Scratching the Surface of Nonclinical Dermal Testing

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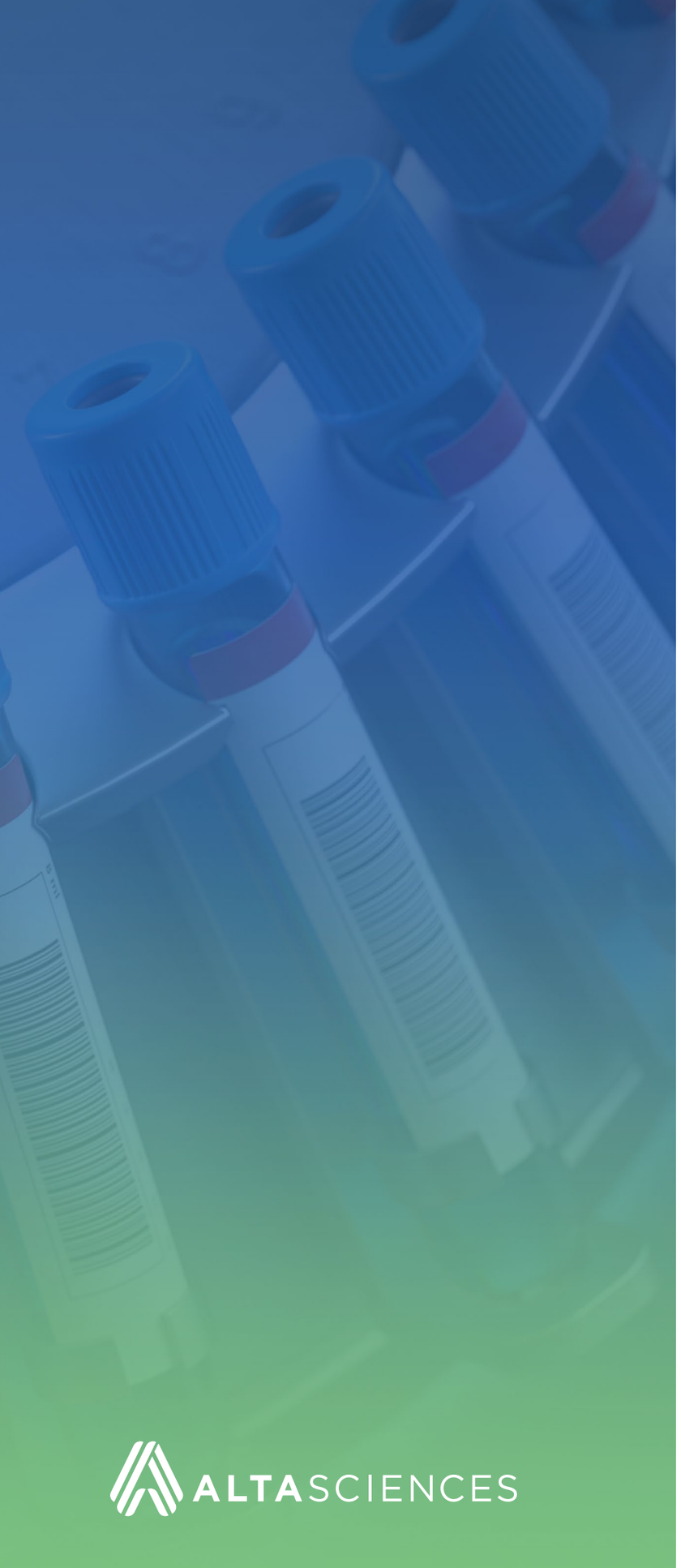

DERMAL RESEARCH POSES UNIQUE CHALLENGES

Here's how and why.

Dermal toxicology examines whether a given compound can trigger systemic or local responses in people or animals via contact with the skin. This important information needs to be provided to the U.S. Food and Drug Administration, as well as other global regulatory authorities, when drugs are submitted for their review and approval.

As with other routes of administration, the FDA does not stipulate exactly how sponsors should conduct nonclinical dermal toxicity studies. The agency's guidelines are designed to give scientists the flexibility to design appropriate studies to obtain the relevant data.

Nonclinical dermal studies are different from other drug studies—and not just because the skin is an organ that provides a significant point of entry for chemical agents. For example, *in vivo* dermal studies pose unique challenges not seen with parenteral or oral studies, like normal anatomical variation in cutaneous morphology and the increased risk of systemic exposure due to animal grooming. Given such challenges, no single approach, method, or species suffices for effectively evaluating dermal toxicity.

Understanding the options for dermal studies—and the pros and cons of each option—streamlines the development process, while decreasing program costs and accelerating the timeline to obtain regulatory approval and move a compound into clinical trials.

