**Flavor and taste modulation**
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# Improving patient compliance

## The use of innovative flavor tonalities and taste modulation solutions in drug development

dsm-firmenich

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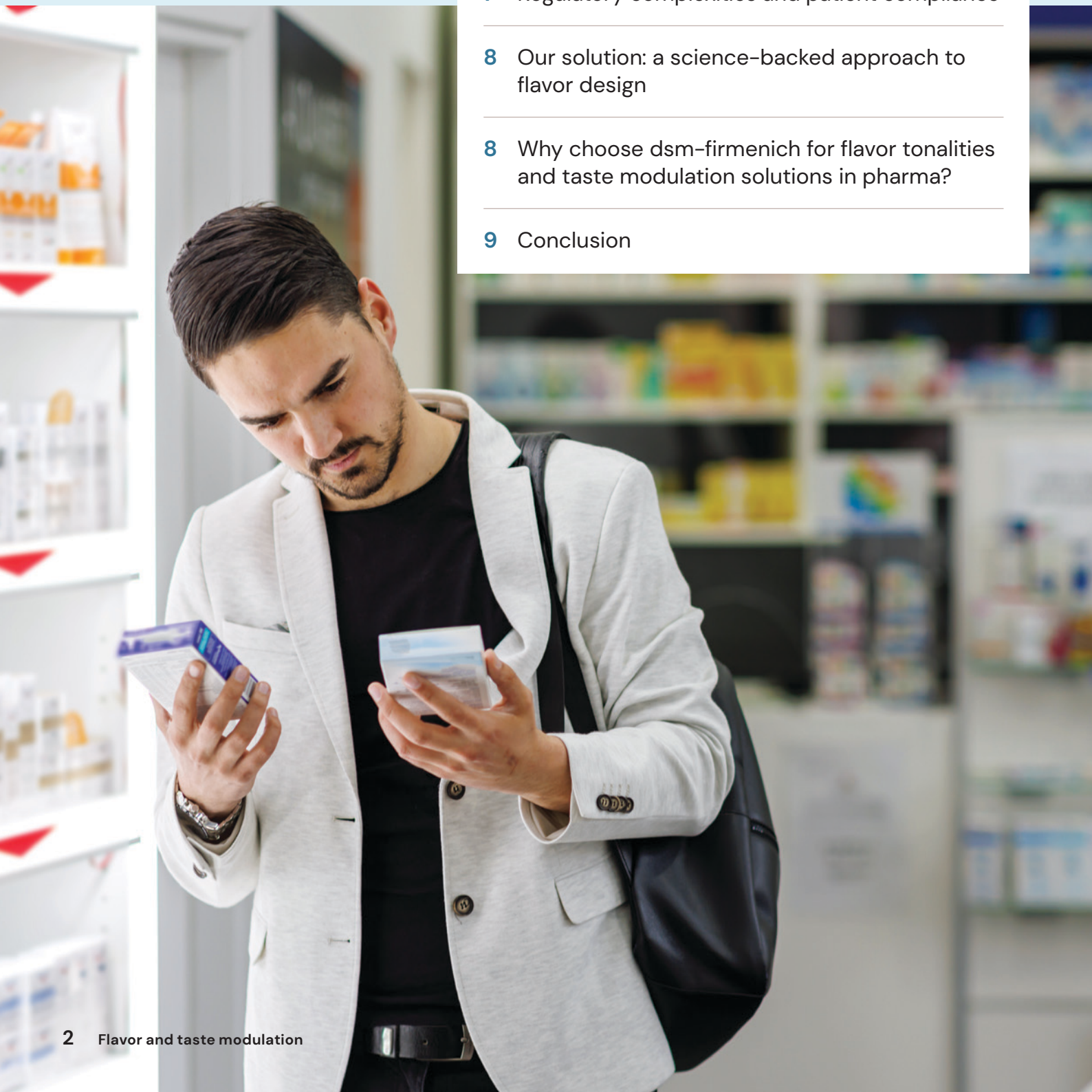

In recent years, the pharmaceutical industry has faced increasing pressure to develop patient-friendly dosage forms.

