WITH DALTON

Peter Pekos

Botanical Drug Development

FDA Guidance Document

Company Vision

"Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

Disclaimer

This technical report is intended to provide a summary on FDA's 2016 Botanical Drug Development Guidance (BDDG) to key stakeholders including regulatory professionals on precision medicine. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

FDA inspected, HC approved, & MRA with EMA

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FDA's 2016

Botanical Drug Development Guidance

In 2016, the Food and Drug Administration (FDA) published a guidance titled “Botanical Drug Development.” In this guidance, the FDA outlines the Center for Drug Evaluation and Research’s (CDER’s) current views on the development plans to be included in new drug applications (NDAs) for botanical drugs, as well as specific suggestions for the submission of investigational new drug applications (INDs) to support future NDA submissions for botanical drugs. General information on the over-the-counter (OTC) drug monograph system for botanical medicines is also included in this guideline. This guidance replaces the “Botanical Drug Products” guidance document issued in June 2004 and is the final version of the August 2015 draft guidance “Botanical Drug Development.”

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History: Approved Botanical Drugs

2018
800 IND submissions

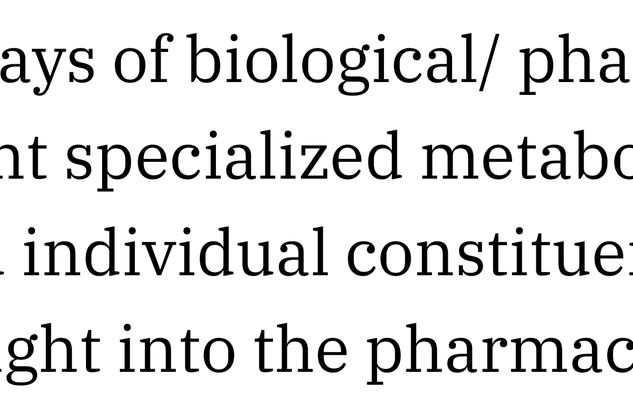
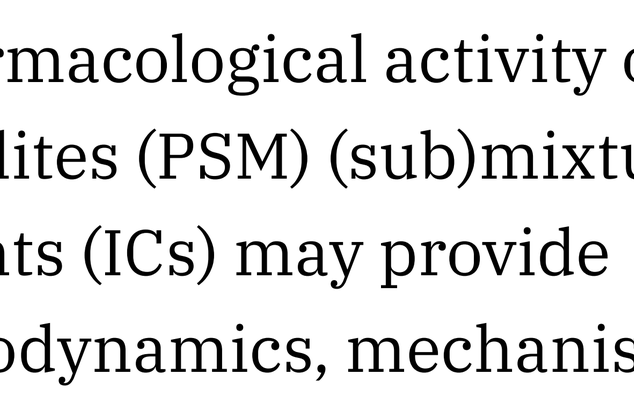
2012
Veregen was approved

2006
Fulyzaq was approved

By 2018, the US FDA had received approximately 800 requests for pre-IND meetings and IND submissions for botanical research. However, despite growing global interest in botanical drug products, only two botanical NDAs have been approved in the U.S. as prescription drugs. Veregen was approved in October 2006 and Fulyzaq (also known as Mytesi) in December 2012. This low approval rate is attributed to the chemical and biological complexity of botanical drugs. The unique composition of botanical drugs create challenges in characterizing their pharmacology, identifying the active ingredient, demonstrating therapeutic efficacy, and ensuring quality consistency.

DID YOU KNOW?

Assays of biological/ pharmacological activity of plant specialized metabolites (PSM) (sub)mixtures and individual constituents (ICs) may provide insight into the pharmacodynamics, mechanism of action, and the role of different ICs in botanical drugs.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What Is a Botanical Drug?

How a botanical product is regulated is dependent on its intended use and how the product is labeled.

Botanical Product Regulated as A Drug

A botanical product consists of vegetable materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof, and is regulated as a drug if it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans. A botanical drug product may be available as a solution (i.e., tea), powder, tablet, capsule, elixir, topical, injection, etc.

Note: Fermentation products and highly purified or chemically modified botanical substances are not considered botanical drug products.

