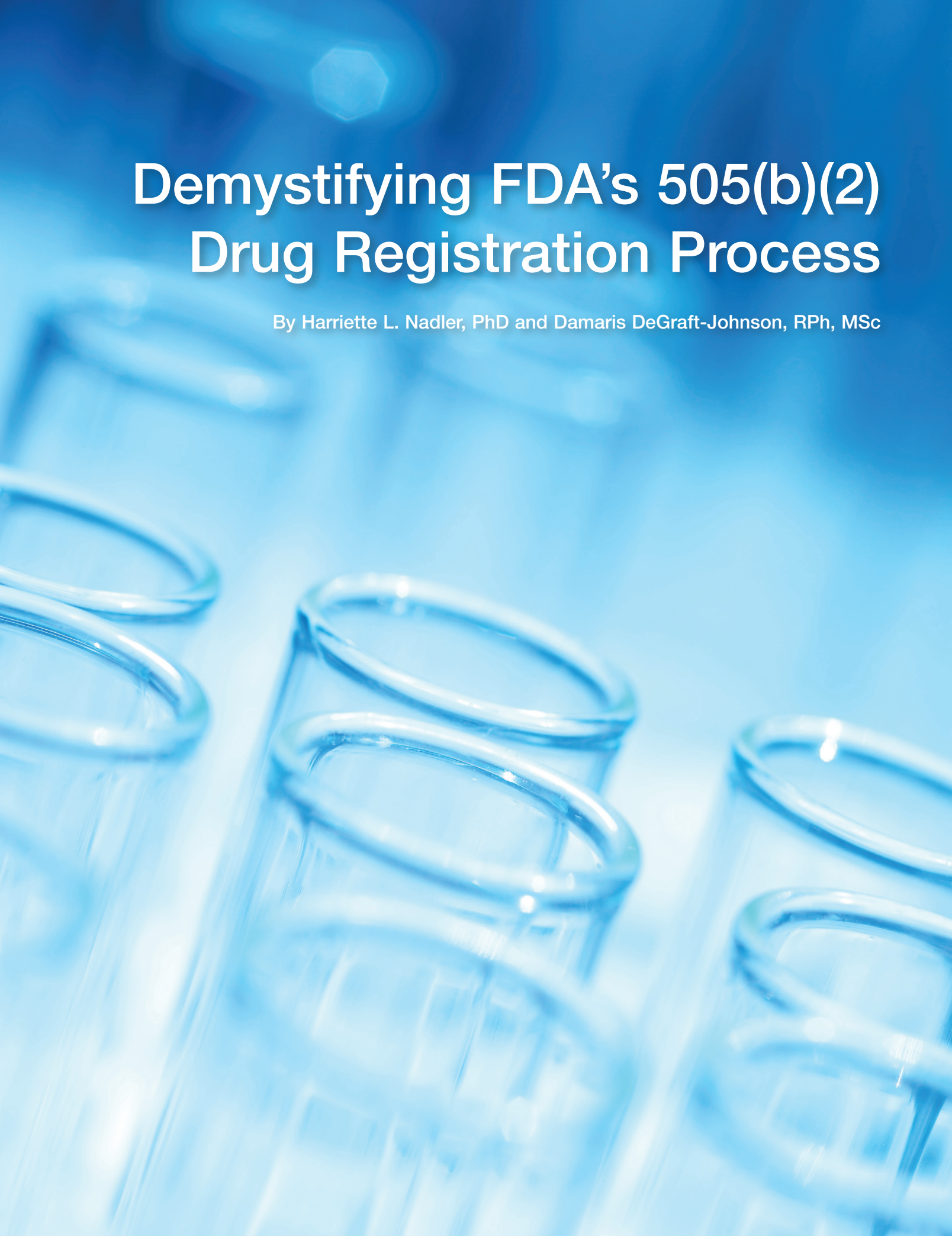


Demystifying FDA's 505(b)(2) Drug Registration Process

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The US Food and Drug Administration's (FDA) legal/regulatory framework offers three pathways to approval of New Drug Applications (NDAs): 505(b)(1), 505(b)(2) and 505(j). This article provides an overview of the 505(b)(2) process in comparison to the other registration processes. In 2008, more than half of the new drugs approved in the US utilized the 505(b)(2) registration pathway. Of the 28 drug approvals in 2008 under this pathway, 50% were products with new formulations and the remainder were principally products with new molecular entities, changed active ingredients and new drug combinations. This reflects an increase from 2006 and 2007, for which the percentages were 20% and 43%, respectively.¹

The 505(b)(2) application process shares some attributes with 505(b)(1) NDAs as well as (505(j) Abbreviated New Drug Applications (ANDAs) for generic products (see **Table 1**).² 505(b)(2) and 505(j) applications share the requirement for conducting bioavailability/bioequivalence (BA/BE) studies of the proposed product with the FDA-approved Reference Listed Drug (RLD). Both may rely on the agency's previous finding of safety and efficacy for

the RLD to support approval.³ Sponsors may submit 505(j) ANDAs only when their new product and the RLD are bioequivalent^{4,5} and have identical characteristics (e.g., active ingredient, dosage form, strength, route of administration, uses, etc.). The standard for approval (substantial evidence of safety and effectiveness) for 505(b)(2) drugs is the same as for 505(b)(1) drugs.^{6,7} However, 505(b)(2) applications may rely upon FDA's previous findings of safety and effectiveness as well as some changes, e.g., of quality attributes, to the RLD. In addition, the sponsor must provide a demonstration of pharmacokinetic (PK) BA/BE of the new product versus that of the RLD.⁸