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The Value of Partnering with Dermal Research Experts

Conducting successful studies depends on partnering with an expert team of toxicologists, veterinarians, and technicians with a solid understanding of the challenges specific to dermal research. It is important to choose a CRO with the experience to design and conduct studies that can reliably and quickly provide you with the data you need, from initial efficacy work through IND-enabling programs and regulatory submissions.

Be sure to partner with a CRO like Altasciences who can:

- Develop dermal models
- Validate dermal models developed elsewhere
- Design and conduct standard and specialty dermal toxicology studies that support your FDA filings

Drugs—whether administered orally, intravenously, or dermally—have the potential to cause both systemic and local adverse effects, like erythema (redness) and edema (swelling), that the FDA will need to review. Evaluating the severity of erythema and edema can be subjective, varying among the individuals performing observations. Altasciences' dermal scientists and technicians undergo rigorous training to minimize potential variability in dermal scoring to deliver consistent, high-quality data.

In addition to designing and conducting nonclinical dermal toxicity studies in support of your FDA filings, the research team performs other nonclinical studies that may benefit from dermal expertise.

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Such studies include:

- Dermal pharmacokinetics and pharmacodynamics
- Wound healing
- Dermal inflammation

Sponsors developing drugs must understand how—and how well—a compound is absorbed, distributed, metabolized, and excreted; as well as any potential accumulation that could lead to unwanted effects as a result of repeated administration.

To better understand these parameters, our scientific team will conduct a series of pharmacokinetic studies to measure the local amount of drug in the skin. In addition, we conduct systemic and pharmacodynamic studies to measure the local or systemic biomarkers that may be affected by the administered drug, for instance, blood glucose levels following insulin administration.

These pharmacokinetic and pharmacodynamic studies can be performed in a wide range of species, including miniature swine, mice, rats, rabbits, guinea pigs, dogs, and nonhuman primates.

Wound Healing

The miniature swine has skin very similar to human skin, and has become the preferred model for wound-healing studies. There are multiple wound-healing models in miniature swine, including full- and partial-thickness excisional wounds, ischemic wounds, and thermal wounds. Diabetic pig models may also be used with any wound type.

To properly conduct wound-healing studies, the veterinary staff should be highly trained in inducing wounds and caring for animals in a compassionate manner that minimizes pain and distress, while maintaining the efficacy of the model. Using a combination of digital measurements and photography of the wound site, we are able to completely characterize the efficacy of a compound.

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Dermal Inflammation

Inflammation of the skin is characterized by erythema and edema, and can be induced in one of several ways:

- Chemical induction
- Pharmacological intervention
- Surgical modification

Inflammatory models may be conducted in multiple species, including:

- Miniature swine, for urticaria (hives)
- Guinea pigs, for atopic dermatitis and dermal sensitization
- Mice, for dermal edema and hypersensitivity
- Rabbits, for local skin irritation

Knowing the irritation or sensitization potential of a dermal compound early in the drug development process makes it possible to rank efficacious molecules based on severity. It also becomes possible to remove highly irritating or sensitizing molecules from the program early on. Obtaining this information as soon as possible saves you time and money.

To support the chosen model, our scientists will select from a wide array of inflammatory and immunological assays dependent on the species being studied.

Dermal toxicology is an ever-evolving field—one in which changes and advances are occurring constantly. Altasciences' toxicologists stay up to date with the latest knowledge and expertise to help you develop relevant studies to collect, analyze, and report data needed for regulatory submissions.

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Questions to Consider for Your Dermal Research Program

In preparation for your nonclinical dermal study, the study design phase is critical to delivering relevant and accurate data. Our research team will consider all possible questions that have the potential to affect the overall program, including:

- What studies are required?
- Is bioanalytical support required to measure the parent compound, metabolites, antidrug antibodies (ADA), or neutralizing antibodies (nAB)?
- What other biomarkers are required?
- Is Good Laboratory Practices (GLP)-compliance required?

Whether you are a large corporation reformulating an existing drug product to improve the patient experience, or an emerging biopharma company with an API that holds promise for a new therapeutic, the research team will ensure they have a thorough understanding of your development program in order to provide you with the guidance and resources needed to support it.

In order to design and conduct the most appropriate studies, Altasciences' research team will discuss these and other matters during initial conversations to ensure the scope of the study is fully understood and your program needs are supported fully.

Questions You Can Expect Our Research Team to Ask

Your Clinical Plan

- What patients will qualify to participate in the clinical trial (gender, age, etc.)?
- How long will the clinical trial be conducted?
- How will the drug be administered?
- At what dosage will the drug be administered?
- What assessments will be conducted at what point?
- What data will you be able to provide us?

