

*By Arie Anahory, Client Operations Manager,
Regulatory Compliance Associates, Inc.*

*By Sue Schniepp, Executive VP of Post-Approval
Pharma and RCA Distinguished Fellow*



505(b)(2) Pathway

The industry's recent innovations in oral drug delivery have given rise to increased controlled release dosage forms. As a sponsor with an interest in reformulating a popular immediate-release tablet to extended-release, the 505(b)(2) pathway will help avoid unnecessary duplication of studies already performed on the previously listed drug. This pathway gives the sponsor and FDA express permission to rely on data not developed by the New Drug Application (NDA) applicant (Camargo Pharmaceutical Services, 2017). This allows for a faster, less expensive route of approval.

Candidate Identification

The sponsor has conducted thorough research into the previously approved reference drug and identified a potential novel extended-release oral dosage form that will qualify under the 505(b)(2) NDA pathway. At this point, I assume the sponsor has referred to the Orange Book, Approved Drug Products With Therapeutic Equivalence Equations, which will identify the Active Pharmaceutical Ingredient (API) formulation associated with the immediate-release drug product's approval under Section 505. The Orange Book will provide safety and efficacy data for which the immediate-release drug was approved. The sponsor should use this information

to determine the next steps of the 505(b)(2) pathway and create an underlying basis of the additional criteria needed to ensure the drug candidate's product quality and performance characteristics are therapeutically equivalent. The 505(b)(2) NDA will require full safety and effectiveness reports for your novel drug candidate but allow at least some of the information required for NDA approval such as safety and efficacy information on the active ingredient to come from studies not conducted by or for the applicant (Camargo Pharmaceutical Services, 2017). The sponsor must only create a bridge between data already known in the previously approved immediate-release tablet, and the novel extended-release tablet (Camargo Pharmaceutical Services, 2017).

For any sponsor, there comes a long list of risks associated with the development of the novel drug product and its path to market. The success of the NDA preparation and submission depends heavily on up-front planning, research and awareness of FDA expectations throughout the entire development process (Camargo Pharmaceutical Services, 2017). In this recommendation, I will outline the 505(b)(2) development path and make assumptions the sponsor should fulfill while highlighting the description of major studies/achievements that will provide data to support the safety and efficacy needed for 505(b)

(2) approval. Prior to the development process, I will assume the sponsor will gather detailed knowledge of FDA filing requirements, and will only use established, well accepted methodologies and design accurately focused clinical studies (Camargo Pharmaceutical Services, 2017).

Research Assumptions

Since the sponsor wishes to seek approval for a new dosage, extended-release, of a previously approved drug, the sponsor will have completed thorough research into the immediate-release API formulation and gather all safety and efficacy data available to properly prepare for the Pre-Investigational New Drug (IND) meeting with the FDA. I will also assume extensive research, outside of the Orange Book, has been conducted into the extended-release tablet formulation and identity needed to produce a steady state of drug release over a certain amount of time and overall accomplish therapeutic equivalence. Thorough research provides the sponsor with an idea of the requirements needed to prove safety and efficacy throughout the 505(b)(2) pathway. Too, the sponsor will have researched methods involving Chemistry, Manufacturing and Controls (CMC) needed to successfully bring this extended-release tablet to market. It is important to note some of these steps can be started simultaneously and developed in parallel (Camargo Pharmaceutical Services, 2017).

Candidate Assessment

Once research has been compiled, the sponsor can begin to assess feasibility of the extended-release tablet. According to Camargo Pharmaceutical Services, to build evidence of a candidate's potential value the sponsor must consider the following:

- **Scientific Viability:** Is the formulation stable and readily prepared? Is the manufacturing scalable? Are active and inactive ingredients available and affordable?
- **Medical Viability:** Does the product have a clear niche in the medical specialty? Is there evidence the product would be appealing to the proposed population?
- **Regulatory Viability:** What clinical trials or other data will be required to gain approval? What distinguishing information can be presented on the labeling for eventual promotional activity?

- **Commercial Viability:** Is there a viable market for the product? What is the optimal pricing? (2017)

During this product planning stage, all data available to the public, and FDA's previous findings of the active ingredient should be used as leverage...

