**Pharma Solutions**
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# Cannabinoid-based Drug Development

## Due diligence considerations across the drug development journey

dsm-firmenich

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**Cannabinoids are showing significant promise in the therapeutic arena beyond their approved use in drug-resistant epilepsy, multiple sclerosis (MS) induced spasticity and neuropathic pain and chemotherapy induced nausea and vomiting – namely in addressing pain management, and central nervous system disorders induced by stress and anxiety.**

Within our industry, this is creating a unique opportunity to enhance patient care by broadening treatment possibilities whilst improving patient compliance and care. At the same time, the cannabinoid market is developing rapidly and the body of science behind cannabinoid-based medicines is growing. This is contributing to a continuously evolving drug development and approval route.

To help stakeholders across the pharmaceutical research and development pathway navigate the complexities of innovation in the cannabinoid space more effectively, this whitepaper discusses key considerations throughout drug discovery – from choosing the right active ingredient from the beginning, to increasing the odds of commercial success, all the way to fine-tuning patient experience and compliance. The paper does not imply that cannabinoids should ever be administered before in-depth clinical data is produced demonstrating their safety and therapeutic benefits or without adequate local regulatory clearance.

# Foreword

**Athanasia Kanli**
Global Market Development Manager
Pharma at dsm-firmenich

**Advancing the cannabinoid research landscape is the only way to make real progress in the field and unlock new therapies for patients worldwide.**

As a science-based, end-to-end partner to the pharmaceutical market, dsm-firmenich understands the intricacies of the cannabinoid arena. We have a profound knowledge of the scientific research driving the market, technical challenges involved in bringing novel therapies to the market, and evolving regulatory pathways; offering a unique innovation platform designed to inspire, nurture and activate purposeful developments in the emerging cannabinoid space. We are ready to break boundaries in cannabinoid innovation to unlock a new medical frontier of cannabinoid-based therapies. Are you?

# What will you learn from the whitepaper?

1. Identify the untapped white space in the cannabinoid market.
2. Key considerations along the cannabinoid drug development journey – during the trial design, regulatory approval and market access phases.
3. Expert insights to unlock the full therapeutic potential of cannabinoids.
4. Recommendations for designing patient-centric cannabinoid therapies.
5. How you can navigate the market with confidence with dsm-firmenich and our partner in cannabinoid innovation, Brains Bioceutical.

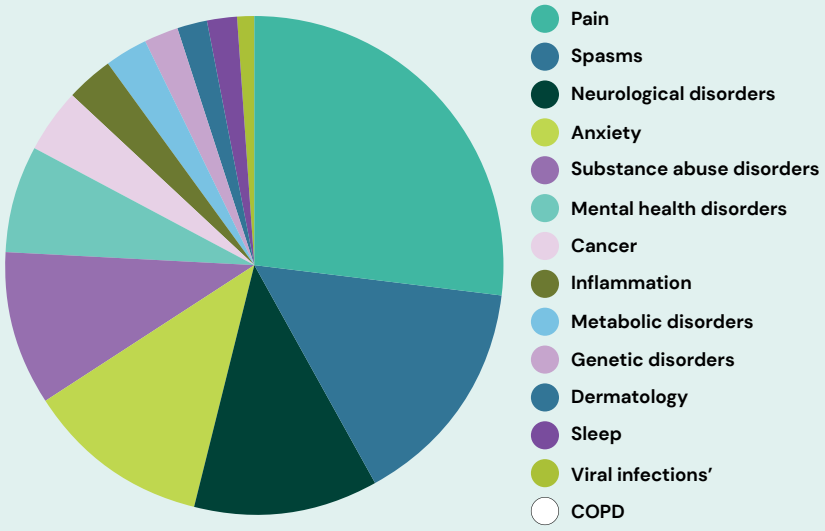
**Discover your roadmap to success in the cannabinoid drug development landscape.**

# The promising potential of cannabinoid-based therapeutics

The cannabinoid market is rapidly advancing, powered by evolving regulatory frameworks aimed at giving patients access to novel therapies, established use in treating conditions such as drug-resistant epilepsy and promising scientific findings demonstrating the therapeutic potential of cannabinoid ingredients across numerous health indications.

