Determining the Most Appropriate Regulatory Submission for a Drug

In the U.S., three regulatory options are available for submission of a new drug application (NDA) to the Food and Drug Administration and include the following regulatory pathways for approval:

- Innovative drug – 505(b)1 NDA
- Modification of previously approved drug or reliance on published studies for a new chemical or molecular entity—505(b)2 NDA
- Manufacture of a generic version of an innovative drug – 505(j) Abbreviated NDA or ANDA

Development of an overall regulatory strategy is an important process in the development of any new drug. The innovative drug is time intensive and requires submission of a complete nonclinical and clinical data package to demonstrate safety and efficacy. In contrast, the ANDA for the generic drug generally only requires demonstration of bioavailability and bioequivalence to the reference listed or originator drug. Utilization of the 505(b)2 approval process, when applicable, typically requires an intermediate level of data with fewer studies and often reduces the time to approval and launching the new drug product. Below we outline some considerations for submitting a 505(b)2 type of drug application that is unique to the U.S.

**Considering a 505(b)2 Regulatory Submission**

A 505(b)2 application is submitted in cases where the applicant is relying on FDA’s previous findings of efficacy and safety. Like the 505(j) application, bioequivalence and bioavailability studies need to be conducted to compare to the reference listed drug. However, additional safety and efficacy studies are needed to address changes in drug characteristics such as: the active ingredient, dosage form, route of exposure, strength, or new indication.
Specific cases where a 505(b)2 application could be considered:

**A new chemical entity or a new molecular entity:** If an applicant did not conduct the studies and cannot obtain right of reference for the original study data, published studies can be submitted to support a drug application. This is commonly described as a literature-based 505(b)2 application and would only be applicable where a 505(b)1 has not yet been submitted to the Agency.

**A new combination product:** Two or more previously approved drugs that are combined into a single new drug product qualify for this type of application. In this case, studies on the original active ingredients can be relied upon, but additional studies are needed to demonstrate the safety and efficacy of the new combination to ensure synergistic or antagonistic effects do not occur.

**Formulation changes:** Changes in the dosage form (e.g., oral capsule to liquid gel capsule), strength, dosing regimen (e.g., twice a day to once a day), or route of administration (e.g., oral to nebulizer/inhaler) can qualify for a 505(b)2 submission. Data needs would include studies that demonstrate that these changes do not affect the bioavailability/bioequivalence of the new product, as well as chemistry, manufacturing and control (CMC) bridging studies to the reference listed drug.

**Modification of the active ingredient:** Alteration of the active ingredient by converting it to a salt or ester, chelating the molecule, or creating a new complex can be supported by this type of submission. Again, data would be required to demonstrate that these modifications result in the same dose received of an active metabolite or that the safety and efficacy profile is unaffected by these changes.

**New indications of an approved drug:** Any new indication of a previously approved drug can be submitted under the 505(b)2 process. Thus, data to support off-label uses of a drug could be compiled and submitted to FDA for formal approval of that indication.

**Implications of a 505(b)2 Application**

Depending on the degree of innovation involved in development of the new product and the quantity of data required in support of the application, market exclusivity for the new drug can range between 3 and 5 years. This exclusivity or patent protection can provide an incentive to develop modifications to existing products, but there are potential drawbacks that also need to be evaluated in an overall regulatory strategy. The extent of innovation will have an impact on the type and complexity of nonclinical and clinical studies needed to demonstrate the safety and efficacy of the new product. Development of a regulatory strategy for bridging the toxicology data, the pharmacokinetic data, and the CMC data is important and should be reviewed with the FDA for agreement on the approach. Consideration of the reference drug(s) may also impact study designs. Early interactions with FDA are encouraged and may be critical to understanding and ultimately complying with the various scientific and regulatory requirements for a drug approval under the 505(b)2 process.

**For more information please contact:**
Karyn Hentz, M.S., RAC, DABT • (571) 227-7208 • khentz@exponent.com

**References**

Exponent’s Nonclinical Services

Exponent’s Center for Toxicology and Mechanistic Biology provides the highest quality technical, regulatory, and safety assessment services to assist our clients with issues related to pharmaceutical and biotechnology products, with a particular focus on nonclinical development and regulatory support. We have several in-house staff with direct pharmaceutical experience, coming to Exponent from both large and small pharmaceutical and biotechnology companies. Our unique range of skills and experience in drug development helps our clients maximize the value of their research and development efforts in bringing medications to the market.

Aspects of the nonclinical developmental process for which Exponent is poised to assist include:

- Development of customized nonclinical testing strategies to reduce costs and maximize the likelihood of moving your candidate into the clinic and beyond
- Identification of appropriate animal models for nonclinical safety assessment
- Expertise in small and large molecules, and other novel therapeutics
- CRO selection, study design and management, including toxicity, safety pharmacology and toxicokinetic evaluations
- Appropriate dose selection for nonclinical safety testing (including carcinogenicity testing) and first-in-human studies
- Nonclinical issues research and resolution
- Particular expertise in developmental/reproductive toxicology, juvenile and genetic toxicology
- Data analysis and regulatory document preparation
- Preparation of pregnancy and lactation labeling content
- Regulatory support in preparation of Investigational New Drug (IND) applications and New Drug Applications (NDAs)
- Knowledge of global regulatory requirements, and responses to regulatory questions
- Representation during meetings with the FDA and other regulatory bodies
- Environmental impact assessments for US and EU regulatory authorities

