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Strategic framework for education and training in Quality by Design (QbD) and process analytical technology (PAT)

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ABSTRACT

The regulatory and technical landscape of the pharmaceutical field is rapidly evolving from one focused predominantly on development of small molecules, using well established manufacturing technologies towards an environment in which biologicals and complex modalities are being developed using advanced science and technology coupled with the application of modern Quality by Design (QbD) principles. In order that Europe keeps pace with these changes and sustains its position as major player in the development and commercialization of medicines, it is essential that measures are put in place to maintain a highly skilled workforce. A number of challenges however exist to equipping academic, industrial and health agency staff with the requisite knowledge, skills and experience to develop the next generation of medicines. In this regard, the EUFEPS QbD and PAT Sciences Network has proposed a structured framework for education, training and continued professional development, which comprises a number of pillars covering the fundamental principles of modern pharmaceutical development including the underpinning aspects of science, engineering and technology innovation. The framework is not prescriptive and is not aimed at describing specific course content in detail. It should however be used as a point of reference for those institutions delivering pharmaceutical based educational courses, to ensure that the necessary skills, knowledge and experience for successful pharmaceutical development are maintained. A positive start has been made and a number of examples of formal higher education courses and short training programs containing elements of this framework have been described. The ultimate vision for this framework however, is to see widespread adoption and proliferation of this curriculum with it forming the backbone of QbD and PAT science based skills development.

1. QbD and PAT Sciences Regulation – Current Status

1.1. Risk Based Approaches

Since the turn of the millenium, the US Food and Drug Administration (FDA) and subsequently the health agencies of Europe and the European Medicines Agency (EMA) have promoted the concept of Quality by Design (QbD), recognizing the need to promote the adoption of science and risk based approaches to pharmaceutical development and manufacturing, whilst moving away from outdated empirical methods and antiquated technology. More recently, the paradigm of QbD has extended its reach globally into the pharmaceutical manufacturing hotbeds of India and China, which not only act as the source of supply for numerous active pharmaceutical ingredients and their associated dosage forms, but are emerging as important markets for high quality medicinal products. In the beginning, new initiatives such as *Pharmaceutical cGMPs for the 21st Century*: *A Risk-Based Approach* and *Guidance for Industry Process Analytical Technology (PAT) — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* were established with an intent to drive the creation of a maximally efficient, agile and flexible manufacturing sector that reliably produces high quality drug products without excessive regulatory oversight. More recently, the FDA has released a draft guidance document entitled 'Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing

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Base', which is focused on facilitating the introduction of emerging manufacturing technologies as a means to improve product quality and maintain the supply of important medicinal products throughout the product lifecycle.

In these documents and in related evolving ICH guidance documents (ICH Q8 (R2), ICH Q9, ICH Q10, ICH Q11 and ICH Q12), there is an increased emphasis on using new scientific understanding and innovative technologies to provide enhanced product and process knowledge and greater assurance of consistent product quality and clinical performance. Appropriate quality risk analysis tools should be used to identify areas of greatest risk, which should form the basis of the control strategy. In this regard, not only should QbD ensure better design of products but also facilitate improved efficiency, increased yields and enhanced product quality. Adoption of these principles should also allow for possible reductions in overall costs of manufacturing, whilst enabling quicker implementation of post-approval changes with reduced regulatory oversight. Although benefits in speed, cost and quality are major drivers for industry, it is ultimately the patient who will benefit most, by gaining timely and uninterrupted access to high quality medicines as and when required.

1.2. Recent Developments

A recent appraisal of the progress being made in the QbD field has been presented by FDA's Christine Moore, at the International Conference on Drug Development, in Texas, USA (February 2013), in which she indicated that many innovator companies are widely adopting Quality by Design (QbD) approaches for pharmaceutical development for new products (A regulatory perspective on the current and future state of pharmaceutical quality). There is growing evidence that QbD in development decreases product variation and is, in addition, good business practice (Kourti and Davis, 2012). Evidence also suggests that the rate of adoption is increasing across generic and biotech companies, with greater interest in concepts such as real-time release testing (RTRT), and continuous quality verification and lean stability approaches. Despite some limitations in realisation of regulatory benefits, the implementation of QbD is providing a platform for greater dialogue between industry and the different health authorities.

