REVIEW

The Future of Pharmaceutical Manufacturing Sciences

JUKKA RANTANEN,[1] JOHANNES KHINAST[2,3]

[1]Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[2]Institute of Process and Particle Engineering, Graz University of Technology, Graz, Austria
[3]Research Center Pharmaceutical Engineering, Graz, Austria

Received 6 December 2014; revised 26 June 2015; accepted 29 June 2015

Published online 17 August 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24594

ABSTRACT: The entire pharmaceutical sector is in an urgent need of both innovative technological solutions and fundamental scientific work, enabling the production of highly engineered drug products. Commercial-scale manufacturing of complex drug delivery systems (DDSs) using the existing technologies is challenging. This review covers important elements of manufacturing sciences, beginning with risk management strategies and design of experiments (DoE) techniques. Experimental techniques should, where possible, be supported by computational approaches. With that regard, state-of-art mechanistic process modeling techniques are described in detail. Implementation of materials science tools paves the way to molecular-based processing of future DDSs. A snapshot of some of the existing tools is presented. Additionally, general engineering principles are discussed covering process measurement and process control solutions. Last part of the review addresses future manufacturing solutions, covering continuous processing and, specifically, hot-melt processing and printing-based technologies. Finally, challenges related to implementing these technologies as a part of future health care systems are discussed.

J Pharm Sci 104:3612–3638, 2015
Keywords: quality by design (QBD); process analytical technology (PAT); mathematical model; materials science; *in silico* modeling

INTRODUCTION

Traditionally, the pharmaceutical and biopharmaceutical industries were not the forerunner of innovative engineering solutions and new principles of chemical engineering. For many decades, the manufacturing of drug products were controlled by a regulatory framework that safeguarded the quality of the final product and performed testing of batch-based operations, raw material and end-product characteristics, fixed process conditions, and in-process material. Limitations related to this quality by testing thinking have widely been acknowledged both for small molecule and biopharmaceutical products.[1,2] In contrast, other fields of processing and related manufacturing sciences have successfully implemented sophisticated technologies to increase our current process and product understanding.

However, over the last years, there has been growing interest in increasing the safety and quality of medications while simultaneously cutting the cost of manufacturing of pharmaceuticals by implementing more structured pharmaceutical development and manufacturing approaches. Especially, the rapidly spreading acceptance of science-based approaches has created a more flexible environment for implementing already-existing and well-established chemical engineering knowledge.[3,4] A rather recent example is the introduction of the United States Food and Drug Administration (US FDA) process analytical technology (PAT) guidance and the quality by design (QbD) approach by the International Conference on Harmonization (ICH). The QbD-based thinking is a perfect opportunity for the pharmaceutical community to take the manufacturing sciences into the new millennium. It has to be, however, emphasized that the concept of PAT is not entirely new, as process analysis/control has been an important area of chemical engineering for decades.[5,6] Nevertheless, PAT introduced the idea of real-time process control and real-time quality assurance (QA) in pharmaceutical manufacturing, being the basis for modern process engineering. An example of it are novel manufacturing methods (e.g., based on continuous flow chemistry) that are now being introduced by industry, academia, and regulators.[7–9] The recently published white paper series from the MIT-Strathclyde symposium on continuous manufacturing (CM) in 2014 highlights the current state of thinking.[10–18] Moreover, the ICH is in the process of developing a new guideline (ICH Q12) that can serve as basis for implementing CM across the industry in a widespread manner.

The use of QbD terminology, including such abbreviations as QTPP (quality target product profile), CQAs (critical quality attributes), and CPP (critical process parameters), is deliberately minimized in this review. Although it is important to understand these concepts, especially QTPP from a patient point of view, when implementing QbD into practical use, this review rather intends to cover the underlying science, introduce the main techniques involved in the QbD approach, and provide an overview of future challenges. One related yet extremely difficult to define concept is process understanding. When do we completely, or even partially, understand a process or a single unit operation completely? Does it happen after implementation of a simple experimental design containing four experiments or only after a full risk analysis coupled with first principles physical modeling? Or are we aiming at *ab initio* molecular modeling approaches to enlighten molecular level phenomena during operations? As the level of process understanding is case specific, this review is organized around the

Correspondence to: Jukka Rantanen (E-mail: jukka.rantanen@sund.ku.dk, Tel.: +45 35 33 65 85; Johannes Khinast (E-mail: khinast@tugraz.at, Tel.: +43 316 873 30400, Fax: +43 316 873 10 30400)

Journal of Pharmaceutical Sciences, Vol. 104, 3612–3638 (2015)

