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Pre-authorisation Evaluation of Medicines for Human Use

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REPORT

Biologics Working Party (BWP), Process Analytical Technologies (PAT) group And Industry

Workshop on Process Analytical Technologies for Biologicals 15th March 2007

1. INTRODUCTION AND BACKGROUND

The QWP/INS group have established the EMEA PAT group, which has been developing an understanding of how the concepts of PAT and new manufacturing and control technologies may be applied, particularly in the area of chemically derived medicinal products.

The PAT team has been expanded to include BWP participants, to actively progress the understanding of the principles of PAT to biological medicinal products.

In order to gain a better understanding in this area and to develop the BWP contribution to ongoing activities which may be associated with PAT, e.g. pharmaceutical development / quality by design and validation and control issues, a workshop to discuss this topic was organised on March 15th 2007, to get scientific input from the stakeholders (BWP, QWP, PAT group representatives, industry associations: EFPIA and EGA and industry representatives).

Regulatory background

Through the ICH process, there has been an ongoing effort to develop a risk based approach to the manufacture, control and regulation of medicinal products. Three main guidelines have been proposed to achieve this:

ICH Q8: Pharmaceutical Development
ICH Q9: Quality Risk Management
ICH Q10: Pharmaceutical Quality Systems (in development)

Industry organisations have stated that their goal is an integrated product development and quality system approach that enables reliable and efficient production of high quality drug substances and medicinal products while facilitating continuous improvement, without extensive regulatory oversight.

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Tools to achieve this goal are combined in the above guidelines. ICH Q8 specifically focuses on a systematic scientific approach to gaining enhanced product understanding. This has been a feature of the European regulatory system for many years, where Pharmaceutical Development studies have been an integral part of the Marketing Authorisation dossier.

The essential elements of ICH Q8 have been outlined in terms of Quality built in by Design (QbD), Process Analytical Technologies (PAT) and Design Space (DS)[1]. Further additional elements which are important considerations are: continuous validation and real time release. These elements move away from the premise of end product quality control testing and move towards a scientific knowledge base, parametric approach which gives assurance that a product of defined quality has been manufactured.

It has been proposed that, where a systematic and rigorous understanding and knowledge of a particular process has been achieved, then the need for regulatory oversight may be reduced. Ultimately, a reduction in end product Quality Control testing or the filing of variations to the Marketing Authorisation Dossier could be envisaged. For example, the greater use of comparability protocols has been advocated by industry as a mechanism that could avoid some of the post-authorisation regulatory filings.

Format of the meeting

The agenda covered general introductory and concluding sessions and confidential sessions with individual companies in order to learn about specific in-house activities under consideration in this area.

A number of specific questions were posed by EFPIA in the concluding session. Not all of these related directly to the subject of the workshop and reflected more on the desire to develop interactions between industry and regulators and to confront the difficulty industry faces with multi-region regulatory requirements. An outcome of increased regulatory harmonisation on a global scale would be welcomed. These questions would be further discussed and responses included in the Questions and Answers document on the EMEA website, at the following location:
(http://www.emea.europa.eu/Inspections/PATQaA.html).

The development of common understandings and direction in the application of the principles of ICH Q8 would be an important goal for the current workshop. Definitions and the use of the terms in ICH Q8 should be agreed by all parties.

2. GENERAL INDUSTRY PRESENTATIONS

EFPIA and EGA representatives presented their perspectives on PAT and Quality by Design for biologics.

EFPIA expressed their goal to have an integrated product development and quality system approach that enables reliable and efficient production of high quality drug substances and medicinal products and facilitates continuous improvements without extensive regulatory oversight.

Quality by Design was presented as a systematic approach to product and process development and lifecycle management that will permit definition of a product and process Design Space including control strategy.

PAT was considered as one of several tools to facilitate better process monitoring and control, leading to better process understanding.

[1] For the purpose of this document, the terms "Quality by Design concepts" have been used to described all the concepts outlined in ICHQ8, related to PAT, design space, and Quality by design.

A Design Space will permit a more flexible Regulatory environment (focused on the critical process and product attributes and less regulatory oversight of minor changes). The level of "regulatory flexibility" should be proportional to the level of demonstrated product and process knowledge, applying risk management principles to regulatory review, both pre- and post-approval.

A step-wise implementation was proposed:

1. QbD principles systematically embedded within development programmes
2. Design space: defined & extended by registration of Acceptable Ranges & Operating Ranges
3. Pre-submission of protocols to reduce the number of prior-approval submissions
    1. Process changes
    2. Site transfer changes
4. Establish more relevant and meaningful release specifications
    1. Parametric release
    2. Skip-lot testing

Current EU variations legislation was mentioned as a challenge for biological manufacturers as it discourages implementation of process improvements and results in the use of significant Industry & Regulatory resources.

3. CONFIDENTIAL INDUSTRY PRESENTATIONS

Three presentations from EFPIA representatives and one from EGA representatives were discussed in confidential sessions. Each representative presented their perspective on QbD concepts and how these concepts are being implemented through real case studies.

Based on the reported examples, the implementation of QbD concepts were considered before or after marketing authorisation, based on the knowledge acquired by the manufacturer. Depending on the strategy selected, several approaches were used to define the design space.

In most cases, the design space was linked to the process controls, process validation and robustness. Some industry representatives argued that the design space should not be limited to the process capability but should be defined in accordance with the Company's knowledge of critical process parameters and their impact on critical quality attributes.

