PATIENT SAFETY

Patient safety is a priority in the development of any new biologic treatment and must also guide all policy and health decisions related to biologic therapies. Because biologics are manufactured through a complex process using living cells that are sensitive to changes in their environment and harvesting techniques, biologics present challenges that are different than those presented by the manufacturing of small molecule drugs.

To ensure patient safety, the regulation of biologics includes a stringent FDA approval process involving clinical trials, assessment of immune responses, labeling requirements, and post-approval safety monitoring. We expect the FDA to require similar metrics in the approval pathway for biosimilars, although the agency is unlikely to require the same amount of data and information that was necessary to approve the innovator biologic.

CLINICAL TRIALS

Before an innovative biologic is approved by the FDA, it must undergo thorough testing in the laboratory and in patients. This typically takes seven to 15 years and can involve thousands of patients, depending upon the prevalence of the condition. The phases of the evaluation are:

Preclinical
- Evaluates potential safety issues using cell cultures and animal models.

Phase 1: *Safety/Tolerability*
- First human test of a new biologic.
- Drug's safety and tolerability is evaluated.
- The testing group is usually very small (20-50 healthy volunteers without the disease).

Phase 2: *Dosage/Proof-of-Concept*
- Larger Group of volunteers (100-300 people with disease biologic intends to treat).
- Determines dose optimization and demonstration of potential safety and efficacy.

Phase 3: *Safety and Effectiveness*
- Demonstrates the safety and effectiveness of the new biologic.
- May compare it with other therapies (if any) already available.
- Can involve thousands of patients.
- May last for multiple years to determine long-term patient safety.

Phase 4: *Post Market*
- Occurs after a drug is on the market.
- Monitors the drug's safety and efficacy when used in a normal medical setting.

IMMUNE RESPONSES/IMMUNOGENICITY

Immunogenicity is the ability of a biologic/biosimilar to stimulate an immune response in a patient, which is of significant clinical importance to patients and thus a critical factor in approving biologics. Unlike small molecule medicines, which are generally unseen by the immune system, biologic molecules are often so large that they can trigger an unwanted immune response. If the immune response is severe, it can neutralize the effect of the medicine, thus leaving the patient without the intended therapeutic benefit.

continues:

IMMUNE RESPONSES/IMMUNOGENICITY | *continued*

In some cases, which are very rare, the immune response may be so severe that not only the medicine but the patient's naturally occurring protein is attacked, leaving the patient without an essential protein.

Similar biological products may cause different immune responses in patients. A small difference, such as a different number of amino acids or a change in the way a molecule is folded may go unnoticed by the immune system or cause a different immune response in a patient. These different responses can present potential safety risks for patients. If different immune responses in the original biologic and the biosimilar are detectable, the need for further trials should be immediately determined. Immune responses, however, may also develop long after a patient has been exposed to the medicine. It is important that biologics be carefully tracked and immune responses accurately attributed to the specific product, manufacturer and even product lot number.

LABELING

Labeling is an important area for all medicinal products, and the FDA has an opportunity to take the lead in setting standards and regulations when it comes to labeling of biosimilars. With pills, the same labeling for an original pill and a generic pill, with some very minor exceptions, is required because the generic must be identical to the original. With biosimilars, however, it is likely that applicants will be required to conduct some clinical testing before approval. Biosimilar labeling may reflect the results from the specific testing conducted by the biosimilar sponsor. To date, FDA has not issued guidance on labeling requirements for biosimilar medicines.

POST-APPROVAL SAFETY MONITORING

Biologics are subject to intensive post-approval monitoring intended to fully assess the safety of a product after it is on the market. With the introduction of biosimilars, we must have a way to trace post-approval safety issues for correlating adverse reports to specific products and manufacturers.

Adverse events must be detected and reported through safety monitoring programs to ensure patient safety problems associated with a specific product and/or manufacturer are addressed quickly and comprehensively. These types of programs may include electronic data collection, investigations and a variety of analysis.

As noted above, patients may develop an unwanted immune response long after initially receiving a biologic medicine. If a patient receives more than one biologic for a particular condition, it may be impossible to determine which product caused the immune response. For chronic diseases, the patient receives regular treatment over a long period of time. The sensitive nature of biologics/biosimilars and the patients they treat makes it even more imperative that there is a strong tracking system for post-approval monitoring as well as strong state policies ensuring patients and physicians, collectively, remain in the driver seat when determining the appropriate product for a particular patient.