Botanical Product Regulated as A Dietary Supplement

A botanical product is regulated under the general umbrella of foods as a dietary supplement if it is intended to supplement a diet. A botanical-based dietary supplement is taken orally and cannot make a disease claim to diagnose, cure, mitigate, treat, or prevent disease.

DID YOU KNOW?

The CDER Botanical Review Team (BRT) works on common botanical issues with:

- The Office of Dietary Supplements at the National Institutes of Health
- FDA's Center for Food Safety and Applied Nutrition (CFSAN)

Note: A botanical product may also be classified as a medical device, or cosmetic.

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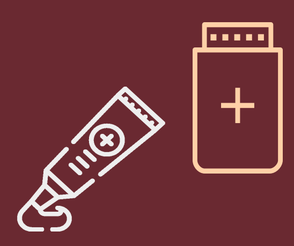
OTC Drug Monograph System for Botanical Drugs

Currently, several botanical drug substances, such as cascara, psyllium, and senna, are included in the OTC drug review, and witch hazel is currently marketed under an OTC drug monograph. To be included in an OTC drug monograph, a botanical drug must be recognized under the United States Pharmacopeia and National Formulary (USP-NF) and in accordance with the safety and efficacy requirements outlined in 21 CFR 330.10(a)(4).

A citizen petition per 21 CFR 10.30 and 330.10(a)(12) or a Time and Extent Application (TEA) per 21 CFR 330.14 may be used to request the modification of an OTC drug monograph to add a botanical drug substance.

Approved Botanical Drugs

To date, two botanical products have fulfilled the botanical guidance definition of a botanical drug product: sinecatechins, Veregen®, and crofelemer, Mytesi™.



Sinecatechins (Veregen) 15% ointment was the first botanical drug product approved by the U.S. FDA. It is derived from green tea leaves and is intended to treat external genital and perianal warts (Condylomata acuminata) in immunocompetent patients 18 years of age and older. The mechanism of action is not yet known, however, in vitro, sinecatechins has anti-oxidative activity (the clinical significance of this finding is unknown).

Mytesi is the second botanical drug product to receive FDA approval. It is indicated for adult HIV/AIDS patients who are receiving antiretroviral treatment for the symptomatic alleviation of non-infectious diarrhea. Crofelemer works by preventing Cl- secretion and the high-volume water loss associated with diarrhea, thus restoring normal Cl- and water flow in the gastrointestinal tract.

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To facilitate the clinical development of botanical drugs, CDER focuses discussions in the guidance on INDs first, especially the initial phases. The guidance also advises sponsors to consult with the relevant Office of New Drugs Review division before filing an IND, since each botanical drug has its own special considerations and may be exempt from IND requirements.

IND Phase 1 and 2

- The quantity of data required to be provided in an IND for a drug varies depending on several variables, such as the volume of existing human experience and clinical trials, the drug's known or suspected risks, and the drug's stage of development.
- For early-phase development (phase 1 and 2 clinical studies), detailed chemistry, manufacturing, and controls (CMC) information (i.e., data on comprehensive characterization of the drug substance) may not be warranted for many botanical drugs; however, CMC data collection should still be initiated during these phases because such preliminary information should be submitted before beginning phase 3 studies. In addition, a botanical drug with a long history of human use can often avoid many toxicology requirements during the early stages of development, but, some degree of safety testing is still required.

IND Phase 1 and 2 Content Requirements

To comply with the requirements outlined in 21 CFR 312.23, the sponsor should specifically address the following issues unique to botanical drugs in the IND submission for phase 1 and 2 studies.

- Description of Product and Documentation of Prior Human Experience
  - Description of Botanical Raw Materials Used and Known Active Constituents or Chemical Constituents
  - Prior Human Experience
- Chemistry, Manufacturing, and Controls
  - Botanical Raw Materials
  - Botanical Drug Substance
  - Botanical Drug Product
  - Placebo
  - Environmental Assessment or Claim of Categorical Exclusion
- Nonclinical Pharmacology/Toxicology
- Clinical Pharmacology
- Clinical Considerations

Note: CMC information outlined is recommended to support early-phase clinical studies for a botanical drug. All available information should be provided.