Cannabidiol (CBD), especially, has been a huge focus of research in the cannabinoid space and scientific evidence behind the molecule is growing rapidly. The evidence is strongest in pain management, spasms and central nervous system (CNS) disorders, like epilepsy. However, the therapeutic capacity of CBD is being explored in multiple therapeutic areas, including mood disorders (stress and anxiety management), sleep, cancer, pain, and more **(Figure 1.)** – and the evidence is undeniably promising.

This is just the beginning. As the global pharmaceutical industry realizes the possibilities of CBD and other minor cannabinoid molecules, fresh advancements in the field continue to capture the attention of innovators worldwide.




219 unique clinical trials in scope

**Figure 1.** Ongoing CBD clinical trials by indication.[1]

**+200**

**Active CBD clinical trials (Q3 2023)[1]**

**25**

**Indications for which CBD may have therapeutic benefits[1]**

**+15%**

**of rise in CBD publications (2010-2023)[3]**

**~40%**

**CBD trials linked to pain management and spasms[2]**

# Enter the cannabinoid market with confidence

**The successful discovery and development of novel molecules, like cannabinoids, is reliant on deep expertise and cutting-edge capabilities at each stage of the drug development journey – from target identification and initial research to market launch, and beyond. But in an ever-evolving marketplace – like the cannabinoid realm – how can innovators mitigate risk of research failure and increase the odds of real therapeutic advancements in the space?**

**Figure 2.** Services offered to support your cannabinoid drug development.

| Discovery & Development | Pre-Clinical Research | Clinical Research | Regulatory Review | Post-Market Monitoring |
|---|---|---|---|---|
| • Commercial viability (growing market and unmet need)<br>• Novel mechanism of action and benefits above standard of care | • Regulatory and scientific evaluation of pre-clinical and clinical evidence<br>• Clinical trial design with meaningful endpoints<br>• Established relationships with CROs, CMOs and KOLs | • Finished dosage forms to support proof of concept & in-human clinical trials<br>• Bioavailability enhanced CBD oral solid dosage formulations<br>• Chemistry, Manufacturing, and Controls (CMC) and Formulation<br>• API compliant with relevant pharma-copeial monographs and general chapters / ICH Guidelines<br>• API manufactured under pharma GMP (ICH Q7) | • Review of regulatory pathway including accelerated pathways and data-pack gap analysis<br>• Regulatory data package (DMF, ASMF) available | |

> Success in this arena requires a 360°-view of the complex, lengthy and demanding cannabinoid drug development pathway. There is an urgency to accelerate patient access to potentially life-changing cannabinoid-based treatments, which requires swift market authorization. However, as cannabinoids are still novel ingredients, few pharmaceutical companies have effectively steered cannabinoid-based treatments through the approval process. In fact, there are currently only three regulatory-approved cannabinoid-based therapies.
>
> Influencing factors include stringent regulatory policies, challenging reimbursement pathways and costly clinical research. The key to progressing the cannabinoid field and making more treatment options available to patients worldwide? A robust clinical plan and market access strategy powered by solid science, regulatory-supported APIs and a shared commitment to improving the lives of patients globally.
>
> – **Athanasia Kanli**, dsm-firmenich

# Choosing the best cannabinoid API

Selecting the right active pharmaceutical ingredient (API) underpins the success of any drug development project. However, not all cannabinoid APIs are created equally. To effectively mitigate the risk of failure during cannabinoid drug development and build robust scientific evidence, it is important to ask, "Is my cannabinoid API trial-ready?". Here are three factors to consider:

## 1 GMP-certification

Good Manufacturing Practice (GMP)-certification is one of the key considerations. A set of standards that guarantees a product is made consistently and reliably according to compendial-defined product specifications, GMP-qualified cannabinoids ensure that patient safety is not compromised during manufacturing of the drug substance. Although non-GMP pharma-grade ingredients may be used for preclinical and early human clinical trials in some regions, for Phase 2 human trials and subsequent market authorization, an API developed under GMP manufacturing, and quality conditions in a facility audited and certified by a national competent authority, is compulsory. Should a drug manufacturer submit a clinical trial with a non-GMP API, they risk that the regulator will not accept the product/plan and force them to switch to a different API supplier for later trials.