**The rise of pill fatigue – especially in chronic disease management – and conditions like dysphagia have significantly impacted patient compliance.**

Furthermore, there has been an increasing awareness of the need to tailor flavor profiles to specific groups, such as children, to help improve the palatability of medicines. Patients, particularly in these vulnerable groups, often refuse medication due to unpleasant tastes or difficulties in swallowing large pills or bitter liquids.[1-3]

Over 60 percent of active pharmaceutical ingredients (APIs) are inherently bitter,[4] while some can present with other unpleasant tastes or feelings in the mouth. This poses a significant challenge in drug formulation. Bitterness, in particular, can cause a strong aversion, leading to poor patient compliance rates and, consequently, suboptimal treatment outcomes. Non-adherence, whether due to taste or texture of medication, remains a major factor in treatment failure.

4 out of 10 consumers say taste is an important purchase driver for over-the-counter products.[5]

Flavoring agents have become crucial in pharmaceutical formulations to tackle the problem of bitterness. These innovations not only improve the palatability of medications, but also play a key role in ensuring that patients complete their prescribed treatments. Taste modulation strategies, from masking and enhancing flavors to advanced technologies like encapsulation, can improve patient compliance and treatment outcomes by developing more patient-friendly dosage forms.

# A focus on bitterness

The perception of bitterness is mediated by a family of taste receptors known as bitter taste-sensing type 2 receptors (TAS2Rs or T2Rs), which are part of the G protein-coupled receptor (GPCR) superfamily.[4] In humans, there are 25 known TAS2Rs, each tuned to detect a wide variety of structurally diverse bitter compounds.[6,7] Some TAS2Rs are broad spectrum, responding to many bitter molecules, while others are highly selective, recognizing only a few specific ligands. When a bitter API activates these receptors, it triggers an involuntary aversive response that can lead to immediate rejection of the medication, particularly in children and the elderly. This rejection is compounded when bitterness lingers or worsens as the medication dissolves in the mouth, causing a long-lasting negative experience. Even minimal levels of bitterness can significantly reduce patient compliance, especially in children.[2] Therefore, reducing or masking bitterness has become a critical focus in drug formulation. Understanding the molecular mechanisms of bitterness perception and how different APIs interact with TAS2Rs is key to developing effective flavor modulation strategies.[4,6,7,8]

# Opportunities to enhance formulations

**There are multiple approaches available to enhance the sensory experience of medications. These solutions can be tailored to address the specific bitterness profiles of APIs, as well as the sensory preferences of different patient demographics.**

## Flavor tonalities

Flavor tonalities are commonly used in pharmaceutical products to improve their taste, with flavors like citrus, vanilla, and mint the most popular as they are widely accepted across demographics. They must be carefully chosen to complement the sensory characteristics of the final formulation, and some tonalities can even help to make bitterness more acceptable by distracting from the unpleasant taste. Flavors can also be used as a healthier alternative to the sugar that has historically been added to sweeten pharmaceutical products – especially those aimed at children – as well as supporting natural product claims, which cannot be made when using artificial sweeteners.

## Taste modulation

Taste modulation technologies can change a person's perception of taste. These include:

- Bitter blockers: compounds that bind to TAS2Rs, preventing the API from activating them. By blocking the receptor directly, these agents inhibit the perception of bitterness at the source.[9]
- Bitter maskers: ingredients that modify the overall taste profile of the medication, masking bitterness through competing sensory inputs. For example, sweetness enhancers can be used to amplify pleasant flavors, thereby masking bitterness.
- Cognitive interference: these can improve the overall taste experience by distracting or suppressing off-taste by providing another interfering taste or mouthfeel.

