

# A Rising Tide

In the 2006 fiscal year, approximately 20 per cent of new drugs were approved through the 505(b)(2) process; two years later, more than half of the new drugs approved in the US were based on this strategy. Judging from the rate at which we are filing investigational new drug (IND) applications today, it is expected that by 2012, the number of 505(b)(2) approvals will likely be 80 per cent

The reasons behind the remarkable success of 505(b)(2) are two-fold. Approvals depend partly on data already accepted by the FDA, therefore fewer studies are required, which in turn mitigates costs and shortens development time. Unlike generic drugs approved under Section 505j, where exclusivity can be held for only 180 days, the 505(b)(2) applicant may qualify for three, five or even seven years of market exclusivity, depending on the extent of the change to the previously approved drug and the type of clinical data included in the new drug applications NDA.

## The 505(b)(2) Process

Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act was established by the Hatch-Waxman Amendments of 1984 to allow sponsors to obtain approval of NDAs containing investigations of safety and effectiveness that were not conducted by or for the applicant, but for which the FDA had already issued an approval. The section was added to avoid unnecessary

duplication of studies already performed on the reference drug. However, sponsors must still provide any additional data necessary to ensure that the differences from the reference drug do not compromise safety and effectiveness.

Although it took 20 years to clear all the legal hurdles to make this a viable development strategy, today 505(b)(2) can provide relatively fast-track approval for a wide range of products, especially for those that represent a limited change from a previously approved drug. Ideal candidates include:

- New indications
- Changes in dosage form, strength, formulation, dosing regimen or route of administration
- New combination products
- New active ingredients
- Pro-drug of an approved drug

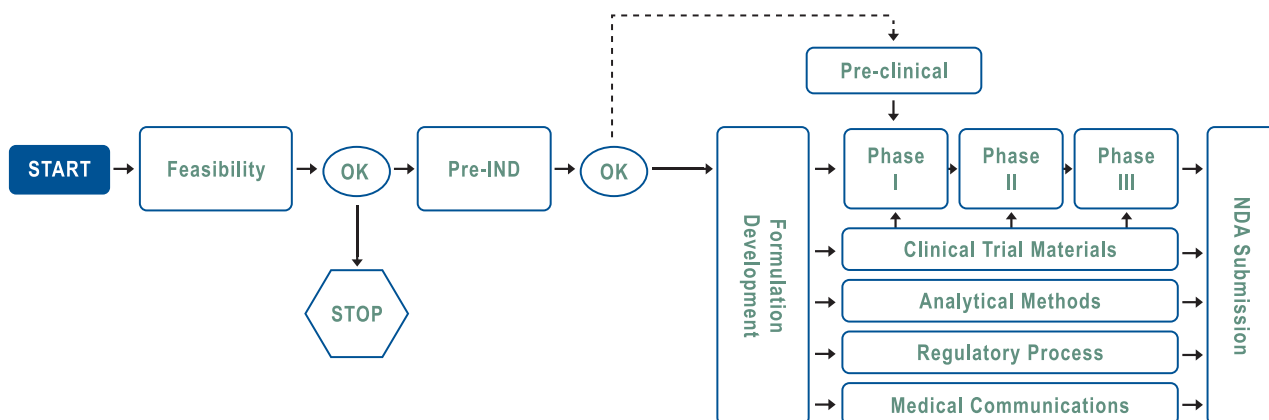
## An Opportunity in DESI

The 1962, the Kefauver-Harris Drug Efficacy Amendment introduced a

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requirement for drug manufacturers to provide proof of the safety and effectiveness of their drugs before approval. The FDA's Drug Efficacy Study Implementation (DESI) programme evaluated the efficacy of all marketed drug products and approved them based on safety grounds alone between 1938 and 1962. Although these DESI-approved drugs may continue to be marketed until the administrative proceedings evaluating their effectiveness have concluded, continued marketing is permitted only if a NDA is approved for such drugs.

Currently, the FDA is pursuing an Unapproved Drug Initiative against as many as 3,000 drugs still on the market without approval, which will have significant negative consequences for



many manufacturers. However, when life gives you lemons, you can choose to make lemonade – and companies are using 505(b)(2) to make the most of their situation. In March 2009, the FDA sent warning letters to seven manufacturers of morphine sulphate (oral solution, 20mg/ml), and gave them six months to stop shipping the drug. While most simply shut down production and destroyed their inventory, Roxane Laboratories saw the warning as an opportunity. They submitted a 505(b)(2) application, and received FDA approval in January 2010, giving them limited marketing exclusivity while their competitors were subject to seizure and injunction if they shipped any more product.

### Regulatory Challenges and Safety Concern

A significant regulatory challenge to this process is determining exactly what additional or 'bridging' data will be

needed to support the proposed changes in the previously-approved drug. Since this is determined on a case-by-case basis, sponsors will need to get advice from regulatory professionals experienced in the 505(b)(2) approval route, as well as from the involved FDA review division.