Your Timeline

- Are you responding to a clinical hold from a regulatory body?
- Do you have a submission date for your Investigational New Drug (IND) application to the FDA? (A similar approach would apply for submissions outside the U.S.)
- Do you have a submission date for your New Drug Application (NDA) to the FDA, Marketing Authorization Application (MAA) to the EMA, or New Drug Submission (NDS) to Health Canada?
- Do you have a deadline imposed by the FDA, EMA, Health Canada, or other regulatory authority?
- When will you decide upon placement of the study/studies?
- When do you want to start the study/studies?
- What other work must take place before the study/studies can begin?
- When do you need the audited draft report?

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Your Test Material

- Can you provide the specific name of the test item?
- What is the type of molecule (i.e., small molecule, biologic, or repurposed compound)?
- If it is not a new chemical entity, has it been granted regulatory approval previously by the agency where you intend to file the IND?
- If it is a biologic, what type (e.g., monoclonal antibody, RNA, DNA, protein, peptide?
- Does the test article or formulation require any additional medical device to administer the dose (e.g., transdermal patch, microneedles, UV light, laser)?
- What is the therapeutic indication?
- What is the mechanism of action?
- Is the test material species-selective in its pharmacological action?
- When will the test material be available?
- How well characterized is the product for testing?
- Do you have an acceptable dose formulation available to start animal studies?
- Do you have an analytical method for formulations analysis?
- How does the test material need to be stored? Is it temperature- or light-sensitive?
- What are the vehicle components? Are they consistent with the FDA Inactive Ingredients Database for content and route of administration?
- Is there anything else about the test item that we need to know to provide relevant study designs?
  - This could include influencing delivery (cell-penetrating peptide, lipid bilayer encapsulation, etc.), efficacy (antibody-drug conjugate), stability, etc.
- Is the manufacturing of the test material representative of the final process to be used for clinical material?

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Your Previous Studies

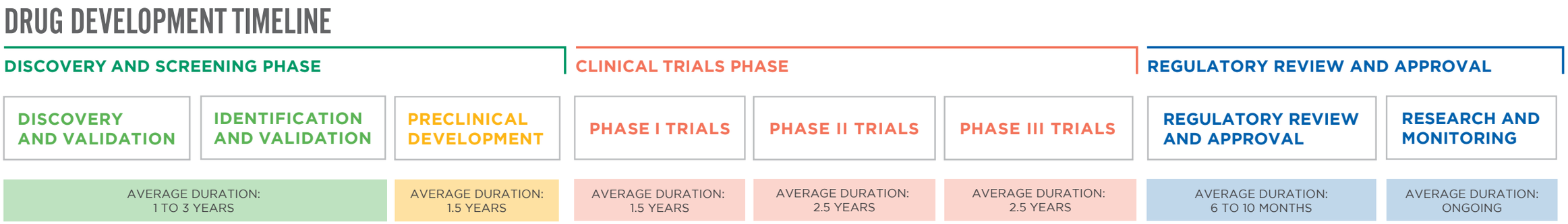
- At what stage of development is the drug product (i.e., preclinical, Phase I, Phase II, Phase III, or commercial development)?
- What is the next major milestone for the drug product (e.g., IND-filing date for entry into Phase I or start of Phase II trials) and when is it?
- What dosing regimen—route, dose, frequency—has been used in efficacy studies?
- Which species have been used for the efficacy work?
- What is the species specificity of the product?
- Does your product cross-react in standard toxicity species?
- What is the projected human dose route and frequency?
- Do you have any animal safety data?
- Is there a bioanalytical method for detecting the compound in plasma and/or tissue?
- If your drug product is a protein, has a method been developed for an anti-drug antibody assay?
- Do you have any pharmacokinetic data?

Producing Relevant Data for Regulatory Agencies

The goal of Altasciences' research team is equally straightforward: to help drug sponsors develop high-quality regulatory applications by designing and conducting nonclinical studies that collect relevant, accurate, and trustworthy scientific information.

Regulatory Agency Expectations

The FDA and other drug regulatory agencies have certain expectations when it comes to nonclinical data. Our experienced scientific team helps you understand those expectations and provides necessary guidance and support when it comes to submitting your applications for approval.



To help you navigate the process, our scientific team needs to be intimately familiar with the quality systems that support studies compliant with both GLPs and Veterinary International Conference on Harmonization (VICH) guidelines. In addition, the scientific team must also be able to provide SEND (Standard for Exchange of Nonclinical Data) reporting that meets FDA requirements for studies supporting an IND or NDA.

Special Expertise

For oral and intravenous medications, the issue of toxicity is systemic, while for medications topically administered via the skin, toxicity can be systemic or local, or both. As a result of its multivariate nature, a dermal medication adds complexity to nonclinical studies, making it particularly important to choose a CRO with expertise in dermal studies.