Beyond Nonclinical

Exponent is positioned to provide guidance across the entire product lifecycle for clients. Examples of areas beyond nonclinical in which Exponent can assist include the selection and prioritization of therapeutic indications and the development of target product profiles; defining the commercial strategy or competitive landscape; streamlining the regulatory approval process through the incorporation of biomarkers and tools for managing patients; the design of post-marketing surveillance strategies; and economic modeling to prioritize pipeline assets and provide predictions regarding success. We also have expertise in development of devices and device-drug combination products. We provide these services by leveraging the knowledge and experience of more than 90 technical disciplines across our firm.
Our Preclinical Support Staff

John DeSesso, Ph.D., DABFM, DABFE, FACFEI, Fellow ATS
(571) 227-7261 • jdesesso@exponent.com

Dr. DeSesso has more than 35 years of experience specializing in the areas of developmental and reproductive toxicology, general toxicology, risk assessment, and human health effects of pharmaceuticals and environmental agents. He has published widely in these areas. He has assisted companies with assessment of data needs; design and interpretation of studies to meet regulatory requirements; preparation of INDs and NDAs for substances related to blood products, diabetes, liver disease, and weight loss; and preparation for and attendance at various FDA and Advisory Panel meetings for these substances. He is an adjunct professor of Biochemistry and Molecular Biology at Georgetown University School of Medicine, where he has been a faculty member for more than 30 years.

Bhaskar Gollapudi, Ph.D.
(989) 486-8782 • bgollapudi@exponent.com

Dr. Gollapudi specializes in genetic and molecular toxicology and chemical carcinogenesis and leads a team of genetic toxicology specialists at Exponent. He has more than 30 years of research and issue management experience at a major multinational industry addressing the safety of a diverse portfolio of substances. He has published more than 100 papers in peer-reviewed journals and edited a book on the application of genomic technologies for safety and risk assessment, is an adjunct Associate Professor at University of Michigan School of Public Health, and serves as Associate Editor of the journal Toxicological Sciences and serves on a number of scientific committees, including the OECD Expert Committee on Genetic Toxicology Guidelines and the Committee on Toxicology of the U.S. National Research Council. Dr. Gollapudi is an invited speaker at a number of national and international scientific conferences and recent recipient of the 2014 Arnold J. Lehman Award from the Society of Toxicology in recognition of his contributions to the field of risk assessment and chemical regulation.

Karyn Hentz, MSPH, RAC, DABT
(571) 227-7208 • khentz@exponent.com

Ms. Hentz is Regulatory Affairs Certified (RAC) in U.S. FDA regulations and provides regulatory support for a range of healthcare products. This work has included assisting companies with the identification of data gaps in their regulatory submissions, and collaboration in the conduct of studies or development of a rationale for waiving specific requirements. When studies have been needed, she has performed study monitoring on behalf of her clients, to ensure compliance and timely preparation of reports to meet regulatory deadlines. She has provided regulatory support for proprietary drug substances, generics, and excipients, leading to the submission of INDs, ANDAs and NDAs.

Jane Staveley, MSPH
(919) 228-6480 • jstaveley@exponent.com

Ms. Staveley is a Senior Managing Scientist with 35 years of experience in environmental toxicology, ecological risk assessment, and product stewardship. She has conducted environmental assessments of pharmaceuticals, both for human and animal use, for submission to the U.S. FDA and European regulatory authorities. This work has involved the placement, monitoring, and interpretation of ecotoxicity and environmental fate studies, as well as the development of novel exposure assessment approaches, including a watershed-level assessment. Ms. Staveley was an invited participant in a 2006 workshop on “Veterinary Medicines in the Environment,” organized by the Society of Environmental Toxicology and Chemistry (SETAC), and she served as the moderator of a U.S. Congressional Briefing in 2010, sponsored by the American Chemical Society, on the topic of “Pharmaceuticals in Our Water: Concerns and Responses.” Dr. Staveley also served on the steering committee of a 2011 workshop sponsored by SETAC and Health Canada on “The Top Research Questions on Pharmaceuticals and Personal Care Products in the Environment.”
Tacey White, Ph.D.
(215) 594-8849 • twhite@exponent.com

Dr. White has over 16 years of experience in pharmaceutical drug development of small and large molecules, with emphasis on developmental and reproductive toxicology (DART), and juvenile and general toxicology. She advises pharmaceutical and biotech companies on nonclinical safety assessment strategies throughout the entire drug development process, including planning customized nonclinical strategies, placing and monitoring studies, developing human risk assessments for toxicity issues, addressing regulatory questions, and contributing to regulatory documents (IBs, INDs, Briefing Books, PIPs/PSPs, NDAs). Within the pharmaceutical industry, she has had extensive experience as a Study Director, safety assessment project team representative, and lead investigator on developmental toxicity mode-of-action studies for a diverse range of pharmaceutical products. She is currently Vice President of the Teratology Society.

Amy Williams, Ph.D., DABT
(571) 227-7226 • awilliams@exponent.com

Dr. Williams is a board-certified toxicologist with more than 20 years of experience in the evaluation of pharmaceuticals, as well as chemical and physical agents, for potential adverse effects on human health. She specializes in general toxicology, developmental and reproductive toxicology, and endocrine disruption. Dr. Williams has assisted companies in the design, monitoring, and interpretation of preclinical safety studies, in the evaluation of excipients, and in the preparation of NDAs for regulatory submission. Dr. Williams also has significant experience communicating health risks to the public.

Relevant Publications


Rehm S, White TE, Zahalka EA, Stanislaus DJ, Boyce RW, Wier PJ. Effects of food restriction on testis and