## Sensates

Sensates, such as cooling or warming agents, can be added to medications to enhance their sensory appeal. These ingredients create a multisensory experience that can distract the patient from the unpleasant taste of the API or provide a sensation that complements the mode of action of the drug product; for instance, warming agents can provide a soothing effect on the throat in cough/throat products, and cooling agents can be effective in counteracting the bitterness of APIs.[10]

## Encapsulation

Encapsulation techniques, such as spray drying, can serve multiple roles in making dosage forms more patient friendly, including:

- protecting flavor compounds during manufacturing and storage, ensuring that the flavor has a longer shelf life;
- ensuring that the taste experience is prolonged if the dosage form stays in the mouth for a longer period of time, or is dissolved prior to administration and requires slow intake;
- helping to make sure that flavor components do not adversely interact with the API.

By integrating one or a combination of these approaches, it is possible to create solutions for formulators that allow them to produce products that are not only effective but also more palatable, ensuring better patient adherence to treatment regimens.

# Considering flavor solutions early in the drug development journey

**Flavoring and flavor profile needs should be taken into consideration during the earliest stages of the drug development process.**

By addressing taste challenges during the initial formulation, pharmaceutical companies can avoid costly reformulations and delayed market entry due to taste-related issues. Several critical factors must be taken into account:

- Demographics: pediatric and geriatric patients are particularly sensitive to certain flavors and textures. For example, children tend to prefer sweeter flavors, while the elderly may have imbalanced taste perception, making them more sensitive to bitterness or other offending notes like metallic. Additionally, flavor preferences can vary across different geographical regions and cultures.
- Regulatory requirements: regulatory standards vary significantly across different regions. They may impact the choice between natural and non-natural options. Other factors – such as halal, kosher, and allergen-free certifications – may also need to be taken into account, depending on the target market.
- Choice of technology: flavor solutions must be chosen depending on the product type and manufacturing process. For example, encapsulation can play a critical role in extending the shelf life of flavor compounds. It helps to protect them from degradation due to moisture, oxygen, or heat during product manufacturing or storage, and reduces chemical interactions between APIs and flavor molecules. Similarly, selection of the appropriate maskers, blockers, or tonality, can make a significant difference in the final flavor solution and ultimate patient experience.
- API interactions: the active ingredients in a drug must not be affected by the chosen flavor solutions. It is essential to ensure that the flavor components do not interact with the API in a way that reduces its efficacy or stability. This can be done by encapsulating the flavor, or designing the flavor composition to limit such interaction if encapsulation is not possible.

The choice of flavor in pharmaceutical formulations typically occurs once the broader formulation is established, usually around Phase II of clinical development. At this stage, safety assessments have been completed, and the formulation is sufficiently advanced that flavor selection can be aligned with the product's regulatory and therapeutic requirements. Considering flavors at this stage allows for a thorough regulatory review of the final excipients and enables palatability studies to be performed to evaluate patient acceptance. This ensures that the final drug product meets both regulatory standards and patient needs.

# Crafting the optimal flavor composition

**Designing the optimal flavor solution for a pharmaceutical product requires a systematic approach, beginning with a clear technical brief and followed by sensory evaluations to refine the flavor profile.**

**Step 1:** technical brief

The technical brief should outline the desired outcomes for the flavor profile, taking into account the API's sensory characteristics, the intended galenical form, the target patient population, and any relevant regulatory constraints. This brief serves as the foundation for the entire flavor development process.

**Step 2:** flavor selection

Flavorists work closely with formulators and marketing to develop the most appropriate solution that will address the API taste challenges while enhancing the overall sensory experience and ensuring fit with the targeted positioning or benefits.

**Step 3:** sensory evaluation

Sensory evaluations may be conducted with an expert panel of testers who assess the flavor profile of the medication in its final form. These evaluations take place in a safe and validated environment following a specific tasting protocol for APIs, which includes clear guidance for the tasting session to ensure patient compliance and safety. These studies are crucial in determining whether the chosen flavor effectively addresses the taste challenges and enhances patient acceptance. Adjustments to the flavor profile may be made based on feedback from these panels, ensuring that the final product meets both regulatory and patient expectations.

**Step 4:** final formulation

Once the flavor profile has been refined through sensory evaluations, the formulation is finalized and can progress to the next phase.