IND Phase 3

During phase 3 studies, further characterization of the botanical drug product will ensure the quality of the drug substance and the validity and reliability of the clinical data acquired. Phase 1 and 2 studies that were not conducted in the US under an IND may be used to support the submission of a phase 3 study under a new IND. However, the botanical ingredient (formulation and dosage form) utilised in the proposed phase 3 trial should be the same as the substance used in phase 1 and 2 trials and preclinical research. The bioequivalence of each tested product will need to be established if various formulations were utilised. Given the more extensive exposure in late-phase clinical studies, additional toxicological data is also required to support safe human usage.

Note: Whenever the source and manufacturing process of the botanical raw material, drug substance, or drug product is changed during development, a comparison of the previous and new sources and manufacturing processes should be provided by the sponsor. This is because even seemingly insignificant changes in the source and/or process could have a significant impact on the clinical effects and raise concerns about the applicability of earlier pharmacological, nonclinical, and clinical data.

IND Phase 3 Content Requirements

- General Regulatory Considerations in Late-Phase Development
- Description of Product and Documentation of Prior Human Experience
- Chemistry, Manufacturing, and Controls
  - Botanical Raw Materials
  - Botanical Drug Substance and Drug Product
- Nonclinical Safety Assessment
  - General Pharmacology/Toxicology
  - Nonclinical Pharmacokinetic/Toxicokinetic Studies
  - Reproductive Toxicology
  - Genotoxicity Studies
  - Carcinogenicity Studies
  - Other Toxicity Studies
  - Regulatory Considerations
- Clinical Pharmacology
- Clinical Considerations
  - Study Design for Multiple Batch Analyses
  - Dose-Response Effect
  - Clinical Studies of Botanical Drugs for Serious Conditions
  - Other Study Design Issues
- Applicability of Combination Drug Regulations

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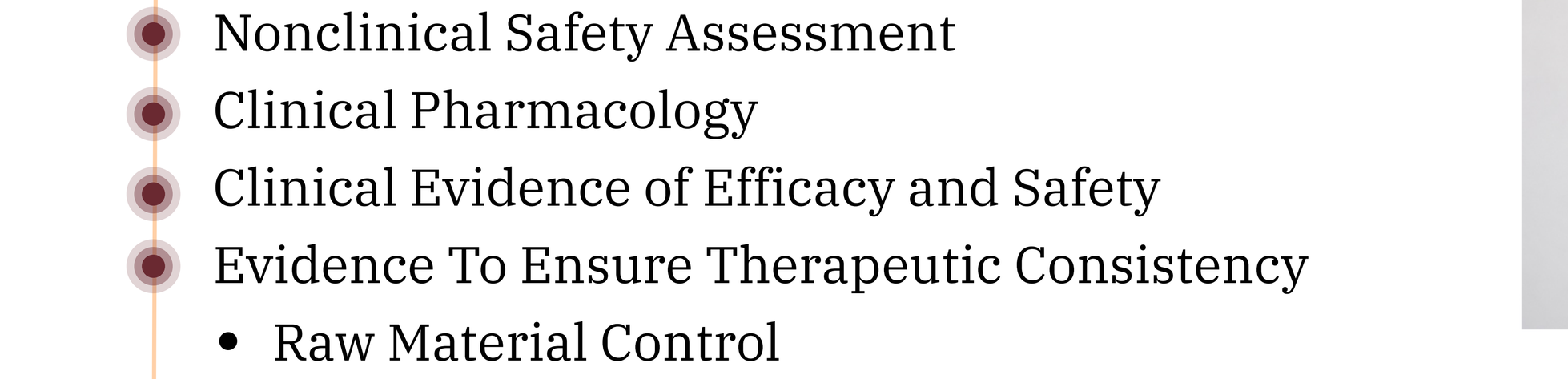
NDA

- For NDA approval, the standards for the safety and efficacy of a botanical drug are the same as those for a conventional chemical drug for the same indication. The quality requirements for a botanical drug, however, may differ from those for a purified chemical drug.
- An NDA for a botanical drug product should be submitted in the Electronic Common Technical Document (eCTD) format.