In certain instances, efficacy, safety and quality attributes of the proposed or changed product need to be proven. A case study is provided to illustrate an instance when PK comparability or BA/BE studies had to be accompanied by new efficacy and safety studies. The 505(b)(2) drug application must meet the same requirements as a standalone NDA submitted under 505(b)(1), but not all of the information required for approval of 505(b)(2) drugs is necessarily derived from studies conducted by the sponsor. And the

Table 1. Similarities and Differences Between Registration Routes

Regulatory Process	505(b)(1)	505(b)(2)	505(j)
Agency Meetings	Yes	Yes	No
User Fees	Yes	Yes	No
Review Classification/Timeline	9 mos. ¹	9 mos. ¹	6-12+ mos.
Required for approval			
Full Reports of Efficacy/Safety Studies	Yes	Maybe	No
PK/Bioavailability/Bioequivalence Studies with RLD	NA	Yes	Yes
CMC Bridging Studies with RLD	NA	Yes	Yes
Toxicology Bridging Studies with RLD	NA	Maybe	NA
Supportive Publications on RLD	NA	Maybe	No
FDA's Findings of Safety & Effectiveness for RLD	NA	Yes ²	Yes ²
Extensive Stability Data	Yes	Maybe	Limited
Examples of Allowed Changes (e.g., from RLD)			
New Molecular (Chemical) Entity	Yes	Yes ³	No
New Active Moiety	Yes	Yes ⁴	No
New Indication	Yes	Yes	No
New Route of Administration	Yes	Yes ⁵	No ⁶
New Formulation	Yes	Yes ⁵	No ⁶
New Ester, Salt or Other Non-covalent Derivative	Yes	Yes ⁵	No
New Dosage Form or Strength	Yes	Yes ⁵	No ⁶
Combination Product	Yes	Yes	Maybe ⁷
Rx/OTC Switch	Yes	Yes	No
Labeling	NA	Maybe	No
Marketing and Patent Issues			
Patented	Yes	Yes	Maybe
Market Exclusivity	Yes	Yes	No ⁸

¹FDA targets nine months for standard reviews, but a typical review is 10-12 months; may receive priority review and orphan drug designation which reduces target review time.

