should be focussed on managing risk of impact of the change in a product-specific way taking account of product understanding / control strategy applied and company quality system (as appropriate under ICH Q 8, 11, 9 and 10).

• Consideration to use of ‘expanded Post Approval Change Management Protocols/Plans’ that allow for management of a particular change across a portfolio of similar products after initial approval of a PACMP. This could be of value for API starting material change management approaches operated by a company with suppliers, for example.
The elaboration of the Quality Overall Summary topic (together with ICH Q12) could potentially address some of the points identified during the workshop related to the presentation of information in Marketing Authorisation Applications including:

- Level of detail in the dossier depends on the purpose/use of the information (e.g. on DoEs, models, risk assessments) and should be balanced against the proposed control strategy and manufacturing commitments. The Quality Overall Summary could help to set this balance.

- The control strategy is often a key differentiator for products developed by enhanced approaches compared with traditional approaches. Providing a summary in the Quality Overall Summary could emphasise this, especially as the CTD structure allows flexibility for the location of a control strategy summary in Module 3.

- Improved communication between assessors and applicant can often avoid misunderstanding:
  - The clarity of the applicant’s submission is important – for an assessor to reach the same conclusions as the applicant the submission content has to be clear and compelling.
  - The clarity of assessors’ questions is important – the context of the query and why the additional information is being sought can be very valuable to ensure an optimal outcome from the review process.
  - The value of the EMA peer review process during assessment of centrally-authorised products is recognised.

### 4.2 Elaboration of Q&As and revisions to the ICH ‘Points to Consider’ document

Elaboration of new Q&As (or the modification of the ICH IWG Points to Consider Paper or existing ICH Q-IWG Q&As) could provide helpful clarification of certain issues identified in
the workshop discussions. Examples of the topics raised at the workshop that could benefit from Q&As include, for example:

- **Design Space**
  - Regulatory opportunities/consequences for design space in submissions – how is the design space being used by the company (in the control strategy).
  - The level of scrutiny and the data requirements to support submission of the design space and discussion of the underlying model should reflect the role of the design space in quality assurance, the degree of reliance on the design space to ensure product quality and the role of the design space in the broader control strategy. In this way design spaces could be categorized as high, medium or low impact in a similar manner to the way models are characterised in the ICH ‘Points to consider’ document.
  - It could be helpful to further explore the definition and regulatory consequences of design spaces compared with PARs in relation to the science underpinning them, the control strategy, and level of risk, based on criticality assessment, to product quality. Opportunities to create a more risk-based lifecycle change categorisation framework would increase the value of sharing enhanced development knowledge in a submission and optimise the value of the design space concept.
  - The regulatory nature of a detailed verification protocol in the context of other regulatory documents, i.e. whether this forms part of the dossier or whether it is a site-based protocol available for inspection, may need further harmonization.

- **Use of Models**
  - Concept of external validation – parallel testing:
• The term ‘parallel testing’ is not defined in ICH, although it is mentioned in the EMA RTRt guideline.

• Parallel testing considerations such as the number of batches to be tested during ‘parallel testing period’, prior to RTRt, will depend on the case e.g. differences between soft sensor models (e.g. predict dissolution from process data) vs analyser-based models (e.g. NIR calibration). The amount of data available at the time of filing might differ between a legacy product, where a wealth of process data exists, and a new product with limited full scale experience.

• In general the parallel testing strategy should be proposed by the applicant but information to be provided in the dossier vs post-approval commitments may need further discussion.

• Where RTRt is based on soft sensor models (i.e. prediction based only on process data) MSPC will probably be required in addition to parallel testing.

  o Model verification is discussed in the ICH ‘Points to Consider’ document, but further clarification may be required, for example, related to considerations of laboratory versus commercial scale.

  o When using MVDA models to support RTRt the important aspects that need to be included in the submission and aspects subject to inspection could be clarified (e.g. scale issues, ensuring the model can accommodate routine process variability).

  o Model maintenance aspects that should be managed within the PQS, provided the change is within the scope of the model. For example, following the
conclusion of parallel testing the model needs to be adapted in a “standard” way e.g. change of rank, pre-treatment or addition of spectra.

- Quality System
  - The IWG Q&A on Quality System information in the dossier could be further clarified, if this is not addressed fully in ICH Q12.
  - Enhancing the clarity of the information about proposed control strategy to be included in the submission and the information to be available for inspection is important to facilitate review/approval of the submission and post-approval changes as part of lifecycle management.

