SPECIAL REPORT

Physician associations comment on FDA's interchangeability guidance

Comments from physician associations on the US Food and Drug Administration's draft guidance on interchangeability of biosimilars are presented in this paper. Various issues were discussed; this paper highlights the comments on extrapolation, interchangeability, switching, labelling and naming, post-marketing and disease experts.

Keywords: Biosimilar, extrapolation, interchangeability, labelling, switching, US FDA

Introduction

The US Food and Drug Administration (FDA) received 52 comments on its draft guidance on the interchangeability of biosimilars with their reference biologicals.

The draft guidance was first released in January 2017 [1] and the comment period ended on 19 May 2017 [2]. Comments from physician associations expressed their concerns about extrapolation of indications, switching, labelling and naming, and post-marketing studies, as well as other issues. Associations that commented on the guideline included the American College of Rheumatology (ACR), the American Society of Clinical Oncology (ASCO), the American Gastroenterological Association (AGA), the American Autoimmune Related Diseases Association (AARDA) and the American Academy of Dermatology Association (AADA), among others.

1. Extrapolation

Extrapolation has long been a concern for both physicians and patients. **AGA** stated in its comments that 'extrapolation of data should not be allowed for any indication where the pathophysiology is known to be different or is yet to be elucidated'. The association added that 'the agency should use caution when allowing extrapolation for pediatric indications'.

ACR stated that it 'does not support automatic extrapolation, but does support extrapolation after carefully identifying a minimum slate of diseases and outcomes to be studied, depending on factors including mechanism of action and predicted immunogenicity'. **ACR** added that 'if an interchangeable drug does not garner FDA approval for all indications of the originator drug, it is possible that the drug could be inappropriately substituted for a patient being treated for a disease for which the drug is not approved'. The ACR therefore believes that 'care must be taken in the final guidance' … to 'ensure that a drug pursuing interchangeability has successfully demonstrated extrapolation for all indications for which the originator is approved'.

2. Switching

AGA commented that it 'agrees with the recommendation to sponsors to use only U.S.-licensed reference products in switching studies', but expressed its concern that the 'FDA may be willing to entertain use of a non-U.S.-licensed product in some cases'.

Section 351(i) of the Public Health Service Act states that an interchangeable product 'may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product'. However, AGA is 'concerned that this practice will have a detrimental impact on patient safety'. The association states that 'health care providers must be empowered to be aware of and prevent non-medical switching if they believe that the patient's safety and health is at risk'.

ACR commented that it 'strongly supports the FDA's proposal to require manufacturers to use robust switching studies to determine whether alternating between a biosimilar and its reference product impacts the safety or efficacy of the drug. Exposing patients in the experimental arm to each drug twice (A, B, A, B), a protocol that requires three switches, is a reasonable attempt to simulate what our patients are likely to experience'.

AADA is concerned that an interchangeable biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. They state that 'patients must be informed and educated about the substitution at the point of sale'. They add that physician notification is important to prevent confusion and 'is crucial for pharmacovigilance'. The association 'stresses the importance of robustly designed switching studies given the potential for negative consequences for patients'. They add that 'forced non-medical switching of stable patients can result in worsening disease, severe flares, some requiring hospitalization, therapeutic failure, antibody development, and risk for greater adverse effects than those associated with current therapy'.

AARDA commented that 'particularly as related to potential substitution and non-medical switching practices, we question whether any biosimilar could be "interchangeable" with the reference product, particularly if autoimmune disease patients are considered'. They add that 'patients with autoimmune diseases who rely on biological products know all too well that different treatments – even if "similar" – can, and very often do, cause varied reactions for different patients, particularly those with complex diseases and/or with multiple diseases'.

ASCO asked for 'clarity among the various terminologies (switching, alternating and substituting) within this area'. They said that 'the explanations and expectations of switching and alternating are described in parallel, and because the result of either type of study could be a designation of interchangeable, the breadth of difference between switching and alternating should be clarified'. **ASCO** added that 'the term "substitution" should be defined for the public to understand that this action is the practice of an interchangeable biosimilar product being dispensed at pharmacy-level in place of the reference product'.

Submitted: 2 June 2017; Revised: 13 June 2017; Accepted: 13 June 2017; Published online first: 19 June 2017

3. Labelling and naming

ACR commented that it has previously asked for:

- 'Statements in each biosimilar FDA label indicating whether the drug is interchangeable (in addition to whether a drug is biosimilar)
- Inclusion of clinical data for biosimilars in FDA labels, via text or hyperlink
- Specific guidance for pharmacists to prevent inadvertent substitution of a non-interchangeable biosimilar as a stand-alone document and as a prominent message inside the *Purple Book* list'

The association also said that it 'supports the FDA's stated plans to use distinguishing suffixes to help minimize "inadvertent substitution," particularly for biosimilars that have not been determined to be interchangeable'.

AADA recommends 'that the biologic product label include whether the biosimilar is interchangeable with any other biologic products (including the reference product and/or other biosimilars on the market) and also for which specific indications interchangeability was demonstrated'.

AADA also commented that the 'FDA should ensure that interchangeable products are distinctly named and labeled, and should emphasize that automatic substitutions and non-medical switching policies are not appropriate for products that have not been designated by FDA as interchangeable'.

4. Post-marketing studies

AGA commented that '"real world" data on biosimilar and interchangeable products must be collected through formal post-marketing observational studies to ensure the longitudinal safety and efficacy for all patient populations being treated with these products'. This should be done since 'rare but potentially serious safety risks may not be detected during preapproval clinical testing'. The association also recommended using a 'central observational registry' to monitor the safety, efficacy and utilization for all biologicals.

ACR said that 'the FDA should also consider requiring manufacturers to submit updated and standardized pharmacovigilance data as a prerequisite to certain post-market labeling changes'.

ASCO applauded FDA for including post-marketing safety monitoring considerations in its guidance. The association added that 'meaningful post-marketing surveillance is essential as more biosimilars enter the market'.

5. Disease experts

AGA advocated that 'gastroenterologists with appropriate disease expertise should be engaged by FDA when interchangeable products are reviewed for approval'. This has so far been the case for biosimilars, where gastroenterologists have been engaged as temporary members of the Arthritis Advisory Committee. AGA therefore urges FDA 'to continue engaging gastroenterologists with appropriate disease specific expertise as part of its advisory committees when a proposed product is seeking a gastrointestinal indication'.

Editor's Comment

Healthcare professionals can find more information on biosimilars and the FDA's policies regarding biosimilarity and interchangeability at https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm241719.htm

Competing interests: None.

Provenance and peer review: Commissioned; internally peer reviewed.

Michelle Derbyshire, PhD, *GaBI Online* Editor

References

1. GaBI Online – Generics and Biosimilars Initiative. FDA issues draft guidance on biosimilar interchangeability [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2017 Jun 13]. Available from: www.gabionline.net/Guidelines/FDA-issues-draft-guidance-on-biosimilar-interchangeability
2. GaBI Online – Generics and Biosimilars Initiative. FDA extends comment period for interchangeability guidance [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2017 Jun 13]. Available from: www.gabi-online.net/Guidelines/FDA-extends-comment-period-for-interchangeability-guidance

DOI: 10.5639/gabij.2017.0603.024