Genentech
A Member of the Roche Group

FDA Draft Guidance for Industry: Considerations in Demonstrating Interchangeability with a Reference Product
Docket No. FDA-2017-D-0154

Comments from Genentech a Member of the Roche Group

General Comments

Genentech, Inc. (Genentech) submits these comments on FDA Draft Guidance on Considerations in Demonstrating Interchangeability with a Reference Product. Genentech is pleased to see the release of this long awaited draft guidance and is supportive of FDA's proposed approach for designating interchangeability for biological products with a reference product. However, there are two important issues regarding interchangeable biologic products that have not been addressed in this, or previous guidance documents issued by FDA, specifically nonproprietary naming, and labeling. These are critical issues that must be addressed to protect patients against inadvertent switching between non-interchangeable products or between different interchangeable products for the same reference product. Distinct names incorporating the random 4 digit suffix and precautionary statements in the labeling warning against substitution with other interchangeable biologic products to the same reference product are needed to appropriately identify these products in the market place, and protect patients from being switched between products that have not undergone the interchangeability assessment described in this draft guidance.

Nonproprietary naming for interchangeable biological products

FDA should issue guidance on nonproprietary naming for interchangeable biological products stating that the distinct suffix of a biosimilar should not change upon a determination of interchangeability. Labeling is the appropriate place to state whether a biological product has or has not been determined to be interchangeable with the reference product. Genentech believes that for prescribing and pharmacovigilance/safety reporting purposes, an interchangeable biological product should retain its unique identifier to distinguish it from the reference product; from biosimilars that are not interchangeable; and from other interchangeable biological products to the same reference product.

Labeling for interchangeable biological products

FDA should issue guidance on labeling for interchangeable biological products in the interest of transparency and patient safety. A statement on interchangeability in the labeling for a biosimilar is consistent with FDA's previously articulated concerns that communicating a biosimilar's interchangeability status is critical to addressing potential patient safety risks of inadvertently switching patients between non-interchangeable products. Labeling with respect to an interchangeable biological product should specify the specific reference product used in the interchangeability assessment, and precautionary statements warning against substitution with bioisimilar products that have not been designated as interchangeable, and other interchangeable biologic products to the same reference product but bearing a different 4 digit suffix.

Managing multiple interchangeable biologic products for the same reference product

With the issuance of this draft guidance describing FDA's proposed approach for designating interchangeability for biological products with a reference product, we expect interchangeable biologic products to begin entering the market in the near future. Eventually multiple interchangeable biologics for a single reference product can be expected in the market place. Given that interchangeable biologic products can be substituted without health care provider intervention there is a potential risk that patients could be switched from one interchangeable biologic product to another over the course of treatment. The current framework addresses the risk of switching or alternating between the reference product and a proposed interchangeable biological product, and limits use of the reference product to the US-licensed product to avoid potential differences in levels of specific structural features that could prime the immune system during switching and multiple exposures to each product. Different interchangeable biologic products to the same reference product would likely have even greater differences between them, creating a higher likelihood for generating undesirable immune responses if switched or alternated between each other and the reference product. It would not be practical to design switching studies to address this scenario; rather FDA should publish guidance on the need for distinct nonproprietary names and appropriate labeling for interchangeable biologic products to protect patients from being switched between products that have not undergone the interchangeability assessment described in this draft guidance.

Scientific rationale for the number of switches in switching studies to support interchangeability for biological products used more than once

Section VI A2 discusses the information and data needed to support a demonstration of interchangeability and states that the number and duration of switches between the reference product and the proposed interchangeable product should take into consideration the clinical condition to be treated, the therapeutic dosing of the product, and the duration of the exposure interval to each product that would be expected to cause the greatest concern in terms of immune response and resulting impact on safety and efficacy, if any. It further states that the switching arm is expected to incorporate at least two separate exposure periods to each of the two products (i.e., at least three switches with each switch crossing over to the alternate product). It would be helpful if FDA could provide the scientific rationale supporting the number of switches relevant to make certain the product is interchangeable. Why three switches instead of four, five or six switches?