During this product planning stage, all data available to the public, and FDA's previous findings of the active ingredient should be used as leverage to establish value of the products concept, and help build the products development strategy to reduce its size, scope, and therefore, cost. (Camargo Pharmaceutical Services, 2017).

Pre-IND

The 505(b)(2) pathway begins with the pre-IND meeting with the FDA, the goals of the pre-IND meeting for a 505(b)(2) product development strategy is to gain FDA input and concurrence with the nonclinical studies, with the chemistry manufacturing, and controls strategy and with clinical research plans in a way that minimizes the number of new studies required (Camargo Pharmaceutical Services, 2017). The Pre-IND meeting with the FDA will also give insight into the additional data/studies needed to successfully prove therapeutic equivalence. When managed successfully, this step in the process can accelerate the drugs approval timeline if previous findings, research and bridging studies presented can prove the extended-release drug products safety and efficacy (Cooper, p.5, 2011). Due to the fact, the sponsor will need to study bioavailability/bioequivalence in the extended-release drug product, an IND will be required.

Formulation Development*

The chemistry, manufacturing and controls strategy is paramount in a 505(b)(2) submission because the formulation and the active pharmaceutical ingredient may be altered compared with the reference product, and the effect of these changes must be evaluated to assess any effects on the safety and efficacy (Camargo Pharmaceutical Services, 2017). As a result, a good deal of the CMC work must be invested prior to initiating Phase I studies. The change of formulation will result in new methods, new technology, new analytical methods, new dosage form, new procedures, etc.

REGULATORY COMPLIANCE ASSOCIATES® INC

Wellness for Business®

Previously conducted research into test methods and metabolic studies will help determine the formulation and systems needed to prove the extended-release tablet meets the statutory approval standard for safety and effectiveness. Matrix systems are very popular for extended-release formulations. These systems will also provide the sponsor with the detailed CMC methods needed to support the quality of the proposed drug product for marketing.

The current USP monograph for the extended release version lists five different test methods that may be used to measure drug release from a developmental formulation to match the USP specification.

Hydrophilic matrices have been extensively reviewed in literature. The current USP monograph for the extended release version lists five different test methods that may be used to measure drug release from a developmental formulation to match the USP specification. Tests differ in media composition and pH, dissolution apparatus, presence of sinkers, and in one case the number of different media to which the delivery device is exposed. USP specification ER formulation based on a hypromellose (HPMC) is a widely used in extended release matrix system. (Colorcon, 2009)

During tablet preparation, a hydrophilic matrix formulation is used and lactose, and other excipients are blended with the API. The tablets are tested for hardness, weight uniformity and friability. Drug release is measured according to the USP methods 1,2 and 3 using an automated dissolution bath. The percent drug release was measured. Depending on the dosage desired by the sponsor different USP delivery technologies can be used utilized to set a method criterion. (Colorcon, 2009)

In addition, in order to predict, accurately and precisely, expected bioavailability characteristics for an extended-release product from a dissolution profile pharmaceutical scientists are using the concept of in vitro/in vivo correlation (IVIVC) (US Department of Human Health and Human Services, et al, p.4, 1997). It is recommended the bioequivalence studies are performed during development with dissolution profiles at the upper and lower dissolution specifications. In some cases the information established through these studies can permit certain formulation and manufacturing changes

without an in vivo bioequivalence study (US Department of Human Health and Human Services, et al, p.3, 1997).

After developing, testing and manufacture of the drug, the sponsor will need to provide specific CMC information to comply with regulations:

- “21 CFR 314.50(d)(1) - the application is required to contain a full description of the chemistry, manufacturing, and controls information. Drug substance: physical and chemical characteristics, manufacturer, method of synthesis and purification, process controls, specifications, and stability.”
- “21 CFR 314.54 - procedures for submission of an application requiring investigations for approval of a new indication for, or other change form, a listed drug – refers to information required under 314.50 that must be submitted for 505(b)(2) applications”. (Cooper, p.7, 2017)

Comparing the new proposed formulation with the reference drug via bridging studies, explaining the rationale for the changed, and establishing that the new drug product is safe, pure and potent can form some the basis for the pharmaceutical development of a 505(b)(2) NDA (Camargo Pharmaceutical Services, 2017). However, complete CMC information must be submitted for the drug substance(s) and the drug product to support the quality of the extended-release product (Cooper, p.19, 2017). In some cases the dissolution test can not only serve as a quality control for the manufacturing process but also as an indicator of how the formulation will perform (US Department of Human Health and Human Services, et al, p.11, 1997).