## 2 Regulatory documentation

Relevant regulatory documentation, including robust data packages and proof of quality, is also mandatory for clinical trials and drug product registration. Is your API supported by the relevant Drug Master File (DMF) or Certification of Suitability (CEP, post July 2024) for launch in the US and Europe, for instance?

## Did you know?

**dsm-firmenich's cannabinoid platform is enabled by Brains Bioceutical – an evidence-based and science-led pioneer of cannabinoid solutions. Brains Bioceutical is a GMP certified manufacturer that produces a CBD isolate in a facility inspected by the national competent authority of the UK. Its CBD API is one of the purest botanical isolates on the market.**

## 3 Natural versus synthetic

Finally, the choice of a natural or synthetic cannabinoid ingredient can make a significant difference. Synthetic CBD APIs can exhibit specific impurities, including a risk of enantiomeric contamination of the drug substance. Safety and toxicity may be of greater concern with chemical compounds as they may be less well-tolerated.[4] On the other hand, plant-based material guarantees the correct structure and stereochemistry – which influences receptor binding and the biological function of the molecule.

It is worth mentioning that a number of authorities worldwide do prohibit the use of synthetic cannabinoids, including synthetic CBD, in therapeutic products; for example, Health Canada prohibits the use of synthetic cannabinoids in Natural Health Products, Brazilian Health Regulatory Agency (ANVISA) prohibits their use as active substances, and the Australian Therapeutic Goods Administration (TGA) prohibits their use in Rx medicines. Plus, the proposed Ph. Eur. monograph for CBD specifically mentions that CBD is derived from natural sources, which means that in order for an API to claim compliance with the Ph.Eur. from next year, it has to be isolated from natural sources. All approved CBD drugs marketed to date are based on plant-sourced ingredients.

**75%** **of patients with epilepsy prefer to take natural CBD.**

It's not just the science driving the market. The cannabinoid market harbors substantial untapped potential propelled by unmet patient needs, growing patient acceptance, heightened prescription of cannabinoid-based therapies and a progressively favorably evolving regulatory environment.[6,1] For example, patients are showing a clear preference for natural solutions versus traditional synthetic pharmaceuticals.[5] Reasons cited include "lack of chemicals" and "better tolerance".

## Does your cannabinoid API meet the following criteria?

- **API developed under GMP manufacturing**
- **High purity and compliant with draft substance monographs of the USP and Ph. Eur., as well as relevant general chapters of these pharmacopoeia and ICH guidelines**
- **Supported by regulatory documentation (DMF, ASMF)**
- **Natural origin**

# Key factors influencing the success of oral solid dosage formulation

**To guarantee the success of a cannabinoid formulation, factors including stability, solubility, drug loading and bioavailability must be given considerate thought. Learn why – and uncover how dsm-firmenich can support.**

## 1 Enhanced stability:

Stability of the active ingredient during storage is paramount to product success. dsm-firmenich has expertise in formulating water and fat-soluble actives using a combination of emulsification, drying and coating technologies to ensure that the end product remains stable independent of the end application format or storage conditions.

## 2 Improved solubility:

The solubility of an active ingredient in an aqueous environment is an important factor towards efficacy and the success of certain applications, like solid oral drug delivery formats. dsm-firmenich has developed proprietary technologies capable of enhancing active solubility and ensuring its cold water dispersibility.

## 3 High drug loading:

Increasing API loading in the formulation has a direct effect on the amount of finished drug product that a patient needs to ingest in order to achieve therapeutic effectiveness. Higher drug loading therefore equals better patient compliance. dsm-firmenich offers technologies where the concentration of API has been optimized to ensure patient compliance without compromising on the physical and chemical stability of the finished drug.