Available FDA Pathways

The FDA offers several pathways to drug sponsors for getting their products to market, including:

505(b)(1) New Drug Application

NDA filings can be complicated and time-consuming, costing as much as $2.6 billion[1]. For drug products that have never been approved by the FDA for the condition your drug addresses, a 505(b)(1) is the most appropriate pathway.

505(b)(2) New Drug Application

For products that are not new chemical entities that would require the scrutiny of a 505(b)(1), but are also not generic equivalents, choose a 505(b)(2).

It may seem like an advertising cliché, but in a 502(b)(2) application, drug sponsors essentially state that their product is “new and improved”—demonstrating how they took a previously approved drug product and made substantive changes such that it creates a wholly different drug product.

Changes can range from dosage strength to a new route of administration, to an entirely different disease indication.

In a 505(b)(2) application—depending upon circumstances—the drug sponsor can rely on previously published information about the original drug’s safety and effectiveness, which can save time and money and avoid the unnecessary duplication of scientific effort.

[1] Innovation in the pharmaceutical industry: New estimates of R&D costs

A 505(b)(2) pathway limits the number of studies a drug sponsor must conduct to round out the scientific information provided to the regulatory agency. However, when a 505(b)(2) application involves a dermal drug product, a drug sponsor needs to provide scientific data concerning:

- Irritation
- Sensitization
- Genotoxicity
- Photosafety

Compared to a 505(b)(1) New Drug Application drug product, a 505(b)(2) Application drug product takes about half the time to progress to clinical trials. The 505(b)(2) application also provides the potential for market exclusivity for three, five, or seven years.

505(j) Approved New Drug Application

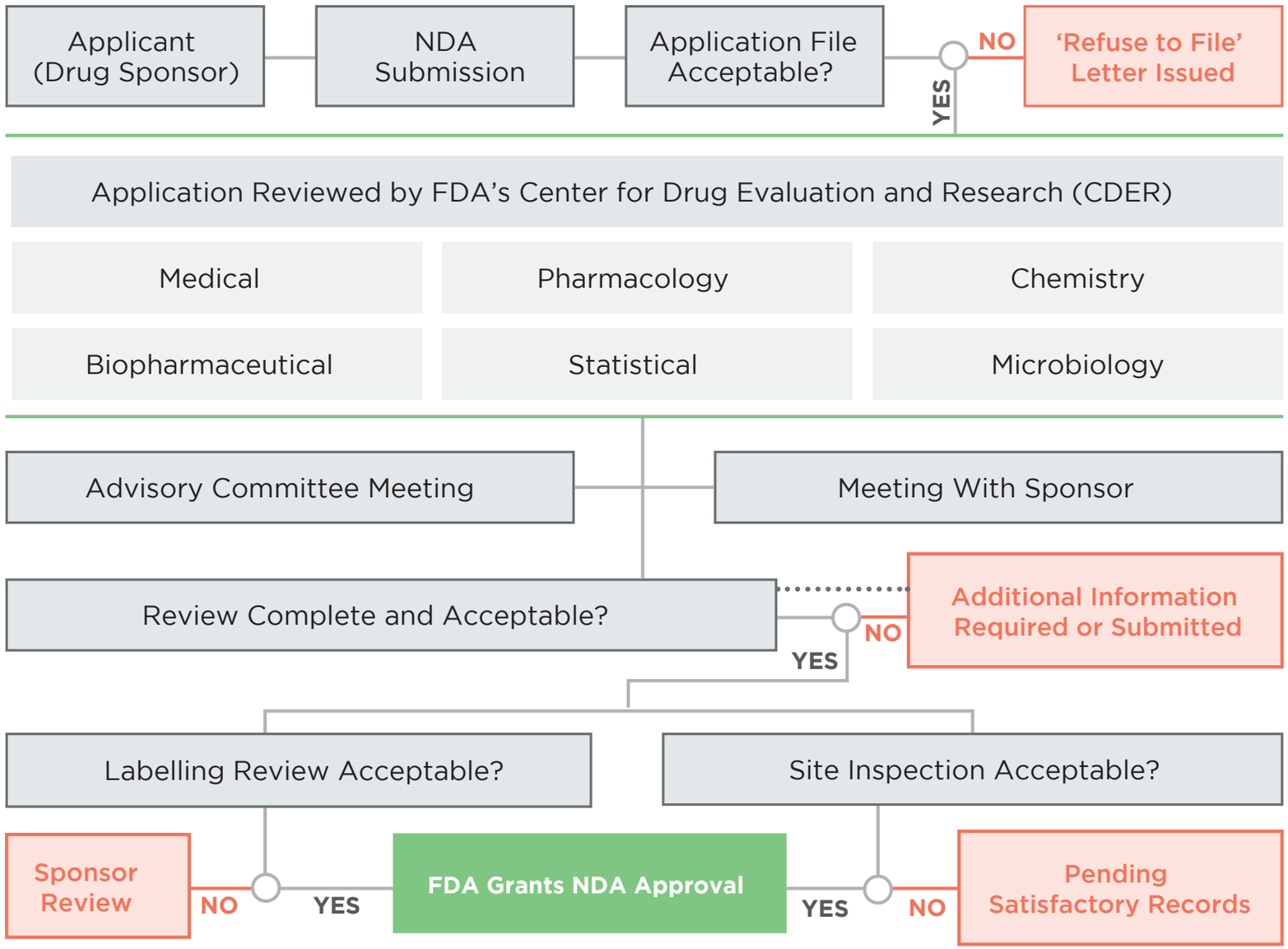
This pathway is used by drug sponsors seeking approval for a generic version of a branded product previously approved through the 505(b)(1) New Drug Application process.