NDA Content Requirements

The most important step of the process and, for botanicals, the most difficult step to satisfy, is the FDA's review and acceptance of the CMC.

- Description of Product and Documentation of Prior Human Experience
- Quality Control
  - Botanical Raw Material
  - Botanical Drug Substance and Drug Product
  - Chemical characterization
  - Manufacturing processes
  - Biological assay
  - Specifications
  - Stability
  - Drug master file
  - Naming consideration
  - Current good manufacturing practices
  - Environmental assessment
- Nonclinical Safety Assessment
- Clinical Pharmacology
- Clinical Evidence of Efficacy and Safety
- Evidence To Ensure Therapeutic Consistency
  - Raw Material Control
  - Quality Control by Chemical Tests and Manufacturing Control
  - Biological Assay(s) and Clinical Data
- Post-marketing Considerations



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Common Barriers to Botanical Drug NDA Submissions and Approvals

Failure to demonstrate clinically relevant and statistically significant efficacy.

DID YOU KNOW?

This is the most common reason why most drugs — not just botanical drugs — fail to reach NDA approval.

Absence of international harmonization of regulatory requirements for botanicals.

Insufficient funding to complete the development process.

Challenges with identifying molecular targets of all bioavailable compounds within the extract (i.e., the overall mechanism of action).

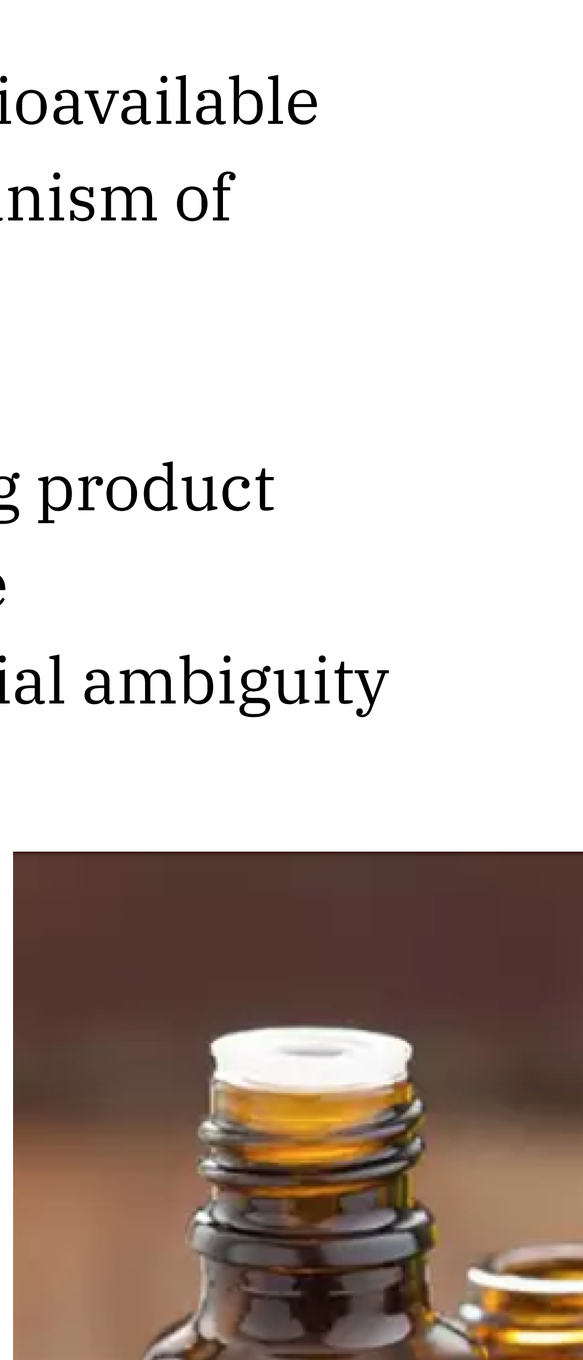
Ensuring that the therapeutic effect of marketed drug product batches remains consistent—a difficult task given the heterogeneous nature of a botanical drug and potential ambiguity about its active ingredients.

Tips on how to support therapeutic consistency:

1. Botanical raw material control (i.e., agricultural practice and collection).

2. Quality control by chemical test(s) (i.e., analytical tests such as spectroscopic and/or chromatographic methods that capture the active or chemical constituents of a botanical drug substance) and manufacturing control (i.e., process validation).