## 4 Optimal bioavailability:

The bioavailability of an active is directly linked to its efficacy and the dose required to achieve therapeutic benefit in the patient. dsm-firmenich offers a range of tailor-made solutions capable of optimizing the absorption and bioavailability of cannabinoids APIs.

# Crafting patient-centric formulations

Dose, route and frequency of administration must be top of mind when developing a therapy that addresses patient needs while championing their convenience or compliance. Equally, it's important to take into account the pathology of the medical condition that the therapy aims to address, right from the outset of product conceptualization. Is it chronic or acute for instance? This question will influence and ultimately define the desired dissolution speed, absorption pathway and drug pharmacokinetic parameters of the finished dosage form.

In the cannabinoid arena, the oral administration route is favored over other routes because it offers several advantages including safety, good patient compliance, ease of ingestion, pain avoidance, and the versatility to accommodate various types of drugs. Furthermore, exposure time is longer, and side effects are significantly less intense when cannabinoids are delivered orally. But which oral route is best?

## Solid versus liquid oral dosage form – which should you choose?

dsm-firmenich believes that solid formats represent the future of cannabinoid innovation – because they can help to achieve enhanced efficacy while simultaneously increasing patient convenience and therapy adherence. The advantages of solid dosage formats include widespread patient acceptance, taste-masking and flavor possibilities and convenience. Conversely, liquid (oil-based) products, which are usually administered via a syringe or dropper, present multiple challenges for patients including accurate dosing and sensory hurdles.

Liquid solutions also require longer periods of time before the active ingredient can reach its maximum concentration within the systemic circulation. This renders them a less attractive option for addressing acute medical conditions. On the other hand, solid dosage forms can be formulated into orally disintegrating tablets or films to support acute treatment.

Due to the highly lipophilic nature of CBD and the limited solubility of CBD API in most commercially available oils, liquid dosage forms exhibit inherently lower concentrations of the active (drug loading) than their solid counterparts. This requires the patient to ingest large volumes of the liquid solution in order to reach the desired therapeutic effect of the API.

Finally, oil-based CBD solutions have demonstrated a high degree of inter-patient variability as well as unpredictable changes in pharmacokinetic behavior when administered at mealtimes.[8] This makes liquid dosages less favorable – for patients and formulators alike.

# Unlock the full therapeutic potential of cannabinoids technical solutions to optimize bioavailability

**As discussed in the sections above, continued development of cannabinoid-based therapies is set to become a game-changer in treating a number of chronic and acute conditions.**

However, the limited solubility and variable bioavailability of cannabinoids in general and CBD specifically, pose substantial obstacles to progress – highlighting the critical need to optimize cannabinoid formulations and develop patient-centric solutions.

Dr. Zdravka Misic, Innovation Project Manager at dsm-firmenich, explains how to solve the insoluble in the cannabinoid arena and help cannabinoid-based drugs reach their full potential as therapeutic agents.

**Benefits of solutions with solid forms with enhanced bioavailability**

- **Lower required dosing to achieve effectiveness**
- **More cost-effective product**
- **Minimize adverse effects**

# Expert view

**Dr. Zdravka Misic**
Innovation Project Manager, Pharma
dsm-firmenich

## 1 Can you explain the challenges associated with cannabinoid bioavailability?

After oral intake, the bioavailability of cannabinoids can be as low as 6% (proportion of a drug which enters the circulation and so is able exert an effect). That's because cannabinoids are highly lipophilic and therefore demonstrate limited solubility in water leading to reduced gastrointestinal absorption. The molecule is also subject to first pass metabolism in the liver – whereby the concentration of the drug is greatly reduced before it reaches systemic circulation, and the desired site of action.

## 2 What is the impact of this for patients?

At present, too many patients have to administer large volumes of liquid CBD to achieve a positive therapeutic outcome. Clinical research has shown that API doses above 300-400 mg per day are required to have any real therapeutic effect – which could increase the risk of unwanted adverse effects.

