ALTASCIENCES

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Hybrid Medicines and 505(b)(2) NDA Approval Pathways

Hybrid medicines are drugs based on a generic molecule and have a different route of administration, format, strength, or indication from the original reference product. They require re-approval for market authorization, partly based on data from the original reference medicine, and partly on data from new clinical trials on the modified version.

Like the Hybrid medicine authorization process in the EU, the 505(b)(2) NDA approval process in the USA applies to generic molecules that have a slight change from the reference medicine, and can use published data, including previous FDA submissions and communications, to support their re-approval by the FDA.

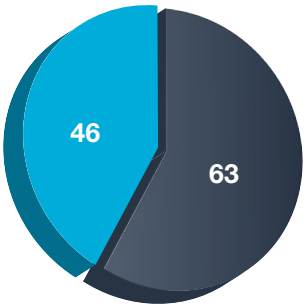
In 2017, more than 50% of New Drug Applications in the USA were 505(b)(2). According to the FDA's *New Drug Therapy Approvals* document, there were 63 505(b)(2) and 46 novel drugs approved that year alone, while in Europe the breakdown was exactly 50/50. In its annual report, the EU reported 30 approvals in each of the following categories:

- Novel
- Hybrid and abridged, generic, well-established use and informed-consent applications

USA New Drug Approvals

505(b)(2)

Novel

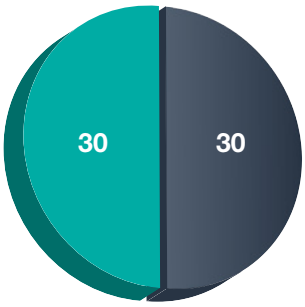


EU Marketing Authorizations

Novel

All other*

*All other includes Hybrid, Abridged, Generic, Well-Established Use



Some Applicable Categories of Drugs for Hybrid or 505(b)(2) Pathways:

Modified-release (MR) drugs are reformulated drugs with an altered timing and/or rate of release of the drug substance. The modifications can offer patients improved efficacy, safety, or convenience not offered by existing dosage forms.

Extended-release medicines can often allow once-a-day dosing compared to twice or three times per day for immediate-release dosage forms. The reduced frequency of dosing improves convenience and/or adherence. The treatment of ADHD, drug and alcohol addiction, pain, and other conditions have been greatly impacted by such improvements.

Delayed-release medicines release a specific portion or portions of drug at a time later than immediately after dosing. Enteric-coated aspirin and other non-steroidal anti inflammatory (NSAID) products are common applications of this modification, which improves the safety profile.

Orally disintegrating tablets (ODT) disintegrate rapidly in the saliva after oral administration. ODT may be taken without the addition of water; the drug is dissolved in the saliva and swallowed, providing benefits to patients who are vomiting or have trouble holding down liquids. Additionally, the bioavailability can be increased with ODT due to pre-gastric absorption.

Combination drugs combine two or more medicines often taken together into a single, fixed-dose combination. There are many examples of combination products available by prescription or over-the-counter. Such combinations facilitate the lives of patients as they can take one dose instead of a few different ones.

New/different routes of administration compared to the reference product such as patches for delivery of birth control, nicotine for anti-smoking, motion sickness medication, and analgesics. Subcutaneous implants have been developed for substance abuse, birth control, and diabetes, among others. Also included are antibiotics in both pill and liquid form.

Abuse-Deterrent Formulations (ADF) – opioid drugs and other commonly abused medications are increasingly being reformulated in ways that reduce the potential for abusive behaviors, such as chewing, snorting, and injecting. Uncrushable pills that limit the ability to snort or inject the drug, sublingual film, and subcutaneous implants are three examples of ADF formulations for existing drugs.

Generally speaking, the approval pathway for a Hybrid medication or a 505(b)(2) is faster, and less costly in terms of research, than for a novel compound. The reference product has proven safety, often eliminating the need for preclinical safety and toxicology studies or greatly reducing the number of studies required. The same applies to efficacy studies, especially if the pharmacokinetics and indication of the new formulation are the same as the original one.

The development path for each reformulation is unique, as the reliance on previous data differs.

Hybrid or 505(b)(2) vs. Generics

Medicines approved via the Hybrid or 505(b)(2) approval pathway have certain market advantages over generics. Because Hybrid medicines deliver additional benefits compared to the reference product (a new delivery system, different formulation, new indication, etc.,) they can be branded, and marketed, with attention to the advancements they bring to treatment.

