## INTRODUCTION

Amgen Inc. (Amgen) welcomes the Food and Drug Administration's (FDA's) release in February of three draft guidance documents on the regulation of biosimilars.[1] We appreciate FDA's commitment to working with stakeholders in a transparent guidance development process to facilitate implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCIA).

As one of the world's first biotechnology companies, Amgen has helped millions of people around the world in the fight against cancer, kidney disease, rheumatoid arthritis, and other serious illnesses, and are committed to putting patients first in everything we do. Our comments on the draft biosimilar guidances are informed by Amgen's 30 years of experience discovering, developing and manufacturing biologics and our more recent engagement in the process of developing biosimilars of non-Amgen products.

Amgen's longstanding support for a biosimilar pathway has been premised on three fundamental principles that have also guided our evaluation of the Agency's draft Scientific, Quality, and Question and Answer Guidance documents. These are: patient safety, sound science, and incentives for innovation. While we agree with much of the content in these draft guidance documents, we believe certain changes are necessary to advance patient safety and to promote confidence in biosimilars marketed in the United States (US).

Amgen remains grounded in both our innovative and biosimilars development by a series of scientific realities that – while sometimes demanding in terms of rigor, time and resources – must underpin patient-focused biologic development programs and inform the nature and extent of scientific evaluation. All biosimilars development programs will grapple with some or all of these challenges and FDA should candidly communicate its expectations in guidance.

I. **Biosimilars are rDNA protein biologic medicines**. In contrast to traditional chemical drugs, rDNA protein biologics are very large molecules that often have the potential to rely on multiple mechanisms of action enabled by one or more

[1] "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" [Docket No. FDA-2011-D-0605] ("draft Scientific Considerations Guidance"); "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product" [Docket No. FDA-2011-D-0602] ("draft Quality Considerations Guidance"); and "Q & As Regarding Implementation of the BPCI Act of 2009" [Docket No. FDA-2011-D-0611] ("draft Q&A Guidance").

aspects of their structure. They are a heterogeneous mixture of related proteins, rather than a homogenous collection of identical molecules; hence biosimilars are neither expected nor required to be the same as the reference product. These remarkable medicines facilitate important clinical benefits for patients, however, the molecular size of these medicines makes them recognizable by a patient's immune system and thus they have a propensity to elicit an immune response that could limit efficacy and/or present a safety concern in some patients. The specific structural features of a molecule that cause immunogenicity are largely unknown.

**II.** **Biosimilars are not generic drugs**. Biologics are typically much more complex than chemical drugs and cannot be completely characterized even with today's scientific capabilities. Unlike generic drugs, biosimilars will be allowed to exhibit some structural differences from their reference product in addition to using different formulations, devices, and perhaps expression systems. However, to be considered "highly similar", the primary amino acid sequence of a proposed biosimilar and its reference product should be the same.

**III.** **Scientific understanding of reference products is often incomplete**. Analytics of protein biologics are improving; however, the understanding of the relationship of molecular structure to clinical function may not be complete. Increased understanding is possible through orthogonal interrogations and biologic assays, however, both can be imprecise and leave factors unmeasured. Although innovative manufacturers seek to characterize structural attributes that are believed to be critical to safety and efficacy before products are licensed, after licensure they regularly identify new critical quality attributes or combinations of attributes that may affect the clinical profile.

IV. **The "highly similar" standard for biosimilarity is burdened with uncertainty**. The uncertainty associated with biosimilarity can exist in two ways depending on the approach a sponsor pursues. Where the sponsor purports to have matched the attributes of the reference product, this approach is only as certain as the knowledge of the reference product's critical quality attributes is complete. Alternatively, where a sponsor seeks to justify subtle differences between the

biosimilar and the reference product, the definition of an acceptable range of differences that are not clinically meaningful is also uncertain.

V. **Clinical testing of biosimilars will be needed for the foreseeable future.** The purpose of clinical testing is to demonstrate equivalent efficacy, safety, and immunogenicity profiles of a biosimilar when investigated in parallel with the reference product. Such clinical testing is neither intended nor designed to establish de novo the complete safety or efficacy profile. Omission of comparative clinical studies evaluating safety and efficacy will be appropriate only if a biosimilar applicant can ensure, through other premarket testing, that there are no clinically meaningful differences between the products' clinical profiles. A clinical evaluation of immunogenicity will always be essential.

VI. **Accurate attribution of adverse events is essential to patient safety.** Biologics are often highly sensitive to the changes in the manufacturing process and the environment and structural alterations can result. Even minor structural differences can have an important clinical effect on patients. FDA should ensure effective pharmacovigilance for all protein products. In particular, the agency should require measures that enable pharmacists, physicians, patients, health authorities, and manufacturers to attribute adverse events to the appropriate biologic (whether a biosimilar or a reference product). The agency should expect manufacturers to employ multiple, redundant means of product identification. Requiring biosimilars to bear distinguishable nonproprietary names is an efficient means of facilitating accurate attribution of adverse events and product traceability.