In the specific case of drug resistant epilepsy, the daily dosage varies between 5-20 mg/kg body weight. In an adult this can equate to more than 1g of API (and 10 mL of oil that must be ingested – that's two teaspoons)!

## 3 What are the advantages of enhancing the bioavailability of cannabinoid formulations?

Optimizing the bioavailability of cannabinoids means that a smaller portion of the drug is needed to be effective – reducing dosage, limiting the probability of side effects and lowering cost of production. Ultimately, enhanced bioavailability would lead to more patient-centric solutions.

Additionally, enhanced bioavailability may enable the development of effective therapies that are compliant with regulatory access pathways, which currently restrict the maximum daily dose of API that can be administered to a patient.

## 4 What cutting-edge technologies are you exploring in this arena?

We want to create a CBD-based solid dosage form with significantly higher drug loading and an optimal pharmacokinetic performance – essentially a more patient-friendly therapy without compromising on effectiveness.

Currently, we're exploring and benchmarking a number of different drug delivery technologies – including liposomal and lipid nanoparticle-based delivery, amorphous solid dispersion technology and nano-emulsification-based solid dosage forms. The aim is to identify the best approach for enhanced CBD bioavailability.

**Dr. Zdravka Misic**
Innovation Project Manager, Pharma
dsm-firmenich

## 5 What have you discovered so far?

Preliminary results are encouraging. Our in-vivo research has already delivered promising results, as we have identified drug delivery technologies comparable to current leading liquid formulations.

For example, we've been able to develop a stable formulation with four times the drug loading of Epidiolex® – a cannabinoid-based treatment for epilepsy. It also supports two times higher drug loading compared to the current leading formulation in the entire cannabinoid space. Our continued work will inform us on which excipients and formulation technologies to take forward as viable candidates for clinical affirmation and eventual product development.

## 6 What is the benefit of this research for cannabinoid innovators?

Ultimately, our research will make a wider array of finished drug formats available in a market dominated by liquid applications, such as oils and soft gel capsules. Moreover, the technologies we are developing could benefit companies looking to overcome similar challenges in the minor cannabinoid sphere.

> In a market dominated by liquid formulations, we're breaking technical boundaries to bring patient-inspired solid dosage formulations to the field. We're presently developing a customized technology platform that will give companies the opportunity to enter the cannabinoid space with IP-protected formulations supporting **high drug loading, good physical and chemical stability** and **superior oral bioavailability.**

# **Key takeaways:** 4 reasons to innovate in the cannabinoid market

**The cannabinoid market holds significant untapped therapeutic possibilities. Yet there are still just a handful of approved pharmaceuticals on the market, highlighting the potential for innovation in the space.**

## 1 Promising applications in human health

Evidence surrounding the efficacy of cannabinoids – particularly CBD – continues to grow in multiple therapeutic areas. Even better – the full potential of the molecule is yet to be realized.

## 2 Potential to meet common, yet unmet patient needs

There is a rising demand for novel therapies to address a number of health indications. Take the rising burden of chronic pain as an example. Globally, 1 in 10 people develop chronic pain every year – and the prevalence is as high as 20-25% in some countries and regions. Pain is by far the most prevalent condition of those treatable with cannabis. However, no single cannabinoid drug has received widespread approval in the treatment of pain.

Scientific research is rapidly expanding to investigate the benefits of CBD in pain-related indications including cancer-related pain, musculoskeletal pain and fibromyalgia, where it may be able to provide temporary relief and improve sleep. One observational study found that 72% of patients with fibromyalgia are substituting conventional pain medications, like NSAIDs and opioids, for CBD products, despite limited CBD evidence. Most patients who substituted decreased or stopped using the pain medications altogether – the most common reasons being fewer side effects, improvements in health and better symptom management.