Generic medicines are considered equivalent to their reference products and, as such, cannot be branded or marketed on their features. Their product insert and safety information are identical to that of the reference product. Generics compete on price while Hybrid or 505(b)(2) products compete based on the improvements they offer (i.e., ease of use, safety, or efficacy). The submission requirements for both type of products have differences as well which is why pre-submission meetings with regulatory bodies (FDA or EMA) are essential and serve to establish the exact data sets required.

Hybrid or 505(b)(2) vs. Generic Submission Requirements

Hybrid or 505(b)(2)

Bioavailability (BA) studies versus approved Reference Listed Drug (RLD):

- If the new formulation is bioequivalent to the RLD, and the indication is the same, the number of subsequent studies is greatly reduced.
- If they are not bioequivalent, safety and efficacy needs to be established and submission requirements may include preclinical and clinical efficacy studies. Whenever possible, submitted data can include previous regulatory decisions or published research.

Most common study requirements

Formulations that are not locally acting:

- Single dose comparative BA fasted
- Single dose comparative BA fed-state

Other studies that may be required based on case-by-case evaluation:

- Preclinical toxicology studies
- PK-PD, DDI, TQT
- Multiple dose comparative BA steady-state
- Clinical endpoint studies

Generic

Bioequivalence (BE) studies versus approved Reference Listed Drug (RLD):

- Once bioequivalence is established, assessment relies on the agency's previous safety and efficacy findings reported for the RLD.
- This criterion only applies when the new product and the RLD are bioequivalent, and possess identical characteristics, for example:
  - Active ingredient
  - Dosage form
  - Strength
  - Route of administration
  - Uses

Most common study requirements

Formulations that are not locally acting:

- Single dose BE fasted
- Single dose BE fed-state – if food effect is noted in label
- Steady-state BE – for EMA when there is accumulation for extended release products

Other formulations will be evaluated case-by-case:

- More study designs may be required based on the drug product or applicable agency

Choosing a Drug Candidate

An appropriate candidate for Hybrid or 505(b)(2) authorization should have a unique, documented, differentiating feature, low development risk, and acceptable profit potential. The changes to the formulation should be significant enough to offer real value for an unmet market need, with low risk of changes to bioequivalence that may necessitate additional efficacy trials (unless the potential market justifies such trials).

If a drug candidate has these qualities, the Hybrid or 505(b)(2) approval process has the potential to deliver a product with significant impact. **Two recent additions that Altasciences helped bring to the pharmaceutical market via Hybrid or 505(b)(2) include:**

Baclocur® (baclofen)

Baclofen was on the market as a treatment for spasticity of voluntary muscle, as seen in multiple sclerosis, marketed under the brand name Lioresal®. Based on reports that baclofen may also be effective as a treatment for alcohol dependence, Ethypharm decided to develop Baclocur® for this new indication. With safety and tolerability of baclofen already established, Ethypharm was able to depend on previous data, with the addition of studies in efficacy for the new indication, and safety studies for the new patient population.

Altasciences conducted a PK study in hepatic impaired patients to see if dose adjustments would be required in this population, as the new indication for alcohol dependence makes it likely that Baclocur® will be used in such patients. In early 2018, the National Agency for the Safety of Medicines and Healthcare Products (ANSM) in France granted market authorization for Baclocur®.

SPRITAM® (levetiracetam)

Levetiracetam is indicated to reduce seizures in epilepsy. The original form was often difficult for patients to swallow, especially for older patients who have dysphagia. Aprecia Pharmaceuticals addressed this issue by developing the world's first 3D-printed tablet, SPRITAM®. The 3D printing process produces porous tablets that instantly dissolve in patients' mouths. Therefore, regardless of strength, patients can easily take SPRITAM®.

Altasciences conducted a bioequivalence study to demonstrate that the new SPRITAM® instant-dissolving formulation was equivalent to the regular tablet. This data allowed Aprecia to rely on the previous safety and efficacy data in their successful 505(b)(2) NDA application.

Some drugs eligible to achieve marketing authorization via a Hybrid or 505(b)(2) process may require additional testing for a variety of potential additional effects, such as somnolence/driving impact, as demonstrated in the following case study by Altasciences for a recent 505(b)(2) submission for a CNS-active drug.