In the next section we provide an executive summary of our recommendations. In subsequent sections we provide more detailed comments on the specific areas addressed by the draft guidances. Amgen's comments address the issues collectively, although they appeared in more than one of the draft guidances. Thus, Amgen has submitted a duplicate copy of these comments to each of the dockets established for the three draft guidances.

## EXECUTIVE SUMMARY AND OVERVIEW

Amgen commends the work of the FDA in drafting guidances that address many of the issues important to implementation of the U.S. biosimilar approval pathway. With some key modifications and additions, these will be useful resources for companies planning to develop and manufacture biosimilars and for patients and physicians who will ultimately determine the success of the new approval pathway. The following is an overview of our recommendations for the three biosimilar draft guidances:

- Acknowledge what we know today and what we do not yet know. The science of biotechnology has come a very long way in three decades but it would be detrimental to patient safety and undermine the goal of achieving a successful approval pathway if policy decisions were premised on aspirations rather than achievements.

- Use more precise language in the final guidance documents, whenever feasible. We recognize that regulatory standards and expectations must be flexible enough to accommodate the uniqueness of each biologic and to adapt to scientific and technical advances. The wide degree of flexibility and lack of clarity reflected in the draft guidances, however, risk undermining the objective of providing meaningful guidance to industry. Enhancing the specificity of the final guidances would improve transparency and facilitate the timely development of safe, pure, and potent biosimilars. We therefore recommend that the final guidance documents address the following points:

    - Define ambiguous terms;

    - Discuss concepts with greater specificity (eg, more discussion of agency expectations and examples); and

    - Acknowledge and address current technical and scientific limitations related to regulatory advice or requirements, and expressly note the challenges presented in evaluating the biosimilarity of proposed biosimilars.

- Make clear that clinical studies will be necessary for the foreseeable future due to the complexity and diversity of human biology and the limits of scientific knowledge today. At the same time, it is appropriate for the agency to acknowledge that analytical studies will increasingly facilitate reduction in the size and scope of clinical studies needed.

- Permit a biosimilar sponsor to use data derived from a study conducted with a foreign comparator to address components of statutory requirements if the foreign comparator product can be determined to be fully representative of the US licensed reference product. As the information relevant to demonstrating this may be held confidential by the reference product sponsor, FDA should specify that foreign comparator product data can be used if two criteria are satisfied: first, a single company manufactures and distributes both the US licensed and foreign comparator product and, second, the biosimilar applicant establishes a scientific basis for relying on comparative data involving the foreign product.

- Acknowledge biosimilars as stand-alone products for purposes of ongoing regulation once they have been approved as safe and effective. A requirement to maintain biosimilarity between the biosimilar and the reference product would unnecessarily complicate the regulatory process without providing meaningful benefit to patients and be likely to increase both regulatory and manufacturing costs.

- Commit to publishing class-specific guidance that discusses the approval standards and other key implementation issues for particular product classes. Class-specific guidance will provide the most meaningful guidance for manufacturers and will foster the confidence in biosimilars needed for physician and patient acceptance of this new class of product.

- Require all biological products to have a distinguishable nonproprietary name in order to facilitate accurate attribution of adverse events. The distinguishable name could consist of a common root and unique suffix, such as a Greek letter or the manufacturer's name, to enable identification of the product and manufacturer as well as to provide clear class affiliation.

- Specify that biosimilar product labeling must provide all information necessary for physicians and patients to make informed choices. This includes a standard

biosimilar label format as well as key biosimilar and reference product data, clearly labeled as such.

- Make clear that the agency is committed and fully intends to respect and enforce protections against disclosure of trade secret and commercial confidential information.

- Address the key issues of drift and attribution of adverse events following product switching before designating any product as interchangeable. Interchangeability is a higher standard of approval than biosimilarity and presents a complex set of regulatory challenges that should be addressed fully in a separate guidance.

- Adopt separate regulations, via notice and comment rulemaking, regarding the retention of reserve samples rather than simply "recommending" reliance on the long-standing requirements for ANDA sponsors. Unique considerations relating to recombinant biological products make this necessary.

- Clearly acknowledge that reference product exclusivity is presumptively granted by the law and the requirement for proof arises only to the extent a product could be considered a subsequent generation product. It would be contrary to the plain language of the statute to shift the burden of proof to the applicant to "make its case" for exclusivity when the applicant files a stand-alone BLA filed under 351(a). Uncertainty about whether a product will be eligible for data protection will severely impede biotech development and will significantly deter investments that improve products and therefore medical advances for patients.