²Reliance on summary information that is included in labeling. FDA does not permit citing innovator's specifics of individual studies in FDA's Summary Basis of Approval for which a right of reference has not been obtained

³Drug is not approved anywhere; drug is approved in non-US region; or is a product or active metabolite of approved drug. There also may be no therapeutic equivalent

⁴Molecule or ion, excluding the appended portions that cause the drug to be an ester, salt or other non-covalent derivative (complex, chelate, etc.), responsible for the physiological or pharmacological action of the drug substance

⁵Some changes may not be allowed; proposed changes need to be discussed with FDA as early as possible.

⁶Citizen's suitability petition submitted to FDA for approval of a change in a listed drug

⁷Permitted when single active ingredient is substituted for one active ingredient of listed combination drug

⁸Except against other generics approved after first application was approved

Table 2: Case Study of a Neurologic Product Approved via the 505(b)(2) Registration Route

FDA review division

Division of Neurology Products

Allowed change from RLD

Alternate route of administration

Sponsor conduct of efficacy/safety studies

- Double-blind efficacy study in patients compared the proposed product (development formulation) to the RLD.
- Primary efficacy endpoint showed a statistically significant difference in the changed product compared with the RLD.
 - Superiority of the changed product versus the RLD could not be claimed in Section 14, Clinical Studies, of the product's labeling without conducting an additional study statistically powered to demonstrate superiority and also establishing concentrations of the drug necessary for the pharmacologic effect.
- Safety/tolerability study of the final commercial product (FCP) in patients using the alternate route of administration was conducted.

Reliance on literature search and agency findings of effectiveness and safety

- Literature summaries of each pertinent individual efficacy study were included in the NDA with details about general design, dose and duration, etc.
- Safety data were extracted and abstracts of studies were prepared and hyperlinked to original articles.

Bridging BA/BE studies

- Stepwise scenario was accepted by FDA for the PK comparability studies in which Product A was a development formulation and Product B (FCP) was the final commercial product.
 - Product A = Product C (RLD) in PK study
 - Product A = Product B (FCP) in PK study
 - FDA's criteria for pharmacokinetic bioequivalence were met.⁴
 - Sponsor demonstrated that rate and extent of absorption of the proposed product and the RLD were sufficiently similar so that abuse liability studies were not required.
- Dose proportionality of low and high dosage forms of changed product in adults was similar to that of RLD as published in literature.
 - FDA considered this demonstration adequate to support the use of the low-dosage form in geriatric or debilitated patients.

Bridging toxicological studies

Single study was required in animals to demonstrate local safety/tolerability of alternate route of administration.

Bridging CMC studies

- Some *in vitro* comparisons of the changed product to the RLD were required to address potential abuse liability.
- Establishment of impurity profiles in accordance with relevant ICH guidelines was required, including evidence of no structural alerts for genotoxicity/carcinogenicity.
- Establishment of appropriate quality control was required to demonstrate performance attributes.
- Deficiencies were not noted by FDA.

Agency advice

Original NDA:

- Agency input regarding selection of the RLD was not sought prior to submission.
- Agency requested additional safety/tolerability data re: the alternate route of administration.
- Agency requested additional PK analyses to show that abuse liability was not a concern.
- **Outcome:** new NDA needed to address deficiencies.

New NDA:

- A strategic pre-NDA meeting was conducted.
- The second filing addressed all agency concerns.
- **Outcome:** NDA approval.

Compliance

GLP deficiencies:

- Reserve or retention drug samples to allow confirmation of identity of drugs assayed in PK BA/BE studies were not available at the clinical sites; however, other representative reserve samples were provided by the sponsor.
- Cross-validation of assays conducted in two different bioanalytical labs was not done; however, other related verification data were provided.
- Concentration estimates only from the high calibration curve were acceptable from a PK BA/BE bridging study.
- **Outcome:** GLP compliance deficiencies were adequately addressed and considered in conjunction with clinical, PK and CMC findings of proposed product and extensive data publicly available for the RLD.