In other cases the design space was linked to "specifications" in accordance with the Company's knowledge of critical quality attributes in relation to impact on non-clinical and/or clinical aspects.

Further examples considered both approaches as an integrated system, or as sequential steps. In all cases, industry representatives anticipated improved knowledge of the product and process, as well as improved consistency, that should lead to regulatory flexibility. One of the main regulatory flexibilities expected was the possibility of implementing changes (i.e. currently variations), within an approved design space, without prior regulatory approval. Some industry representatives nuanced this expectation by incorporating a risk based approach.

Some case studies proposed the introduction of QbD concepts before marketing authorisation, during the early stages of product and process development. Others proposed to introduce these principles after marketing authorisation, based on the knowledge acquired on a given the product and process in relation to clinical experience through development and commercialisation.

In most of the cases presented, the applications of QbD concepts were limited to one or two production step(s). The process parameters or quality attributes being monitored, as well as the analytical technologies employed were not significantly different from those currently being used in the production of biological products. In some instances, representatives expressed their fears regarding the risk of product contamination when introducing or maintaining in-situ probes.

In some cases PAT applications were not used in production as such but were used in process development to get a better understanding of the process, giving a possibility to design out critical steps.

Most cases studies included the development of predictive models. In some of them, an integrated system linking analytical technology to a model was established for a given step to adjust process parameters in a real-time manner. One example illustrated the importance of continuous verification of a model, as a parameter not initially identified as critical may become critical in some situations and may require re-evaluation of the model. Regulatory authority representatives expressed their concerns that regarding the risk of missing a critical parameter or attribute during model development, that may have unforeseen clinical impact.

4. DISCUSSION AND CONCLUSION

ICHQ8 introduces QbD concepts that have been part of the development of biologics for many years without the same terminology, and their regulatory consequences (regulatory flexibility). Although the biological drug substance was clearly not part of the scope of this document, these concepts should also be applicable to biological products. However, taking into account the complexity of the molecule and process, the application of these concepts will require careful consideration, and may lead to more limited use of this approach.

Several discussions were raised regarding the establishment of the design space in relation to specifications and clinical experience. It was recognised that only a limited number of batches is used in confirmatory clinical studies, and the variability of products used in these trials may not cover a sufficiently wide panel necessary support the target design space, and which may be more limited than that observed during normal production. It was mentioned that relevant clinical and non-clinical studies should be considered to extend the actual design space supported by confirmatory clinical studies.

Some industry representatives requested the possibility of defining a design space wider than the one supported by clinical experience, even if no further details were given on how this should be justified. Other representatives expressed their desire to revise ICH Q6B, as they considered some of the concepts to be too rigid, and proposed to limit them to only critical quality attributes. There is ongoing debate in the area of setting of specifications which has some overlap to be considered in the area of QbD.

Regulatory authority representatives mentioned that the setting of specifications should take into account manufacturing processes, analytical procedures, product stability, preclinical and clinical studies. These specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities. When QbD concepts are appropriately implemented and approved, the possibility of using parametric release, skip testing or real-time release is anticipated to be applicable to biologics. These approaches are not in disagreement with the definition of specifications as described by ICH Q6B. Nevertheless, when tested, a given product or material must comply with its approved specification.

Since the understanding of the concept of design space as referred to above differs between companies, for example with regard to process controls and specifications, to avoid misunderstanding it is very important that clear definitions are agreed by all parties.

The necessity of traditional validation approach based on 3 conformance lots was also challenged. As discussed in the EMEA PAT Q&A *(see EMEA website)*, the application of QbD concepts is anticipated to enhance process understanding and monitoring, and therefore, a state of continuous validation could be achieved. Such approaches could, therefore be envisaged if adequately justified. It was pointed out by the speakers that even if the traditional concept of three consecutive batches was

no longer mandatory there will still be a need to provide assurance that commercial scale performs appropriately.

The EU Commission's initiative of "Better Regulation" was welcomed, and the need to improve the EU variations system was stressed. Among the proposals made by industry representatives, it was acknowledged that modification of the variation system should take into account QbD concepts and risk management principles. Any resulting regulatory flexibility should be proportional to the level of product and process knowledge which has been demonstrated.

At the operational level, most of the industry representatives are currently developing or evaluating PAT tools, and are in the process of gathering data. The case studies presented tend to show that the application of the QbD concepts should improve product consistency and process robustness, when assessment is based on critical attributes or parameters. However, the data presented were rather limited in terms of innovative PAT tools employed. One of the more novel approaches was the development of a model for continuous process control and process adaptation for a given step, moving away from the paradigm of fixed processes and controls. Of the industry representatives, some were at more advanced stages than others, leading to the expectation of regulatory submissions in the medium to long term in most cases.

This workshop was a great opportunity to share the aspirations and concerns of the stakeholders (BWP, QWP, PAT group representatives and industry associations EFPIA and EGA) regarding QbD concepts and PAT. Industry representatives proposed further collaboration to EMEA representatives on these ongoing activities and asked for further opportunities to meet and share experiences with Regulators. It is advocated that contact is made with EMEA representatives of the PAT group, where industry interest can be shared and the possibility of meetings to progress scientific dialogue between regulators and industry can be determined. It is expected that the BWP will be directly involved in decisions concerning biological medicinal products.

Industry made a number of proposals for follow up, resulting from the workshop. Amongst these was the possibility of training – both of industry and regulatory personnel and for future joint meetings where initiatives and understanding could be shared in a similar format to the current workshop.