One recent case where this was not the course of action involves Vivus, Inc, which submitted an NDA for Qnexa, a fixed dose combination of phentermine and topiramate to support weight management. According to Vivus, there were over six million prescriptions for phentermine and over nine million prescriptions for topiramate in 2009. The development rationale was that by combining the two drugs, the doses of each component might be lower than the monotherapy and thus allow for long-term treatment of obesity. Indeed, the combination was shown to be more efficacious than the total weight loss achieved from each component alone.

When the FDA's Endocrinologic and Metabolic Drugs Advisory Committee met to review the NDA application, efficacy was not an issue; however, there were concerns about safety – specifically psychiatric adverse events including suicidality, neurocognitive adverse events, cardiovascular safety (you may recall the controversy around the anti-obesity drug fen-phen), incidence of metabolic acidosis and teratogenicity. Of these, the FDA appeared to be most concerned about the teratogenicity; topiramate is a known teratogen in several animal species, and the expectation was that Qnexa would be used chronically by pregnant women. Vivus' briefing information on the topic was inadequate to overcome the committee's concerns, and the company is faced with – at minimum – significant additional expenses.

The 505(b)(2) pathway does not absolve sponsors and research organisations from preparing a detailed and carefully



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thought-out development programme. This must be done to anticipate and address likely regulatory concerns. Working closely with regulatory consultants throughout the process will help ensure the drug stays on track.

### Approval Without an IND

In 505(b)(2) drug development, sponsors are often studying the bioavailability/bioequivalence (BA/BE) of a test drug versus a reference listed drug (RLD) as part of the process. Because of this, it can sometimes be confusing to sponsors as to whether an IND is necessary. An IND is required when a drug is involved in a clinical investigation that is not exempt from the regulations. Guidance recently issued by the FDA gives greater clarity to what a 'drug' and a 'clinical investigation' are, and which clinical investigations are exempt for the IND process. An IND is not required if:

- The drug product is lawfully marketed in the US
- There is no intent to report the investigation to FDA as a well-controlled study in support of a new indication, or to use it to support any other significant change in the labelling of the drug
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug
- The investigation does not involve a route of administration, dose, patient population or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii))
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50)
- The investigation is conducted in compliance with the requirements of § 312.7, in that it is not intended to promote or commercialise the drug product

Most drug development activity is undertaken with commercialisation in mind, therefore regulatory approvals without an IND are rare. In a few cases, the new product approval is based on the literature and the only study required is a Phase I bridging study to compare the systemic levels between the proposed drug product and the reference product. When done properly, these studies allow a company to reference the safety and efficacy information that is already known for the original drug and proceed directly to NDA submissions.

### Affect on CMC

The chemistry, manufacturing and controls (CMC) section often comes into play in a 505(b)(2) submission because the formulation, components or API has been altered, and the impact of any of these changes must be evaluated in terms of the safety and efficacy of the proposed drug product. However, a review of the evolution of the formulation, and the data supporting the comparability of the different formulations along with a CMC bridging study, can usually form the basis for the pharmaceutical development section. Taking care to review the implications of changes during the development process, as well as incorporating prudent comparability protocols at the right point in the programme, can provide the coherent pharmaceutical development summary needed for approval.

### Growing Importance in Drug Development

In the few years since clearing legal hurdles for the 505(b)(2) process, it has rendered significant changes on the drug development landscape. Today, as the patents for Lipitor, Flomax, Plavix and perhaps 100 other protected drugs are set to expire, smart marketers are seeking ways to create new differentiated

products, new market niches and marketing exclusivity through 505(b)(2) development programmes.

This path allows a sponsor to get out of the competitive environment of generics, while still enjoying a development process that eliminates most preclinical studies, as well as extensive safety and efficacy tests, which dramatically reduce costs and time-to-market. Additionally, the 505(b)(2) process may be more attractive to investors because the product differentiation can provide significantly better market potential.

On the downside, many venture capitalists (VCs) do not understand the process and cling to the somewhat outdated belief that generics have 'less risk and better returns'. In addition, the investment community is concerned that two or more companies might develop the same product – the first one to gain approval will make the other products go back through the ANDA process.

For many products and companies, however, 505(b)(2) offers a clear path to faster and less costly approval, a differentiated product and a period of marketing exclusivity. The rising tide of drugs approved under this strategy is testament to its growing importance in the drug development market.

### About the author



Ken Phelps is President and CEO of Camargo Pharmaceutical Services. He used more than three decades of experience in the health science and services industry to found the company in 2003. As an expert in drug development, specifically the 505(b)(2) regulatory approval pathway, he has aided in the successful FDA approval of numerous compounds. Prior to founding Camargo, his broad background in drug development had led to a number of executive level assignments in the areas of quality control, project management and regulatory, clinical and medical affairs at Duramed Pharmaceuticals (now Barr Pharmaceuticals).  
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