Drug sponsors are permitted to reference publicly available data, and must demonstrate only their product's chemical equivalence to the previously approved branded product through analytical and biomedical studies. Nonclinical trials are not required for this pathway.

SUMMARY OF THE DIFFERENCES BETWEEN THE THREE FDA PATHWAYS

	505(b)		505(j)
	505(b)(1)-NDA	505(b)(2)-NDA	ANDA
Scientitic Studies	Full	Partial	Bioequivalence
New Active Moiety	Yes	Yes	No
New Indication	Yes	Yes	No
New Dosage Form	Yes	Yes	Limited
New Strength	Yes	Yes	No
Patent	Yes	Yes	No
Market Exclusivity	Yes	Yes	No

505(B)(1) NEW DRUG APPLICATION APPROVAL PROCESS



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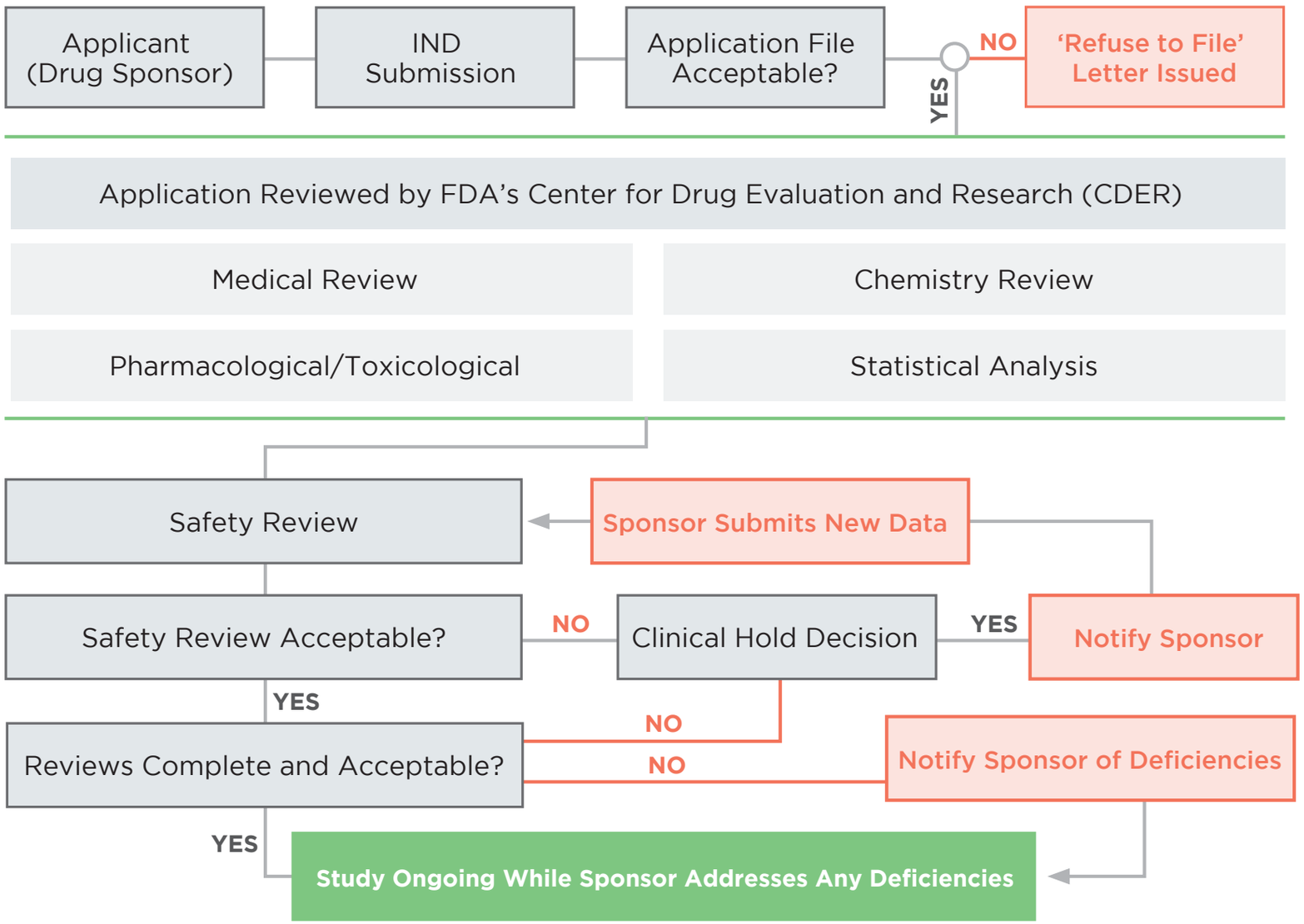
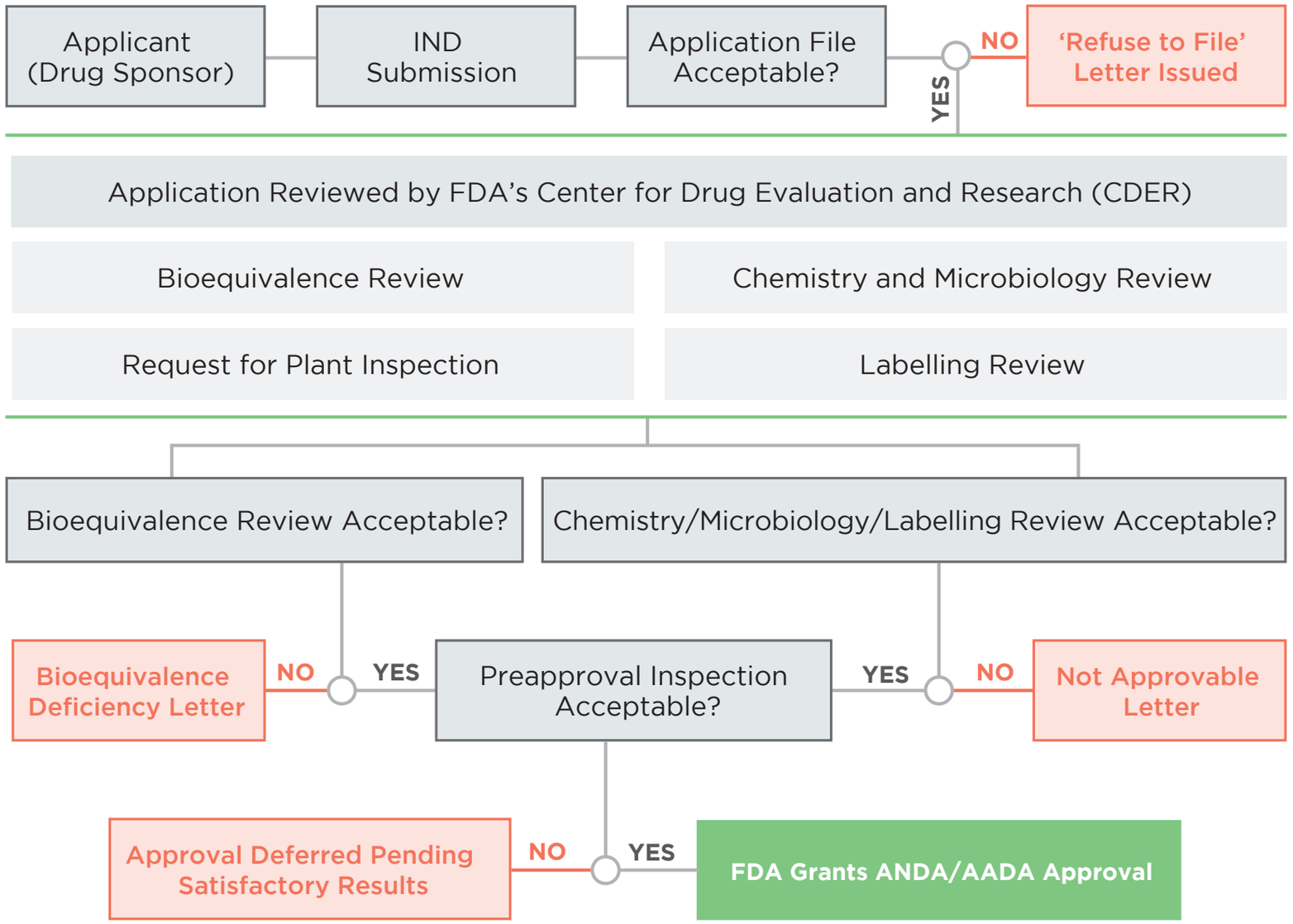
505(B)(2) NEW DRUG APPLICATION APPROVAL PROCESS