3. Biological assay (i.e., a biological assay that reflects the drug's known or intended mechanism of action) and clinical data.



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Global Regulatory Differences on Botanicals

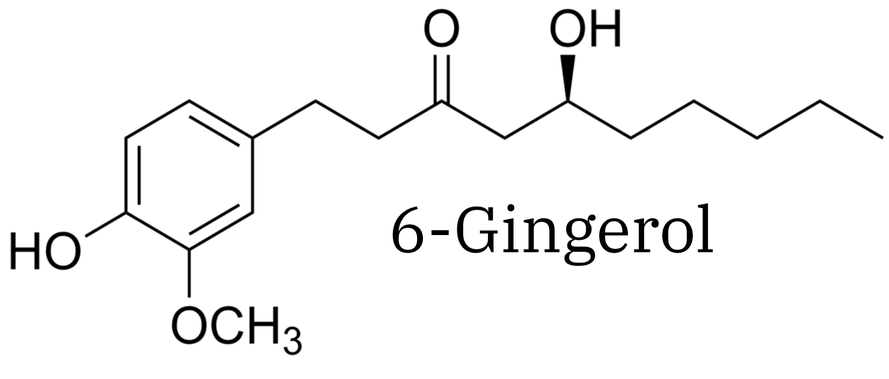
As mentioned above, regulatory requirements vary among regulatory authorities, such as the European Medicines Agency (EMA) and Health Canada (HC).

In EU member states, botanicals are regulated as herbal medicinal products by EMA's Committee on Herbal Medicinal Products (HMPC). To market a herbal medicine in EU member states, three key pathways can be taken: traditional use registration, well-established use marketing authorisation, and stand-alone or mixed application.

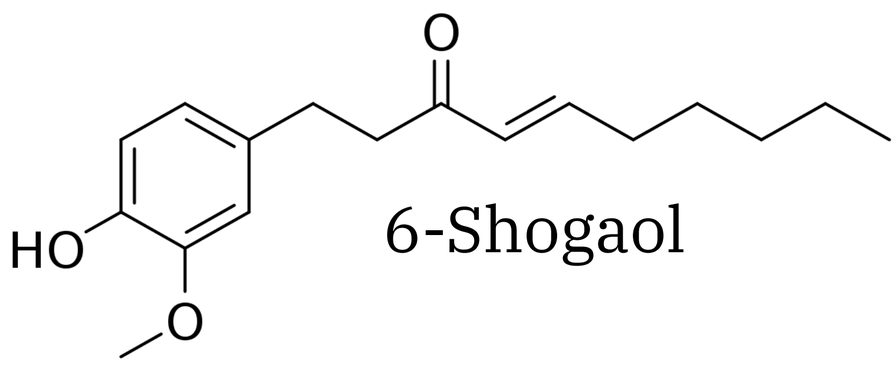
In Canada, botanicals are regulated as natural health products under HC's Natural and Non-prescription Health Products Directorate (NNHPD). HC defines NHPs as naturally occurring substances that are used to restore or maintain good health including herbal remedies, homeopathic medicines, and traditional medicines. To market a natural health product in Canada, the sponsor must obtain a natural product number (NPN), or DIN-HM for homeopathic medicines, from the NNHPD.

Botanical: Ginger - Health Benefits

Ginger has been used as a medicinal herb for thousands of years to treat a wide range of ailments. The health benefits of ginger are mainly attributed to its phenolic compounds, such as gingerols and shogaols. Research shows that ginger is an effective antioxidant, anti-inflammatory agent, antinausea compound, and anti-cancer agent. However, more studies on the effects of long-term consumption, specific molecular targets, and mechanisms of action are required.