The clinical trial materials for Phase I studies (often demonstrations of clinical bio-equivalence) must be representative of the commercial manufacturing process, including packaging (Camargo Pharmaceutical Services, 2017). Establishing the drug is safe, pure and potent will drive the basis for the pharmaceutical development section of the 505(b)(2) and will also mark a very large achievement as the sponsor has completed 1-3 years of discovery (Camargo Pharmaceutical Services, 2017).

Nonclinical

Because the extended-release candidate has known safety profiles and previous demonstrations of efficacy, nonclinical studies and safety and efficacy tests may

not be necessary to achieve 505(b)(2) approval. (Camargo Pharmaceutical Services, 2017)

Phase I

In some cases, the 505(b)(2) pathway enables the Phase I process to be reduced to a single study. Known as Phase I bridging study, is used to compare the human pharmacokinetic profile of the extended-release tablet with that of the reference immediate-release tablet. Done properly the extended-release tablet will reference the established safety information to the immediate-release tablet. (Camargo Pharmaceutical Services, 2017)

In specific, a dissolution method can study will be needed to prove bioavailability and efficacy over a course of time. Because the immediate-release tablet dosage form will have peaks and troughs of API, the sponsor must carefully equate previous clinical trials to requirements to be met of active concentration of the drug in the blood stream at a longer period of time.

According to the Guidance for Industry, Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, human data should be supplied for regulatory consideration of an IVIVC (US Department of Human Health and Human Services, et al, p.4, 1997). Bioavailability studies for IVIVC should be performed with enough subjects to characterize adequately the performance of the extended-release tablet. One approach is generally based on the performance of the bioavailability lots, a minimum of three time points is recommended to reach specifications. (US Department of Human Health and Human Services, et al, p.4, 1997).

The extended-release product will be compared with the referenced product using pharmacokinetic assessments. (Camargo Pharmaceutical Services, 2017) This end of this phase will account for 1-2 years of non-clinical research.

Phase II & Phase III

505(b)(2) development programs require no Phase II or Phase III studies, dosage form and formulation changes may rely on Phase I pharmacokinetic studies alone. Data previously accepted by the FDA as part of a marketing application, foreign clinical trial data or

data available to the public domain may be applied here. (Camargo Pharmaceutical Services, 2017)

NDA Submission & Overall Recommendation

To enhance the quality, organization and completeness of an NDA submission, it is vital the sponsor is aware of all relevant FDA and ICH guidelines. The final 505(b)(2) NDA submission will contain full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by the sponsor. Though the 505(b)(2) process is relatively quicker, and can be developed and reach FDA approval in as little as 30 months (Camargo Pharmaceutical Services, 2017), emphasis must be put focused on achievements in chemistry, manufacturing and controls, formulation development, and Phase I* studies in order to prove the extended-release tablet not only therapeutically equivalent to the immediate-release tablet, but also prove its safety and efficacy.

Resources

1. Camargo Pharmaceutical Services (2017), What is 505(b)(2). The Global 505(b)(2) Experts Camargo Pharmaceutical Services. <https://camargopharma.com/what-is-505b2/>
2. Colorcon (2009). Methocel, Modulation of Drug Release from Hypromellose (HPMC) Matrices: Suppression of the Initial Burst Effect. BPSI Holdings, LLC. Pages 1-5 http://www.colorcon.com/literature/marketing/mr/Extended%20Release/METHOCEL/English/ads_methocel_mod_drug_rel.pdf
3. Cooper, Monica, (2011) CMC Considerations for 505(b)(2) Applications. U. S Food and Drug Administration. Pages 1-20 https://www.pbwt.com/content/uploads/2016/09/Cooper.M.AAPS_.10.27.2011.pdf
4. U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (1997). Guidance for Industry, Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. The Drug Information Branch, HFD-210. Pages 1-24 <https://www.fda.gov/downloads/drugs/guidances/ucm070239.pdf>