Supporting Altasciences Case Study: Achieving a 505(b)(2) Regulatory Approval

Clinical Trial Details

- **Indication:** A number of neurological disorders
- **Population Type:** Healthy Normal Participants

Purpose

The sponsor was developing a product that isolated the active enantiomer to make an extended release formulation. These modifications were significant enough to warrant additional clinical studies to help provide a robust dossier for the FDA to review.

As their trusted partner, Altasciences conducted three key studies for the sponsor:

1. A driving simulator study to assess a patient's ability to drive or operate heavy machinery after an acute dose or at steady state
2. A bioavailability study comparing two lots of extended-release investigational products manufactured via different processes
3. A study to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses (MAD) of the investigational product from the bioavailability study

	Driving Study	Bioavailability Study	MAD Study
# of Participants	72	24	24
Time to Recruit Panel	4 weeks	4 weeks	4 weeks
Study Design	Randomized, Double-Blind, 3-Period Crossover	Laboratory-Blinded, Randomized, Balanced, Single-dose, 3-Treatment, 3-Period, 6-Sequence, Crossover	Open-Label, Multiple-Dose, 1-Period
Key Inclusion Criteria	• Possess a valid driver's licence • Drove 10,000 miles (16,000 km) in the last 3 years • Sufficient score on simulator sickness questionnaire	• Appropriate contraception methods used by both male/female subjects	• Appropriate contraception methods used by both male/female subjects • Ability to comply with study requirements (stay in clinic for a period of 14 days)
Key Exclusion Criteria	• History of difficulty falling asleep	• No known drug hypersensitivity	• No known drug hypersensitivity
Services Provided	Clinic	Clinic, DM, Biostatistics, MW	Clinic, DM, Biostatistics, MW

Methods

Driving Simulation

Altasciences' core expertise includes more than just straightforward bioavailability and bioequivalence studies. We also conduct specialty studies that are becoming increasingly critical to successful completion of a submission for regulatory approval.

In the course of this study, we worked with the sponsor to help design and conduct a driving study that would generate data for a fulsome assessment on the impact of the drug's sedating effects, and potentially help justify a modification of the label compared to the RLD.

The driving study was a randomized, multiple-dose, double-blind, placebo-controlled, Latin-square design with 3-period (full) crossover study, with subjects randomized to treatment sequences (one treatment group per period for 3 periods). Subjects completed all 3 treatment periods within the treatment group they were randomized to.

During each treatment period, subjects were dosed with active treatment (two dose levels), or matching placebo BID and diphenhydramine or placebo every morning (QAM) for 15 days. The study drug (morning dose) was administered by site staff on Days 1, 6, 11, 15, 21, 26, 31, 35, 41, 46, 51, and 55. Subjects self-administered the drug at home on all other study days.

Cognitive testing and driving simulation were conducted approximately 2.5 hours and 3 hours post dosing, respectively. Subjects continued their assigned study dosing at home, with titration of the study drug at 5-day intervals. Subjects returned to the clinical research unit for morning dosing on titration days. Prior to the Day 15 dose for each treatment period, subjects returned to the clinic and remained overnight. They were dosed the following morning and underwent cognitive and driving simulation testing approximately 2.5 and 3 hours post morning dose.

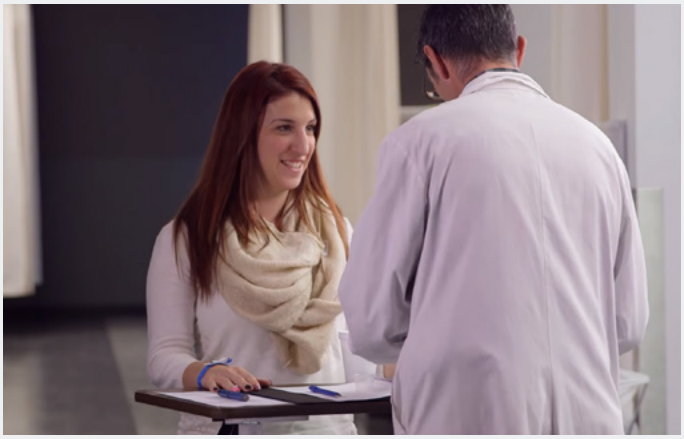
The study included cognitive testing via CogScreen® Symbol Digit Coding and driving performance via Cognitive Research Corporation's Driving Simulator (CRCDS Mini-Sim).

