What are the Regulatory Differences Between an NDA and BLA?

To formally request approval to market a new drug in the United States, sponsors must submit either a New Drug Application (NDA) or a Biologics License Application (BLA) to the FDA. As their names suggest, BLAs relate to biological products while NDAs generally pertain to traditional small molecule drugs. While they share the same goal of obtaining marketing approval, they also vary slightly in content and scope. In this post, we explore the similarities and differences between the two marketing applications, as well as special considerations based on recent regulatory changes.

What are New Drug Applications (NDA) & Biologics License Applications (BLA)?

An NDA is an application to permit the sale and marketing of a new drug in the United States. A traditional NDA consists of data and information about the drug as gained from both nonclinical and clinical studies, as well as a summary of formulation development and manufacturing processes, and proposed labeling information to be included in the drug's packaging.

In general, an NDA should contain enough data for the FDA to determine if the drug is safe and effective for its proposed use, if the benefits of taking the drug outweigh the risks, and if the drug product is manufactured in a way that preserves its identity, strength, quality, and purity. Drugs that are approved via an NDA pathway are regulated under Section 505 of the Food, Drug, & Cosmetics (FD&C) Act.

A BLA is a request to introduce, or deliver for introduction, a biological product into interstate commerce. Like an NDA, a BLA should include all information about the biological product that was gained over the development process and should demonstrate the biologic's safety, purity, and potency. The BLA also contains the proposed labeling information to be included in the drug's packaging. Per the Biologics and Price Competition and Innovation (BPCI) Act of 2009, as of March 23rd, 2020, all biological products must be approved through the BLA pathway, and therefore will be licensed under Section 351 of the Public Health Service (PHS) Act, in addition to being regulated by the FD&C Act.

What is a Biological Product?

Biological products are a subset of drugs defined by Section 351 of the PHS Act as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, ... applicable to the prevention, treatment, or cure of a disease or condition of human beings." The definition

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was later amended by the BPCI Act of 2009 and the Further Consolidated Appropriations Act of 2020 to include proteins (excluding peptides). Because biological products are typically derived from living systems, their large, complex structures are often difficult to characterize. This is a key distinction from traditional drug molecules, which are chemically synthesized and structurally both simpler and smaller in size.

The manufacturing process for biological products is also more complicated, due to genetic variability in the source material. Because of this, it is critical that BLAs contain a thorough description of product development and relevant manufacturing procedures, as well as all steps taken to ensure that the final biological product performs consistently across batches.

Key Differences Between BLAs & NDAs

While BLAs and NDAs serve the same purpose of gaining approval to market a drug in the United States, they differ slightly in terms of their application content and submission requirements. Regarding approval criteria, NDAs must fulfill three conditions:

- The drug is safe and effective for the proposed use and that the benefits outweigh the risks
- The labeling is appropriate and contains all necessary information about the drug
- Manufacturing methods preserve the drug's identity, strength, quality, and purity

Similarly, contents of a BLA should establish that the biological product is safe and potent; however, because biological products are processed from living material, BLA content must also demonstrate purity specifically in terms of showing that the final product does not contain extraneous material.

Due to the complexities of manufacturing biological products, a pre-license inspection of the facility is generally required before a BLA is approved. Pre-approval inspections sometimes also take place during an NDA review, but are typically conducted based on risk assessment by the Agency.

Once a BLA is approved, the Sponsor is granted a license for the biological product, which permits its introduction into interstate commerce per Section 351 of the PHS Act. This licensing process is not a part of the NDA, as drugs that are approved by NDA are regulated only by the FD&C Act, and not the PHS Act.

Until very recently, certain biological products could be approved under an NDA rather than a BLA. However, according to the Biologics Price Competition and Innovation Act (further discussed below) this is no longer the case, and all biological product approvals now occur through a BLA.

Regulatory Agencies

There are two Centers within the FDA that are responsible for the review and approval of drug marketing applications and general regulatory oversight: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). While all conventional drug products (i.e., small molecules) are regulated by CDER, biological products can be regulated by either CDER or CBER, depending on the product's classification as discussed above.

The majority of BLA submissions are assigned to CBER; however, BLAs for certain biological product categories are reviewed by CDER instead. These product categories include monoclonal antibodies for in vivo use, most proteins for therapeutic use (e.g., cytokines, enzymes, and other novel proteins except those assigned to CBER, such as vaccines and blood products), immunomodulators, and growth factors. Regardless of the category, NDAs for all drug products fall under the jurisdiction of CDER.

Key Similarities Between BLA & NDA

Like an NDA, a BLA is submitted to the FDA in order to market a new drug in the US. As they share the same goal of obtaining marketing approval, NDAs and BLAs are similar in that both must contain enough information to demonstrate the efficacy and safety of the drug, as well as demonstrate an ideal risk:benefit ratio, in order to be successful. Additionally, many of the same regulations apply to NDAs and BLAs, including labeling and advertising rules, accelerated approval pathways, pediatric study requirements, and PDUFA fees.

Regardless of whether a sponsor is submitting an NDA or BLA, the same pre-marketing regulations apply. This includes initial filing of an IND and subsequent maintenance of the IND throughout the drug development program until the marketing application is submitted. The structure and contents of the IND do not differ between drugs and biological products.

Biologics Price Competition and Innovation Act

It is important to note that on March 23, 2020, the Biologics Price Competition and Innovation (BPCI) Act went into effect. Along with introducing an abbreviated approval pathway for highly similar biological products (i.e., biosimilars), this act mandated that moving forward, all biological products must be submitted for marketing approval through a BLA, and not an NDA. For biological products that had been previously approved via NDA (e.g., protein products), the approved marketing application will be "deemed to be a license" (i.e., serve as an approved BLA) for the biological product under Section 351 of the PHS Act.

Conclusions

NDAs and BLAs are the two types of applications that are submitted in order to market a new drug in the United States. While they are both submitted to gain FDA drug approval, they differ in terms of product categories, approval criteria, and certain regulations. Nuventra consultants are widely experienced in the preparation and submission of both BLAs and NDAs for numerous drugs and indications.

If you have questions about preparing your marketing application or need assistance with its development, Nuventra is here to help. Contact us today to see how we can support you on your pathway to FDA approval.

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