GCP deficiencies:

- Source documentation for a secondary endpoint was not sufficient.
- **Outcome:** deficiencies did not preclude approval.

Labeling

- Evidence of favorable PK or PD (pharmacodynamic or efficacy) differences between routes of administration was considered inadequate to warrant new efficacy claims.
- Efficacy studies were conducted with a development formulation, not the final commercial product; this observation did not preclude approval.
- Consequently, aside from small changes in Sections 6 and 12 of the labeling, Adverse Events and Clinical Pharmacology, respectively, the approved labeling content was very close to that of the RLD.

sponsor may not have obtained a right of reference to the RLD, especially to the raw data (i.e., not in the public domain) used to summarize findings for approval.⁹

Providing Clinical Evidence of Safety and Effectiveness

For 505(b)(1) and 505(b)(2) drugs that warrant efficacy and safety studies, full safety, efficacy and selected clinical pharmacology reports (in instances agreed by FDA, e.g., BA/BE bridge studies), it is strongly suggested that sponsors seek advice from vendors providing management of electronic submissions to meet NDA requirements, including submission of raw datasets (e.g., CDISC-compliant) from efficacy, safety and BA/BE studies. When efficacy and safety studies are required, substantial evidence of efficacy must be established in one or more adequate and well-controlled trial(s).¹⁰

Depending upon the nature and scope of efficacy studies required by FDA for 505(b)(2) drugs, an integrated summary of efficacy may be required. This requirement is more likely when the sponsor conducts PK bioequivalence studies and efficacy and safety studies to demonstrate that the drug's profile was not significantly altered as a result of the allowed changes. The sponsor is expected to integrate, compare and contrast the changed product with the RLD within the integrated summary, which should also contain postmarketing safety surveillance data for the RLD, if available.

If the sponsor relies upon the agency's previous findings of safety and efficacy for an approved product, a scientific bridge (BA/BE) to the RLD is required. This study compares the systemic levels of the proposed product with that of the RLD. The new product must be as bioavailable as the RLD (unless it has some other advantage, e.g., a smaller peak/trough ratio) and the release profile must be at least as favorable as that of the RLD.

The sponsor should propose an RLD to the review division for its agreement before the BA/BE, toxicological and CMC bridging programs are conducted. It is possible to have more than one RLD, e.g., previously approved immediate release and controlled release products. Failure to obtain the review division's approval of a sponsor's planned RLD could lead to a refuse-to-file action.

The sponsor should conduct a literature search regarding the active ingredient to help develop the product's NDA strategy. FDA's Summary Basis of Approval (SBA) for similar or competitive products should also be compared with the sponsor's plans to demonstrate BA/BE.

A literature search is conducted using such databases as the National Library of Medicine's Medline or Toxnet to find abstracts and potential published literature that may support the new product's approval. Depending upon the amount

of time elapsed between the RLD's approval and NDA submission of the proposed product, the literature search may require a significant amount of resources and time that needs to be incorporated into NDA submission timelines. The literature search should be comprehensive and cover the RLD and all closely related compounds for efficacy, clinical and nonclinical safety, clinical pharmacology and pharmacokinetics. The abstracts are then carefully reviewed to broadly confirm the sponsor's conclusions and proposals and to bring to light new data that may impact the proposed product's safety and efficacy profile.

The extent to which published literature can be used to support approval of a new drug product should be discussed with the review division. To support the change from the RLD, FDA will likely need to rely upon some primary data obtained by the sponsor in the case of a new indication or combination product. In contrast, when dealing with a new molecular entity that is a prodrug or active metabolite of the RLD, the sponsor may be able to rely upon the agency's previous findings for efficacy and safety, but an abbreviated toxicology program may be required. Example studies may include a 14–90 day program in an appropriate species with companion toxicokinetics and/or genotoxicity testing.