FDA Specific Questions

With respect to interchangeable products, are there considerations in addition to comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products?

Interchangeability is a point in time assessment between the reference product and the proposed interchangeable biological product at which time they are shown to be highly similar to each other with no impact on safety and efficacy following switching studies. Over time changes to the reference product and the biosimilar product, although within the acceptable quality attribute ranges originally approved for each, may no longer remain highly similar to each other due to product drift.

ICH Q5e addresses use of comparability assessments for sponsors that make post-approval changes to their products. This framework is appropriate for sponsors of innovator products and biosimilar products to assess the impact of manufacturing changes on their respective products to ensure changes made to the manufacturing process do not impact safety and efficacy of the product originally licensed by the health authorities. However, due to the potential for product drift over time, this framework alone may not be appropriate for assessing impact of manufacturing changes for interchangeable products.

To address the potential for product drift between the reference product and its interchangeable biological product following a manufacturing change to the interchangeable biological product, a three way bridging study should be conducted using ICH Q5e as the framework for analytical and functional comparison. The three way bridging study should be conducted between the current reference product, the pre-change interchangeable biological product and the post-change interchangeable biological product In addition,

there should be a three way bridging clinical PK and PD (if available) study for all three products. All three pairwise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity.

How, if at all, should the Agency consider conditions of use that are licensed for the reference product after an interchangeable product has been licensed?

Adding additional conditions of use that are licensed for the reference product after an interchangeable product has been licensed should be limited only to a scenario in which the biologics license application holder for the reference product received approval for a new condition of use after the original licensure of the interchangeable product. Under this scenario the interchangeable product applicant could seek licensure for this additional condition of use by submitting an efficacy supplement to the 351(k) application that contains the necessary scientific justification for extrapolating data to support a determination of interchangeability for the new condition of use (see lines 532-550 in Interchangeability draft guidance), including draft labeling revised to include the additional condition of use sought.

Specific Comments

Line 116-119
Comment: The guidance states… *"We note that although a sponsor may seek licensure for a proposed interchangeable product for fewer than all conditions of use for which the reference product is licensed, we recommend that a sponsor seek licensure for all of the reference product's licensed conditions of use when possible."* This statement appears to contradict the statement in line 76-79 which states… *"FDA expects that sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use."* In order to meet the standard of "can be expected to produce the same clinical result as the reference standard in any given patient", an interchangeable product applicant should be expected to obtain licensure for all the reference product's licensed conditions of use at the time of licensure, unless a condition of use on the reference product's label is protected by exclusivity or an existing patent.

Proposed Change: Revise line 116-119 to read… *"We recommend that a sponsor seek licensure for all of the reference product's licensed conditions of use,* unless a condition of use on the reference product's label is protected by exclusivity or an existing patent."

Line 429-430
Comment: To determine PK steady state, multiple concentrations should be sampled.

Proposed Change: Revise line 429-430 to read…*"Multiple trough PK sampling should be conducted after each switch to ensure that steady state is attained."*

Section VI A 2a and b
Comment: For both the switching study design analysis (A.2.a, line 380) and the Integrated Study Design (A.2.b, line 447) language should be incorporated to include (as a secondary/exploratory analysis) incorporating Population Pharmacokinetic analyses.

Proposed Change: For both study designs language should be incorporated in the guidance to reflect the utility of population pharmacokinetic approaches to the analysis of data. The utility of analytical concepts such as overall variability and intra-occasion variability (between product or treatment periods) as well as collection of data for analysis as population PK model covariate effect on PK parameters such as bioavailability (if extravascular administration) or clearance, such as trial, products, or subject factors, such as laboratory tests, antidrug antibody (neutralizing antibody), changes in disease/performance status; these should include longitudinal measurements throughout the treatment periods (and switching periods).

Sincerely,

Eric Olson
Vice President, U.S. Product Development Regulatory