505(J) APPROVED NEW DRUG APPLICATION APPROVAL PROCESS



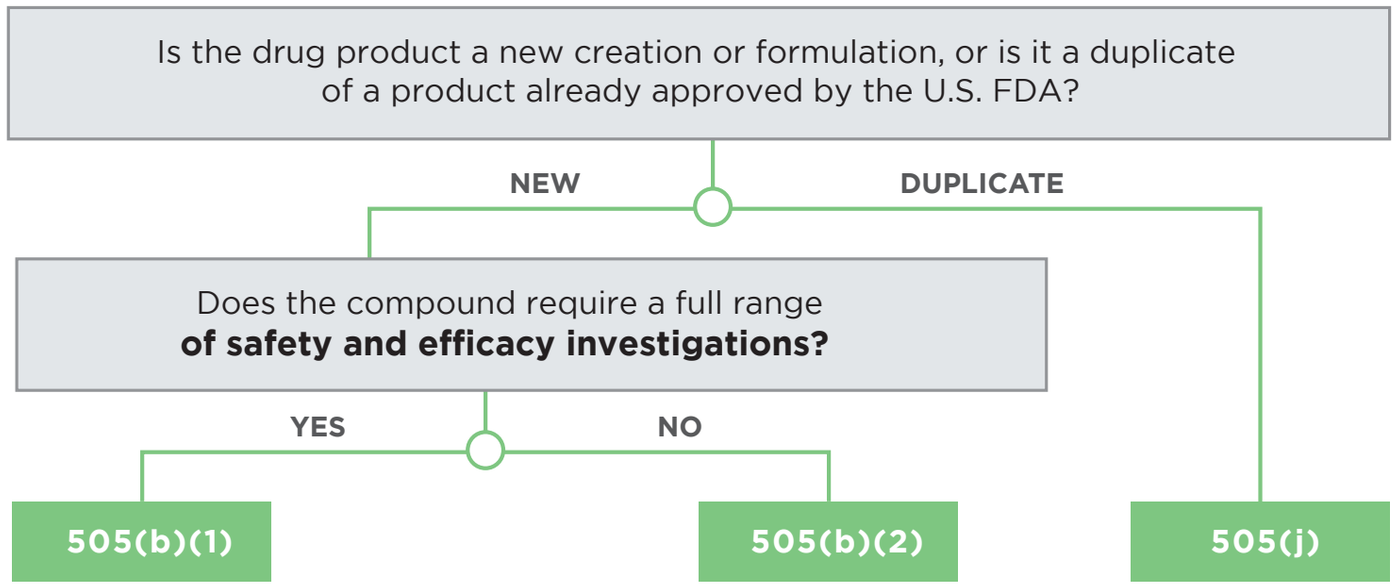
Choosing the Right Pathway

Choosing the right pathway is critical. The FDA can—and has—rejected 505(b)(2) filings because administrators deemed the proposed drug products to be chemical equivalents more appropriate for 505(j) filings.

In order to avoid costly missteps, you should engage in a dialogue with regulatory agencies early and often before running studies. In addition, contact your CRO/CDMO for guidance about available FDA pathways, as well as nonclinical studies that best support your application.

The FDA expects to see the following information in a drug application:

- General provisions
- Organization
- Scientific and operational team
- Facilities
- Equipment
- Testing facilities operations
- Test and control
- Protocols
- Records and reports