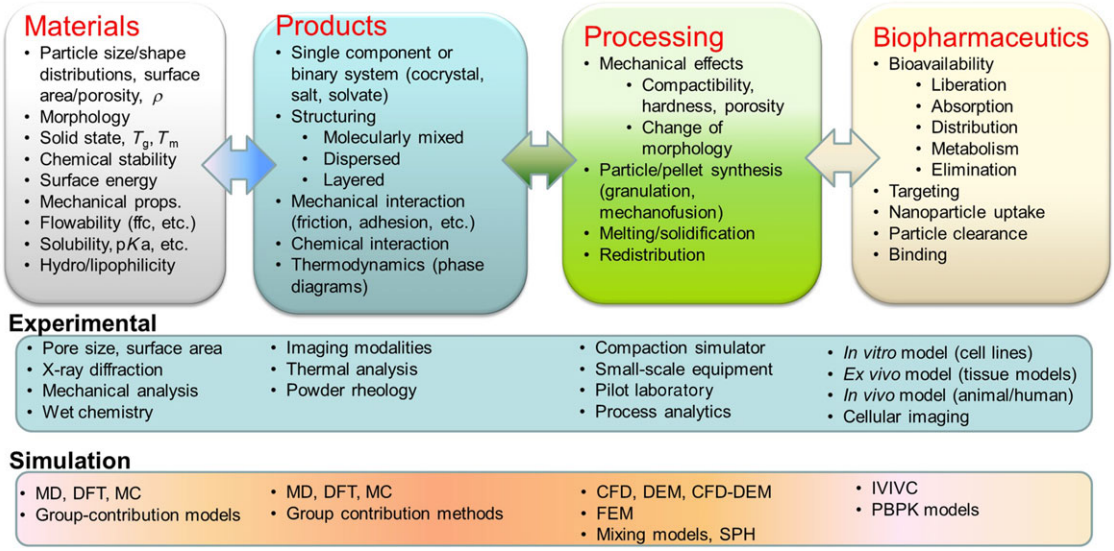

Figure 1. Engineering view of pharmaceutical development (MD, molecular dynamics; DFT, density functional theory computations; MC, Monte Carlo methods; CFD, computational fluid dynamics; DEM, discrete element method; FEM, finite element method; SPH, smoothed particle hydrodynamics; IVIVC, *in vitro–in vivo* correlations; PBPK, physiologically based pharmacokinetics).

practical tools and has the objective of providing an overview of these tools together with future perspective.

One visible part of all PAT and QbD activities during the past decades has been sensor development.[19] In many cases, near infrared (NIR) spectroscopy has been used almost as a synonym for PAT. Note that science-based manufacturing of pharmaceuticals involve not only application of novel process analytical sensors and measurement solutions, but also the utilization of other fundamental tools for increasing our understanding by implementation of risk management strategy, formalized design of experiments (DoE), advanced data analysis techniques, first-principles based process modeling and control, and fundamental material characterization together with molecular modeling.

These fundamental tools of science-based manufacturing are not part of a standard pharmaceutical teaching curriculum and, in the future, special attention should be paid to identifying the elements that should be introduced into pharmaceutical education. As consequence, the future development of the elements of pharmaceutical engineering in various educational programs requires special attention. This "step forward" in education is also needed to safeguard the development of a regulatory framework, as several emerging areas of manufacturing are still not generally accepted or even fully defined. The concept of CM provides us with a fascinating opportunity to revise the entire idea of a traditional batch operation. Although continuous operations are well defined and exist in the field of chemical engineering sciences, their implementation in the pharmaceutical context requires fundamental research. Another important concept is the implementation of real-time release, which requires a sound combination between manufacturing sciences and a new type of thinking in the fields of analytical sciences and risk management. Moreover, current developments in process validation emphasize the need for implementing the QbD thinking.

Prescribing medicine today is based on a "one size fits all" principle. However, more personalized (combination) solutions in several critical therapy areas are required. The latest developments in genomics and diagnostics have enabled the advent of new innovative drug products relying on a combination of diagnostic tools and personalized dose. All this paves the way to a future health care system based on personalized medicines, as recently outlined in the precision medicine initiative (PMI).[20] The current level of innovation in dosage form design and manufacturing of these products cannot meet the needs of personalized medicine. As such, novel manufacturing solutions, enabling the flexible manufacturing of personalized dosages, are required.

In summary, we are currently observing a change in the paradigm change, with engineering principles and product design becoming the guiding principle of pharmaceutical development. That is, we are adopting a way of thinking, according to which pharmaceutical ingredients, pharmaceutical products, the related manufacturing processes, and the biopharmaceutical properties are considered simultaneously and quantitatively. Figure 1 demonstrates this engineering view of pharmaceutical development.

We have to understand the compounds and materials, predict and/or measure compound properties, and define and characterize their constitutive behavior. Moreover, we have to understand how ingredients interact (thermodynamics vs. kinetics) and how the delivery requirements determine the ingredients and the corresponding processing. With regard to the process, we must understand and identify the critical variables and their effect on quality and develop and validate mathematical models, which largely contributed to the successful operation of chemical and petro-chemical plants. Most importantly, however, the patient has to be the center of focus.[21]

This review aims to cover the recent developments in the manufacturing sciences related to QbD-based thinking and to outline the future direction of scientific research in this field, supporting a further development of the regulatory framework.