At dsm-firmenich, we guide our partners through every step of the flavor development process, from the technical brief to final formulation. Our expertise ensures innovative, tailored, and compliant solutions with improved palatability. These patient-friendly dosage forms help to increase patient compliance and elevate health with safe and effective therapies.

# Regulatory complexities and patient compliance

The global regulatory landscape for these solutions in pharmaceuticals is highly complex and region specific. Flavors are generally regulated under food regulations relating to the use of flavorings as ingredients. In Europe, Regulation (EC) No 1334/2008 defines flavoring substances as chemical compounds that modify or enhance the taste or odor of a product, and provides guidelines to ensure the safety, quality, and transparency regarding ingredients used.[11] In addition, the EU maintains a list of flavoring substances approved for use in food. Any flavoring or modifying substance used in a medicinal product must be on that list and meet safety criteria established by the European Food Safety Authority (EFSA).[12] The use of these substances is tightly controlled, especially in terms of purity and maximum allowable levels. In the US, the Food and Drug Administration (FDA) classifies flavors into four main categories: natural flavors; natural with other natural flavors (WONF); artificial flavors; and blended natural and artificial flavors, which has implications for the marketing and labeling of products.[13]

The European Medicines Agency (EMA) oversees the approval and use of excipients – including flavors – in drug products in Europe. These must be included in the marketing authorization applications (MAA) and must demonstrate that they do not adversely affect the safety or efficacy of the medicine. Similarly, the FDA in the US requires thorough evaluation to ensure that these ingredients do not interact with APIs or compromise the safety and efficacy of the drug. Flavoring substances usually have 'generally recognized as safe' (GRAS) status, so must be included in regulatory filings – like new drug applications (NDAs) – and must comply with safety standards.

In addition to these regional variations, pharmaceutical companies must also consider labeling requirements, such as the need to disclose certain flavor components or adhere to standards for allergens, organic status, vegetarian, or vegan. Navigating these regulatory complexities requires a thorough understanding of the legal frameworks in each market, as well as close collaboration with regulatory bodies.

# Our solution: a science-backed approach to flavor design

dsm-firmenich combines cutting-edge scientific research with decades of experience in flavor development to offer tailored solutions that address the unique challenges of pharmaceutical formulations. We have developed a rich palette of flavor tonalities that can be tailored to specific formulations, from core flavors like citrus, to more complex and on-trend options. Our patented technologies, resulting from industry-leading receptor-based research, are able to minimize the inherent bitter or metallic off-notes typically associated with APIs through precise flavor masking. Our portfolio also includes a spectrum of sugar reduction solutions – to hit the sweet spot while providing healthier profiles - and a range of sensates designed to enhance the patient's sensory experience.

Our expertise extends beyond flavor modulation to include advanced encapsulation techniques, which bring differentiated properties to the flavoring substances. By integrating these technologies into the early stages of drug development, we can help our clients to create patient-friendly formulations that meet both regulatory requirements and market expectations.


# Why choose dsm-firmenich for flavor tonalities and taste modulation solutions in pharma?

### Extensive portfolio:

Specialty ingredients including flavor tonalities, natural extracts, and taste modulators to meet specific formulation needs.

### Dedicated pharma teams:

Our company has years of experience in creating flavors for the pharmaceutical market, and our specialists are equipped with a deep understanding of pharmaceutical challenges.

### Global regulatory expertise:

We are well-versed in the nuances of regulatory standards across various regions, ensuring compliance and market readiness.

### Innovative technologies:

Our receptor-based discovery platform and encapsulation techniques offer unique solutions for masking bitterness and optimizing flavors release.

### Tailored solutions:

We can provide flavor solutions that meet the specific needs of your formulation, ensuring both patient satisfaction and regulatory robustness.

# Conclusion

Incorporating taste solutions early in the drug development process is crucial for a successful formulation design. By leveraging advanced flavor tonalities and modulation technologies, dsm-firmenich can help pharmaceutical companies create medications that not only deliver therapeutic benefits but are also pleasant to take. We invite you to partner with us to develop patient-friendly formulations that meet the highest standards of efficacy, safety, and compliance.

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