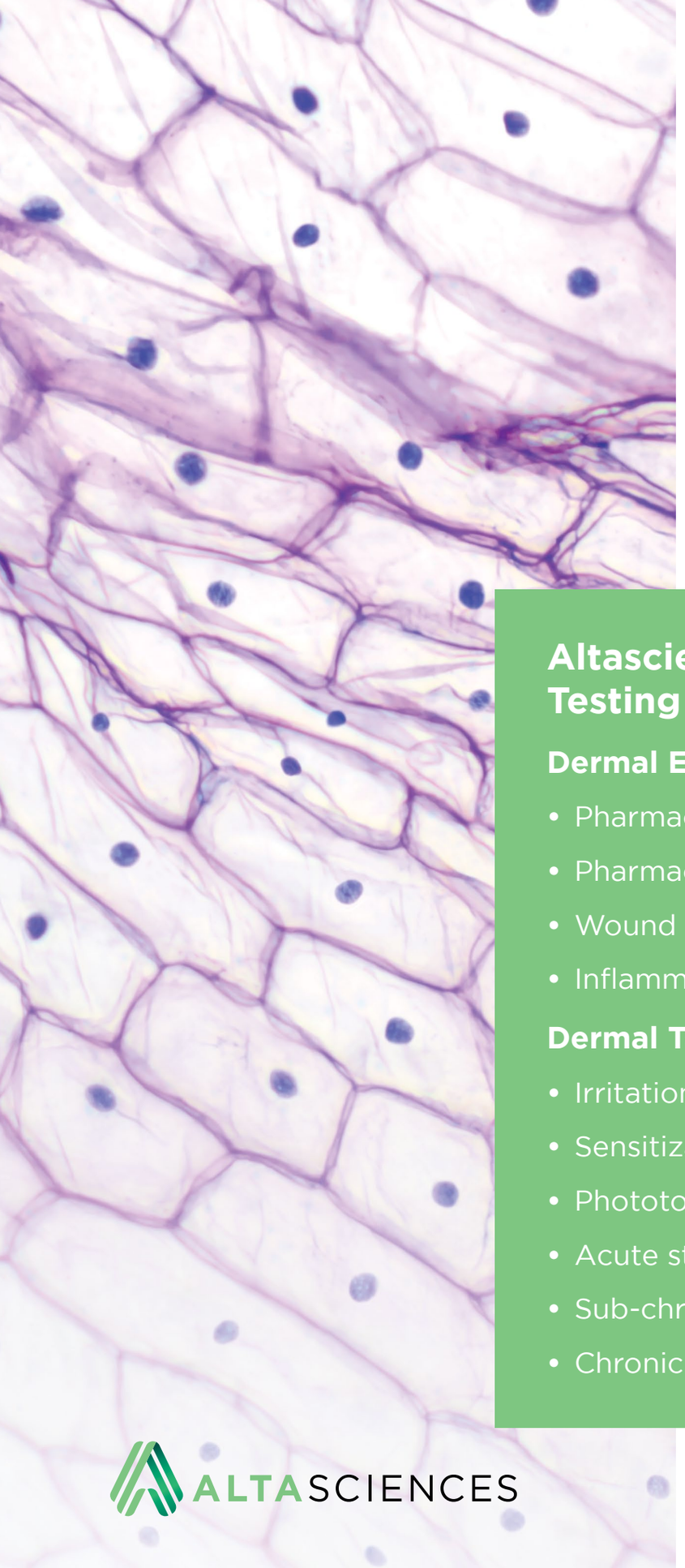
Of Particular Importance: A History of Compliance

The FDA has articulated its expectations concerning the nonclinical organization and its people; nonclinical facilities and equipment; testing facilities operations; how the nonclinical organization performs tests and controls during studies; and protocols, records, and reports[2]. Compliance with these regulations ensures the quality and integrity of safety data submitted to the FDA as part of your application.

Altasciences has a long history of nonclinical excellence and regulatory compliance, holding accreditation from:

- The Association for Assessment and Accreditation of Laboratory Animal Care
- The Food and Drug Administration
- The U.S. Department of Agriculture

[2] CFR - Code of Federal Regulations Title 21



Why Altasciences for Dermal Research?

Altasciences' team of toxicologists, veterinarians, and technicians move in unison to provide a wide range of dermal services to bring your molecule from discovery through clinical trials to proof-of-concept, and beyond. Our team can work with you to develop dermal models, validate existing dermal models, and perform both GLP and non-GLP toxicology studies to support both 505(b)(2) and new chemical entity regulatory filings.

Altasciences' Dermal Testing Capabilities:

Dermal Efficacy

- Pharmacokinetics
- Pharmacodynamics
- Wound healing
- Inflammation

Dermal Toxicology

- Irritation
- Sensitization
- Phototoxicity
- Acute studies
- Sub-chronic studies
- Chronic studies

Dermal Experts

Altasciences' scientific experts bring decades of experience supporting multiple dermal drug development programs from initial efficacy to clinical proof of concept.

Dedicated Dermal Team

We have assembled a dedicated team to increase the accuracy of dermal scoring and consistently provide you with high-quality data.

Dedicated Dermal Facilities

We have customized our vivarium to ensure the integrity of test article exposure and transfer.

Dedicated Dermal SOPs

We have implemented special dermal SOPs to minimize any potential challenges in dermal dosing and mitigate risk of cross-contamination.

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Altasciences is a forward-thinking drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to **preclinical** and **clinical pharmacology** studies, including **formulation, manufacturing, and analytical services**. For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include **preclinical safety testing**, **clinical pharmacology and proof of concept**, **bioanalysis**, **program management**, **medical writing**, **biostatistics**, **clinical monitoring**, and **data management**, all customizable to specific sponsor requirements.

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

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