## 3 Growing physician and patient acceptance

There is an increasing number of referrals by healthcare professional each year, indicating greater familiarity and acceptance of medical cannabis among physicians. It is anticipated that there will be a further surge in positive outlook as medical cannabis gains traction as a treatment avenue, fueled by education and mounting evidence.[13,14]

## 4 Favorable regulatory landscape

Regulatory bodies, like the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) are increasingly recognizing the promise of cannabinoids molecules. They are taking steps to improve regulatory and patient access pathways for the lawful marketing of appropriate cannabinoid-based drugs, especially products developed using naturally-derived cannabinoids.

This has contributed to the approval of Epidiolex® for epilepsy and Sativex® for multiple sclerosis; better patient access to CBD-based therapies under prescription in several regions worldwide; and OTC drug pathways in selected geographies (Australia, South Africa).

# Glossary

| | |
|---|---|
| **Pharmaceutical cannabis-based products** | Formulated, processed or synthetic cannabis sold as a finished product after undergoing full clinical trials and holding a medical marketing authorization (e.g. Cesamet®, Sativex® and Epidiolex®). |
| **Medical cannabis** | A cannabinoid-based non-registered medicine (unlicensed) – and sold as an unlicensed medicine. |
| **Cannabinoids** | A group of bioactive compounds found in the Cannabis sativa plant or synthetic compounds that can interact with the endocannabinoid system. The cannabis plant produces approximately 80-100 cannabinoid molecules. |
| **CBD** | Cannabidiol (CBD) is one of the main cannabinoids which can be either synthesized or derived naturally from Cannabis sativa plants. CBD is non-psychoactive and exhibits wide-ranging properties that may benefit health and wellness. It is found in large quantities in hemp. |
| **THC** | Tetrahydrocannabinol (THC) is the other major cannabinoid present in cannabis. THC produces the "high" associated with ingesting cannabis. It is mainly found in the marijuana plant. |
| **Rare cannabinoid** | Also known as novel or minor cannabinoids, rare cannabinoids (CBx) are every other cannabinoid found in cannabis besides CBD and THC. As their name indicates, CBx are found in lower concentrations in the Cannabis sativa plant than the major cannabinoids. |
| **Natural vs synthetic CBD** | Natural CBD is derived from the Cannabis sativa (mainly hemp) plant. Synthesized CBD has been developed artificially but is considered to be chemically identical to naturally-occurring CBD. |

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# dsm-firmenich, supporting you at every stage of your cannabinoid drug development journey

**Continued investment in early-stage drug development is critical to uncovering new pharmaceuticals that will expand treatment options and benefit patient health.**

Together, dsm-firmenich and Brains Bioceutical are bringing progress to life in the cannabinoid market. Collectively, we offer a unique end-to-end innovation platform designed to unlock customized cannabinoid therapeutics for research and development – with a spotlight on exploring the science behind cannabinoids in promising indications, including pain management, stress and anxiety.

### About Brains Bioceutical

Our cannabinoid innovation platform is strengthened by our partnership with Brains Bioceutical – an evidence-based and science-led pioneer of cannabinoid solutions. Brains Bioceutical produces high quality, GMP-certified cannabinoid APIs to unlock new opportunities for research and development in the pharmaceutical industry and mitigate the risk of quality-related failure in clinical assessments. With a full range of licenses and registrations, its trial-ready cannabinoid portfolio provides confidence in scientific progress and product advancements.

BRAINS BIO®

## Our cannabinoid offering

- ✓ Robust cannabinoid API portfolio that is trial-ready, the highest quality and available in finished dosage form. Rich pipeline of minor cannabinoids also in development.
- ✓ The ingredient expertise and technical knowledge needed to overcome even the most complex formulation and application challenges to improve the performance of cannabinoid pharmaceuticals.
- ✓ Expert services at every step of the drug development journey, including the regulatory know-how and scientific services necessary to navigate the ever-changing cannabinoid market with confidence.
- ✓ A commitment to innovation, supported by a unique ecosystem of CDMOs and partners who enhance our in-house capabilities.

Ready to inspire the next generation of drug therapies?

Partner with dsm-firmenich to inform new possibilities for global patient health.

**Where others see cannabinoids, we see unlimited potential.**



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