1.3. Increasing Demands but Limited Success

As companies invest and gain experience with QbD, there are increasing demands placed upon both the health authorities and the industry (Final deliverable for FDA Understanding Challenges to QbD Project, December 18, 2009). These demands are inextricably linked to omissions in the implementation of QbD across health agencies and the industry. Issues yet to be addressed, include: expansion of new approaches to legacy products and more widely across generic drugs and biologicals; adoption of eased post-approval change reporting requirements through use of risk based assessments and the development of scientific methodologies to establish clinically relevant specifications (Selen et al., 2014). In each of these examples, greater harmonisation of expectations across the health sector including health agencies is required. As only emerging guidance exists on submission content, it is likely that wide variation will be experienced in the quality and details provided in the dossiers, generating consequences such as inconsistencies in health agency reviews, both between and within the regulatory bodies. Some anecdotal evidence in this regard leads to a conclusion that some regulators tend to maintain an outdated tick-box mind set, with little credence given to the risk based strategies articulated in QbD submissions to date.

When considering each of these issues in combination, a clear reticence is evident amongst pharmaceutical manufacturers to move towards routine QbD filings. They do not report the wealth of data and knowledge generated in their development studies, despite modern science and risk based approaches being actively utilised in their projects. Until these hurdles are satisfactorily addressed, the perceived benefits of QbD will not be realised nor accepted, neither by industry or health agencies.

1.4. Ways forward

To address this conundrum, it is necessary that a number of measures be put in place to ensure enhanced implementation of science and risk based approaches, alongside the establishment of modern quality systems. The first priority is to establish joint exploration, evaluation/development, and adoption of new sciences based methodologies and practices for use in quality risk assessment, bridging between the technical design parameters of pharmaceutical products and processes, and their consequent clinical performance. This should, in particular, enable better communication of the risks to the regulators. Most likely, there are simple tools that can be used to help to build towards a greater level of trust in the data submitted, which in turn would facilitate moving towards milder post-approval requirements for change. A call to establish funding initiatives in this area was recommended in the previous position paper by the EUFEPS QbD and PAT Sciences Network (Aksu et al., 2012).

Further interaction and dialogue between the industry, regulators, and academic experts is, however, required to develop an agreeable position, where the benefits of QbD can be derived by all. Furthermore, a systematic approach to education and professional development is required to ensure that development scientists, process engineers, academics, regulators and suppliers to the pharmaceutical industry are familiar with concepts and science underpinning the QbD paradigm. A recent article by the Association of the British Pharmaceutical Industry (ABPI) describes key skills, which are vital to growth of the pharmaceutical industry in the UK (Bridging the skills gaps in the biopharmaceutical industry – Maintaining the UK's leading position in life sciences, 2015). Manufacturing has been highlighted as an area of critical importance, with mathematics, statistics and computational modeling skills being essential for future success. The sections below describe some the challenges and strategic needs for skills development alongside a proposed framework to address these gaps in the pharmaceutical sector.

2. Unmet Needs in Training and Education for Industry, Regulators and Academia

2.1. Challenges and Unmet Needs

As outlined in earlier sections, the underpinning science supporting pharmaceutical development is rapidly evolving, whilst the nature of therapeutic entities, delivery systems and the procedures by which they are manufactured are also undergoing constant change. This brings with it challenges for the education and training of those involved in their development, which cuts across the whole pharmaceutical sciences discipline (Atkinson et al., 2012; Crommelin et al., 2010). Manufacturing of future pharmaceuticals will increasingly include elements of modeling and simulation supported by the state-of-the-art analytical methods providing an in-depth insight into the factors influencing product quality (Rantanen and Khinast, 2015).

New compounds entering the market are no longer dominated solely by small molecules, but by an increasing prevalence of biologicals, supplemented by the emergence of newer modalities such as nucleic acids and cell therapies in the pipelines of R&D driven organizations. This means that new types of processing and engineering approaches are needed, both for product design and for manufacture. At the same time, we are meeting with increasing demand for more flexible dosing systems to address some of the likely challenges of personalized medicine. These issues cannot be resolved entirely through the application of existing technologies, but require profound focus on innovation in pharmaceutical technology and manufacturing. However, at a time when the emergence of new approaches is required in these disciplines,