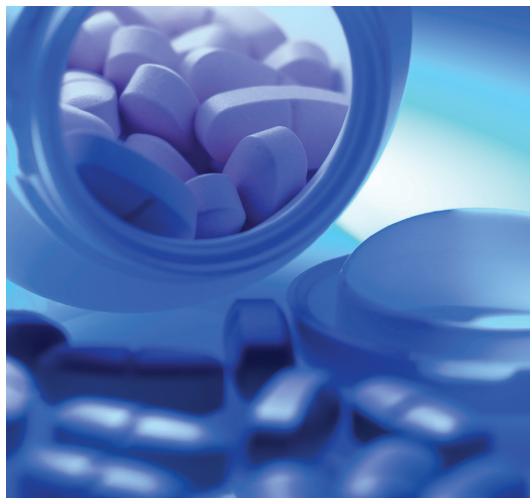
New molecular entities that are not prodrugs or metabolites of a previously approved drug may lack a therapeutic equivalent to use as an RLD. In such instances, clinical studies will be required and may include one or more efficacy and safety studies as well as PK studies or *in vivo* drug-drug interaction studies.

Providing Additional Evidence of Nonclinical Safety

In certain instances (e.g., differences in active ingredient such as a change in salt form or a change in synthesis/supplier of active ingredient, or a new dosage form/formulation), a changed impurity or degradation profile may require new toxicological studies to bridge the proposed product with the RLD. It is also important to keep up to date with FDA requirements concerning structural alerts and safety assessments for genotoxic/carcinogenic impurities and exposure thresholds.¹¹

Providing Evidence of Comparability Through CMC Bridging Studies

Proactive determination and development of quality attributes that differentiate the proposed product from the RLD are critical. Depending upon the types of changes made to the RLD, consideration should be given to whether such attributes are related to desired *in vivo* performance characteristics (e.g., PK profile) and how these characteristics and relationships will



be demonstrated, justified and, if appropriate, related to the RLD.

It is also important to consider what, if any, additional characteristics of the active moiety may impact product manufacturing conditions, performance and other quality attributes, as well as potential impact of sources supply, as compared to that of the RLD. The amount of stability data required to support a 505(b)(2) application depends upon the extent of changes from the RLD. In some instances, FDA may allow less than 12 months of real-time data. Such considerations should be part of the integrated proposed product's development plans and lifecycle management.

FDA Advice

Currently, ongoing agency advice (including meetings) may only be obtained for 505(b)(1) and 505(b)(2) drugs. Specific agency advice, e.g., regarding proposed BA/BE protocols, may be obtained for 505(j) drugs. These agency interactions provide opportunities to proactively review the sponsor's strategy and obtain FDA input for the selection of the RLD, number and scope of safety/efficacy and toxicological studies and CMC programs. The sponsor should request meetings with the review division as early as possible.

The most common 505(b)(2) application flaw, in many instances, is the lack of appropriate data to support the proposed modification(s) of the RLD. Failure to meet with the review division and obtain input for the planned BA/BE and other clinical or nonclinical studies, if applicable, as well as selection of the RLD, can result in significant delays, increased costs, time and resource deployment or, in the worst case scenario, a nonapproval action (see **Table 2**). Meetings with the agency can keep the sponsor up to date on FDA's current thinking within the context of a constantly changing regulatory environment. If sponsors are seeking to include clinical data in the Section 14, Clinical Studies section of the product's FDA labeling (package insert), they are encouraged to obtain the review division's advice early in the development process.