Revisions of the ICH Q8/Q9/Q10 Points-to-Consider document could be considered in a number of areas including, for example:

- Level of detail in submissions: the ‘H/M/L impact’ concept described in ‘Use of models’ could be extended in other areas i.e. the level of detail to be included for DoEs, risk assessments etc. depends on the purpose/use in the control strategy and assurance of quality

- Risk and Criticality: Not all ‘critical’ parameters are equal in terms of their risk to product quality - a position on the relative criticality of a parameter / material attribute / process input and the relationship to its understanding / control / residual risk should be developed

- Risk and Criticality: the relationship between risk and process parameter criticality should be aligned with current regulatory thinking (i.e. criticality is based on the impact of a process parameter on CQAs and risk mitigation does not change criticality).
4.3 Areas for Further Discussion

Within the EU regulatory framework there are a number of aspects which could be explored to resolve some specific regional aspects discussed at the workshop. These include:

- EU GMP Annex 16 and opportunities for Qualified Person (QP) discretion in relation to the handling of low risk non-CPPs, particularly in assessing quality against the operating limits recorded in the file, especially for potential insignificant deviations associated with non-CPPs. A key principle is using product/process understanding to resolve issues during manufacture – knowledge provides the basis for QP discretion. From the example discussed in workshop, QPs should be allowed discretion for repeated deviations of low-risk parameters against the operating limits recorded in the file, based on an assessment of quality.

- If not fully addressed by ICH Q12, establishing that inclusion of PQS details in the registration dossier would not subject the PQS to EU Variation controls. This could have application to the ICH Q11 Q&As currently under development - could the requirements of a QMS be defined that will enable the MAH to, for example, assess minor changes or starting materials under the QMS?

- Some aspects of the regulatory framework may need to be reconsidered (e.g. Variations categorisation) or clarified to facilitate the success of the implementation of ICH Q8-11.

Disclaimer
The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

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Conflict of Interest Declaration

The following authors are employees and/or stock shareholders of the following companies: Graham Cook (Pfizer); Georges France (Novartis; GSK); David Tainsh (GSK)
The following authors declare that they have no competing interests: Øyvind Holte; Giampiero Lorenti

**References**

Table I: Example of risk assessment summary table from case study 1 showing highest failure modes in each category and quantitative scores

<table>
<thead>
<tr>
<th>CQAs</th>
<th>Raw Materials</th>
<th>Dry Mix</th>
<th>Wet Granulation</th>
<th>Drying</th>
<th>...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>None</td>
<td>None</td>
<td>- sticking (40)</td>
<td>- loss of fines (18)</td>
<td></td>
</tr>
<tr>
<td>Degradation</td>
<td>None</td>
<td>None</td>
<td>- hold time (36)</td>
<td>- temperature (16)</td>
<td></td>
</tr>
<tr>
<td>products</td>
<td></td>
<td></td>
<td></td>
<td>- sampling for LOD (24)</td>
<td></td>
</tr>
<tr>
<td>Uniformity</td>
<td>- physical properties (64)</td>
<td>- mixing time/speed (12)</td>
<td>- extreme granule size (60)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>of dosage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution</td>
<td>- particle size (32)</td>
<td>None</td>
<td>- granule densification (80)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- disintegrant FRC (60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology</td>
<td>None</td>
<td>None</td>
<td>- hold time (36)</td>
<td>- sampling for LOD (24)</td>
<td></td>
</tr>
</tbody>
</table>
Table II: Example of risk assessment summary table (FMEA for Purity control) from ICH Q-IWG Training

<table>
<thead>
<tr>
<th>Unit Operation</th>
<th>Parameter</th>
<th>IMPACT</th>
<th>PROB</th>
<th>DETECT</th>
<th>RPN</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distillative Solvent Switch Temperature / Time, etc.</td>
<td>1 5 1 5</td>
<td>5</td>
<td>Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distillative Solvent Switch Water content at end of Distillation (Crystallization Feed)</td>
<td>9 5 1 45</td>
<td>45</td>
<td>Higher water = higher degradation In process control assay should ensure detection and control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystallization -- API Feed Solution Feed Temperature</td>
<td>9 5 1 45</td>
<td>45</td>
<td>Higher temperature = higher degradation Temperature alarms should enable quick detection and control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystallization -- API Feed Solution Addition Time</td>
<td>9 1 5 45</td>
<td>45</td>
<td>Longer time = higher degradation Detection of prolonged addition time may occur too late to prevent some degradation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystallization Seed wt percentage</td>
<td>1 1 1 1</td>
<td>1</td>
<td>This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystallization Antisolvent percentage (charge ratio)</td>
<td>1 1 1 1</td>
<td>1</td>
<td>This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystallization Crystallization temperature</td>
<td>1 5 1 5</td>
<td>5</td>
<td>Temperature is low enough that no degradation will occur.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystallization Other crystallization parameters</td>
<td>1 1 1 1</td>
<td>1</td>
<td>These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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