Quality by Design (QbD) is a global regulatory initiative that enhances pharmaceutical development through the design of the manufacturing process and controls to consistently deliver a product that performs as intended. The principles of pharmaceutical development relevant to QbD are described in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance documents ICHQ8-11. In 2008, the Food and Drug Administration (FDA) initiated a QbD pilot program for biological products wherein companies could contribute either with full biological license applications or supplements. Many biopharmaceutical firms participated in the pilot program, and progress was made on establishing the basis for pre- and post-approval filings. One outcome of the pilot was an approval, granted in 2010, for an expanded change protocol for multiproduct/multisite transfer of drug substance processes for production of monoclonal antibodies at Roche/Genentech.

The A-mAb case study provided another substantial contribution to the field. It described a variety of approaches to the major elements of QbD used by 7 companies (Pfizer, GlaxoSmithKline, Genentech, Abbott, Amgen, Lilly, MedImmune) with experience in the development and commercialization of biologics. This publication presented a diverse set of solutions to common problems, but, because many companies were involved, it lacked a self-consistent formalism.

Advances in refining the applications of QbD principles have continued in recent years, although progress is slower than hoped. Roche/Genentech has licensed 2 therapeutic recombinant monoclonal antibody products, obinutuzumab (Gazyva®) and atezolizumab (Tencentriq®), in the US using QbD principals. We believe these represent the first approvals for biologics that were comprehensively based on QbD information, including approved design space claims as well as a post-approval lifecycle management plans, contained in the license application.

Roche/Genentech recently published 7 articles describing the application of the principles of QbD for development and licensure of therapeutic monoclonal antibodies. These articles present a self-consistent set of risk assessments and logical elements developed over the last decade, based on refinement through the FDA and European Medicines Agency pilot QbD programs and approvals of obinutuzumab and atezolizumab. They provide a standardized basis for the global health authorities to assess new product license applications from Roche/Genentech, and seek to establish transparent communication of the links between the manufacturing process and product storage, product quality and impact to patients, the commercial control strategy, and post-licensure change management. The articles cover all key elements of QbD, including establishment of critical quality attributes, definition of a design space, identification of critical process parameters, assembly of the commercial control system, description of the post-approval life cycle management, considerations of an overarching risk assessment that addresses elective decisions taken at the time of license application, and analysis of how the full set of assessments manage the residual risk to product quality. The refinement of these tools benefited from the substantial experience the company has gained in over 25 years of biological drug development, which included licensure and production of 9 commercial monoclonal antibodies and the use of applicable process and product platform knowledge.

Roche/Genentech view these articles as an open-source sharing of the results of a decade-long internal investment. We hope that the tools will be used by other companies (adapted to their particular product requirements, if needed), which could advance the adoption of improved methodologies in support of license applications for products with enhanced product and process knowledge. This formalism will be used for all biologics in the Roche/Genentech pipeline, and, when combined with the use of process and product platform knowledge, should result in significant efficiencies and resource savings during late-stage development. We also hope that this will enable post-licensure flexibility for production and the appropriate regulatory oversight for process parameter changes within the design space. The large commercial and clinical biologics portfolio at Roche/Genentech will build on this QbD foundation for both life-cycle management and the commercialization phase.

Although discussed in the context of antibody products, the tools we describe in the articles should be applicable to other protein therapeutics, and perhaps to small molecules and other pharmaceutical modalities as well. We encourage publication of future refinements of these tools and advances.
in their applications for the benefit of the larger industrial and regulatory community. Sharing of such information could result in superior approaches to product license applications in the future, as well as streamlining of late-stage product development, and the review and approval phases of the biologics product lifecycle.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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