Patented and Nonpatented Market Exclusivities

Exclusivity based on patents provides the patent owner the right to exclude others from specific uses of their products for a specified period. To obtain product approval, the sponsor must provide patent certification, i.e., authenticating statements claiming the drug or a method of using the drug that is submitted in the NDA. 505(b)(1) drugs may have patents on both the active ingredient and formulation/method of use, whereas 505(b)(2) and 505(j) drugs may patent the formulation/method of use, but not often the active ingredient. Listed patents have the potential to delay subsequent 505(b)(2) and ANDA approvals. Typically, a three-year exclusivity period may be granted for a changed drug product containing an active moiety that has been previously approved, when the application contains reports of new clinical investigations (other than BA/BE studies).¹²

A five-year exclusivity period is granted to NDAs for products containing new molecular or chemical entities (NMEs, NCEs) never previously approved by FDA, either alone or in combination. If sponsors plan to submit 505(b)(2) applications to obtain a new indication for a previously approved product, the exclusivity period needs to be discussed with the review division. Additional periods of exclusivity, not based upon the sponsor's patent(s), are available for 505(b)(1) and 505(b)(2) products designated as orphan drugs or those for which pediatric studies (agreed with the agency) have been completed.¹³

A 180-day exclusivity period is granted to the first sponsor of a generic version of an RLD that submits a paragraph IV certification challenging the validity or lack of infringement of a patent for an RLD listed in the *Orange Book*.¹⁴

Marketing Advantages of the Drug Registration Processes

Development of 505(b)(1) drugs usually requires extensive investigational programs with a considerable risk of failed studies and associated costs, time and other resources. In contrast, the 505(b)(2) route has a relatively lower risk because frequently, the active moiety of the drug has already been proven to be safe and effective. The development costs are generally less because fewer clinical and/or toxicological studies are required. However, the potential to include data from new clinical studies in Section 14, Clinical Studies may be limited, depending upon the clinical programs' design and outcome. The 505(b)(1) route allows more flexibility regarding inclusion of findings from adequate and well-controlled clinical studies in Section 14, Clinical Studies, of the product's FDA labeling (see **Table 2**). 505(j) drugs essentially have the labeling of the RLD.

Glossary

505(b)(1) New Drug Application—A full, formal process under section 505(b)(1) of the *Food, Drug, and Cosmetic Act* for the approval and marketing of drug products via an NDA.

505(b)(2) New Drug Application—A more streamlined process under section 505(b)(2) of the *FD&C Act* that allows a sponsor to rely partially on existing clinical pharmacology and safety and efficacy data via an NDA.

505(j) Abbreviated New Drug Application—A route under section 505(j) of the *FD&C Act* designed to allow identical or copycat drugs to be rapidly approved via an ANDA.

Active ingredient—Any drug component intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or any function of the body of man.

Active moiety—A molecule or ion, excluding the appended portions that cause the drug to be an ester, salt or other noncovalent derivative (complex, chelate, etc.), responsible for the physiological or pharmacological action of the drug substance.

BA/BE—“Bioequivalence” is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in the proposed product becomes available (i.e., bioavailable) at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study as the RLD (Reference Listed Drug). FDA’s criteria for pharmacokinetic bioequivalence are met when the geometric mean ratios of peak concentrations (C_{max}) and exposures ($AUC_{0-\infty}$) of the two drugs and their 90% confidence intervals fall within FDA’s acceptance range of 0.80 to 1.25.

CDISC—A set of industry-wide Clinical Data Interchange Standards Consortium data compliance standards for electronic patient datasets to be submitted in NDAs.

Citizen’s suitability petition—This petition is submitted to FDA by a citizen requesting approval of a change in a LD (Listed Drug).

CMC—Chemistry, Manufacturing, and Controls section of NDAs required for 505(b)(1), 505(b)(2) and 505(j) drug products.

Integrated summaries of efficacy and safety—Across-study or integrated analyses of studies that are the basis of approval, rather than a summary of results from individual adequate and well-controlled studies. Other relevant studies for an integrated analysis also include studies that may not support the claim(s) and studies that may not have been conducted by the sponsor.

Listed Drug—Listed drug status is evidenced by the product’s inclusion in the current edition or supplement of FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*). This status applies to 505(b)(1), 505(b)(2), and 505(j) drugs that have not been withdrawn or suspended from sale.