Bioavailability

For the relative bioavailability study, a screening period of up to 28 days ensured that 24 male and female subjects were enrolled. For all 3 treatment periods, subjects reported to the clinic on the evening prior to dose administration and fasted overnight for at least 10 hours. Subjects were randomized to either Treatment A, Treatment B, or Treatment C on the morning of the first treatment period. The study drug was administered after pre-dose clinical assessments were made and a blood sample (0 hour) had been taken. The subjects remained at the clinic for 36 hours after dosing, during which time blood samples were collected at 14 intervals. There was a 7-day washout period between each treatment period.

Multiple Ascending Dose

In the multiple ascending dose study, subjects entered the clinic on the evening prior to the first dose and received multiple-dose oral administration of the investigational product, starting on Day 1. Similar to the BA study, subjects were admitted to the clinic on the evening prior and fasted for at least 10 hours prior to the first drug administration. Subjects also had pre-dose clinical assessments and a 0-hour blood draw. Subjects received the initial dose of drug on Day 1. On Day 4, dose was increased by 20 mg and on Day 7 by another 20 mg. Dosing was conducted using AM/PM dosing exactly 12 hours apart. Pharmacokinetic assessments were conducted throughout the study, both during AM and PM dosing. Subjects remained sequestered at the study site for the duration of the clinical study (through Day 13). The total duration of this study, excluding screening, was expected to be at least 14 days.



Results

In the driving study, sensitive, objective measures of sedation, including driving performance, alertness, and attention, demonstrated that performance following the initial dose of the study drug was non-sedating. Steady-state treatment with the study drug at two-fold the starting dose had a potentially mild sedating effect, which was less severe than that caused by a common over-the-counter antihistamine (i.e., diphenhydramine HCl 50 mg).

For the bioavailability study, the rate and extent of absorption was equivalent between the reference product and the extended-release product manufactured with the alternate manufacturing process.

All three studies met their primary endpoints and were successfully conducted. Important to note is that the studies generated the data the sponsor required, and recruitment and data delivery timelines were met, allowing the sponsor to achieve their submission deadline. In conducting these three different types of studies, Altasciences' experts worked closely with the sponsor to develop the protocols, schedule and recruit each study with the appropriate subjects to conduct the trial as outlined and provide data to address key areas of the sponsor's 505(b)(2) submission:

1. A driving study to assess drug impairment for the product monograph
2. A bioavailability study comparing two lots of the new formulation
3. Dose escalation evaluations of the new extended release formulation, showing it to be safe and well-tolerated

Since the drug is one that will likely be titrated by physicians in the patient population, having this data provides regulatory reviewers with another key piece of information to make a sound benefit-risk decision.

Altasciences can design, conduct, analyze and report on all the clinical pharmacology studies required for an NDA and this example shows how we can provide support across numerous studies types all while delivering superior levels of quality.

What Sets Altasciences Apart

Altasciences is a multiple award-winning CRO with decades of experience conducting research for modified drugs taking the Hybrid or 505(b)(2) approval pathway. In fact, since 2010, we have designed and conducted more than 250 studies that followed these pathways.

We have a robust study participant database, allowing us to quickly fill panels on time. In analysis and reporting, we have an impressive 98% on-time reporting rate. There are over 600 beds in our clinical facilities, located in Fargo, ND, and Kansas City, KS, as well as Montreal, Quebec. Our facilities are fully accredited and inspected by both the FDA and the EMA.

Multiple Routes of Administration

- Sublingual
- Intra-articular injection
- Infusion
- Inhalation
- Intranasal
- Transdermal
- Vaginal
- Rectal

If you are considering a Hybrid or 505(b)(2) marketing authorization submission, trust Altasciences to conduct the research required by your regulatory agency. Contact us with your program needs, and we'll get your required studies up and running, fast.

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About Altasciences

Altasciences is a forward-thinking, mid-size contract research organization offering pharmaceutical and biotechnology companies of all sizes a proven, flexible approach to preclinical and early phase clinical studies, from lead candidate selection to proof of concept. For over 25 years, Altasciences has been integrating into clients' projects to help support educated, faster, and more complete early drug development decisions. Altasciences' full-service solutions include preclinical safety testing, clinical pharmacology, bioanalysis, program management, medical writing, biostatistics, data management and more, all of which can be tailored to specific sponsor requirements.

Altasciences… helping sponsors get better drugs to the people who need them, faster.