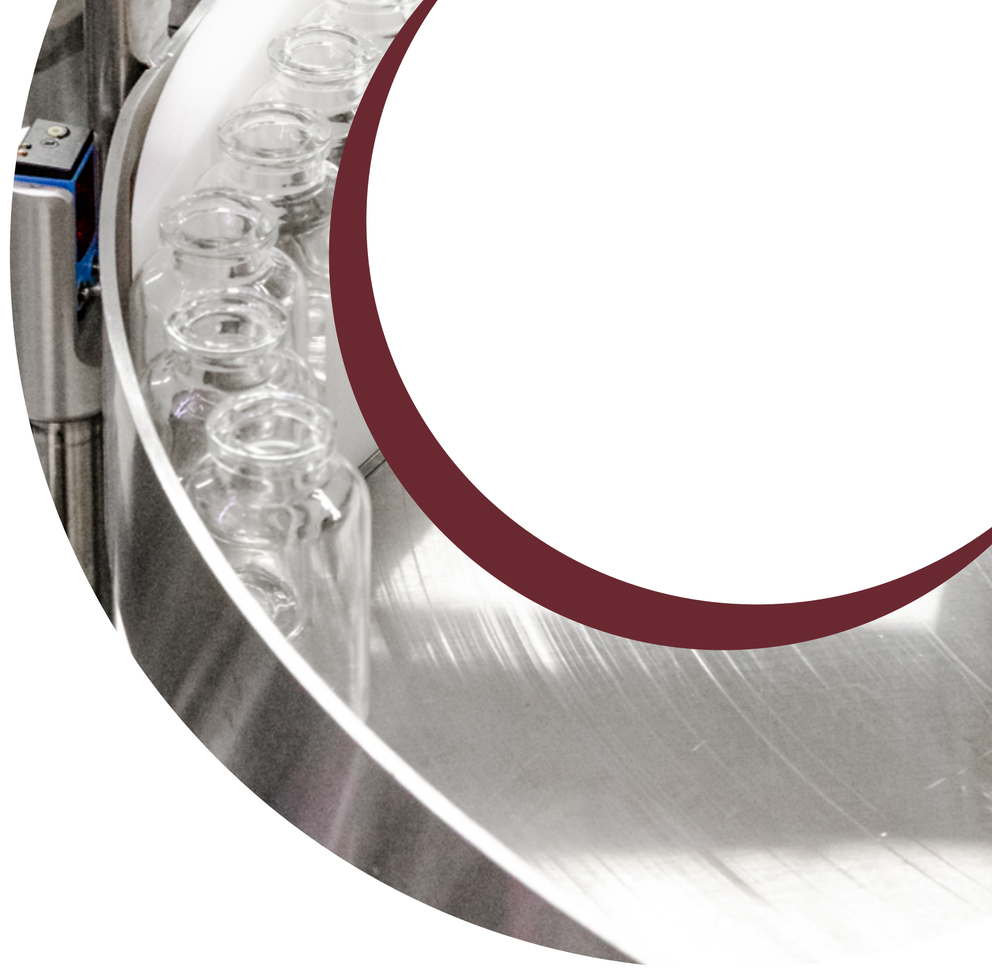


6-Gingerol



6-Shogaol

At Dalton, we offer an extensive range of over 3,000 chemical compounds including natural products, such as gingerols and shogaols. More information about our services can be found on the following page.



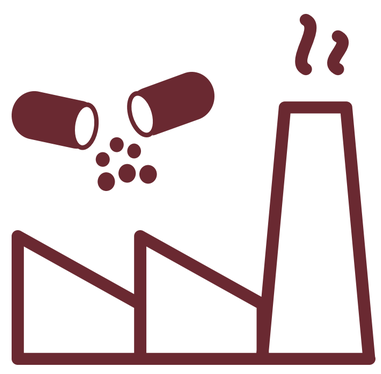
Dalton's *Services*

We bring over 35 years of experience developing products for our clients that are compliant, transferable, and scalable.

At Dalton we can help with drug innovation through our cGMP APIs. Our skilled scientists can support your drug discovery process through API synthesis for all stages of pre-clinical and clinical trials as well as small scale commercial manufacturing. We provide integrated process development, API manufacturing and finished dose manufacturing at a single location with the expertise required for developing a process that is robust, transferable, and scalable to meet your requirements.

A few of our services include:

- cGMP Sterile Filling
- GMP API manufacturing
- API Proceses Development
- Contract Research
- Medicinal Chemistry



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For more information on services we provide, visit our website.

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