Literature—Published reports of adequate and well-controlled studies that report safety and effectiveness, or final monographs published in the *Federal Register* (and the corresponding supportive data) cited to obtain NDA approval.

Market exclusivity—The sponsor of 505(b)(1) or 505(b)(2) drugs must provide patent certification, i.e., authenticating statements claiming the drug or method of using the drug submitted in the NDA, to obtain this exclusivity. To obtain market exclusivity for 505(j) drugs, only the sponsor of the first generic version of the drug is eligible. Patent certifications for generic products may refer only to formulations/method of use, not active ingredients.

New molecular or chemical entity—A drug that has not been approved by FDA previously, either alone or in combination with another drug product. NMEs and NCEs are also drugs with a new mechanism of action.

Nonpatent exclusivity—Pediatric and orphan drug exclusivities have been developed to promote innovation and competition in products for underserved markets, e.g., pediatric and adolescent populations (*Pediatric Research Equity Act*) and orphan drugs (*Orphan Drug Act*). FDA can require (unless a waiver or deferral is granted) the conduct of studies in the pediatric population when the disease occurs in both the adult and pediatric populations. Orphan drugs are designed to affect conditions that afflict a relatively small number of people in the US or for which there is no reasonable expectation of the recovery of research and development costs.

Orange Book—This is FDA’s current version of *Approved Drug Products With Therapeutic Equivalence Evaluations*, so named because of the color of its cover. The book and its supplements list drugs approved by FDA.

Paragraph IV certification—The generic sponsor must provide one of two types of certification: the innovator’s product patent is invalid or the patent will not be infringed by the manufacture, use or sale of the generic product.

Patent certification—The sponsor must provide patent numbers and expiration dates of any patent claiming the drug or a method of using the drug. After an NDA has been approved, the sponsor must confirm the patent information already submitted and must submit the same information for patents that subsequently are issued.

Patent exclusivity—Patents vest in their owners the right to exclude others from making, using, selling or marketing the patented drug for a limited time.

Right of reference or use of data—Grants permission for access by the company for whom clinical investigations are conducted or from the person who conducted the studies.

RLD—A Reference Listed Drug is a drug product with the same active moiety previously approved by the agency that is used as a basis of comparison with the proposed product only after agreement with the review division.

SBA—FDA’s Summary Basis of Approval of a drug with an approval action is listed at the FDA website: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

505(b)(2) drugs with new routes of administration, e.g., sustained release techniques or a change from oral to transdermal administration, may produce fewer side effects due to systemic absorption. Such changes may also increase the drug's consistency and effectiveness as well as enhance compliance. The increased period of exclusivity allowed 505(b)(2) products provides more time for sponsors to develop a marketing strategy compared to ANDA products.

Conclusion

Careful consideration of the desired marketing claims and exclusivity, changes to the RLD and the data required to support approval of those changes are critical for effective regulatory strategy and product development. Timely and ongoing agency advice to confirm and approve sponsor plans for the drug development program will increase the likelihood of successful filing and registration. As evidenced by the high frequency of recent 505(b)(2) drug approvals, many sponsors are finding this pathway to be very pragmatic.

References

1. Available at www.accessdata.fda.gov/scripts/cder/drugsatfda, 2009.
2. *Guidance for Industry: Applications Covered by Section 505(b)(2)* (Draft, October 1999).
3. *Ibid.*
4. *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations, Revision 1* (Draft, March 2003).
5. *Ibid.* 1.

6. *Ibid.* 2.
7. *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).
8. *Ibid.* 2.
9. *Ibid.*
10. *Ibid.* 6.
11. *Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (Draft, December 2008).
12. Patent and Non-Patent Exclusivities, Kim Dettelbach, 2007. Available at www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm118696.pdf.
13. *Ibid.*
14. *Ibid.*

(A future article will present case histories and examples of allowed changes to Reference Listed Drugs (RLDs) that have not been reviewed in this article and 505(b)(2) drug application(s) without an RLD.)

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