COVER STORY BY JEFF WORTHINGTON

The Yuck Factor

DISPELLING THE BITTER-SWEET MYTHS FOR DEVELOPING PALATABLE PHARMACEUTICALS

AS ANY PARENT WHO HAS ADMINISTERED OR struggled to give medicine to their infant or child can attest, eliminating or at least minimizing the "yuck factor" in the development of acceptable, age-appropriate formulations is an ongoing challenge for drug makers.

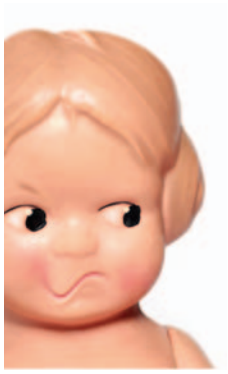
Many active pharmaceutical ingredients (APIs) are extremely bitter, which can make the development of palatable formulations daunting. Because palatability has never been the major sales driver in most therapeutic categories, the art and science of taste masking are not well imbued within the pharmaceutical industry. In the absence of this knowledge, the rich mythology of taste masking inevitably takes hold. It is time to dispel the fiction and half-truths of these myths,

which conspire to the development of flavor quality products that are unacceptable to many patients.

MYTH #1: FLAVOR PREFERENCE DETERMINES ACCEPTABILITY

The market for pediatric medicines continues to grow, with many experts forecasting quicker segment expansion than the market itself. [See "Pediatric Formulation Development is Experiencing a Welcome Growth Spurt," *PFQ*, August/September 2005, p. 20 and "How Sweet It Is: Reducing the Bitterness of Drugs," *PFQ*, September 2006, p. 24.]

In the United States, regulatory requirements and economic incentives have spurred pediatric research, enhancing our understanding of the appropriate use of medications in children. The FDA had already received 375 pediatric study requests from industry as of May 2005 and the agency had issued 300 written requests for pediatric studies. As a result, 113 drugs have been granted an additional six months of market exclusivity. Legislation currently advancing through the European Parliament builds on the U.S. regulatory experience and is expected to contribute to continued growth of the pediatric market.



When it comes to orally delivered medicine, most consumers are looking for an acceptable taste, which generally translates to drug products with moderate sensory characteristics – not too bitter, hard, gritty, chalky and irritating. Whether the formulation is orange, cherry, grape or mint-flavored is not as important as the lack of these negative attributes. In other words, it is the overall sensory quality of the product — not the type of flavor — that is the primary determinant of acceptability.

Another major driver is consumer accessibility to a seemingly limitless variety of foods and beverages, representing a myriad of aromas, flavors, colors and textures. Foods and beverage choices are based on a complex set of factors, including hunger and thirst, time-of-day and occasion, type and level of activity, health and wellness considerations, indulgence and reward, and countless other factors.

Despite this enormous variety, most consumers can easily identify their favorite flavor of many foods and beverages – from ice cream and chocolate to juice and soda to barbeque sauce and condiments. Thus it would seem natural to think in terms of favorite flavor of medicine. But when patients, few consumers look forward to taking their medicine, and flavor choices, particularly for prescription medications, are limited or nonexistent as most companies work to develop a single formulation suitable for worldwide marketing.

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The more appropriate questions to ask at the early development stage are related to the API and the targeted patient population. What are the critical sensory attributes of the API? How strong are these attributes? Do they linger, and if so, how long? Answers to these questions provide an indication of the magnitude of the taste masking challenge. This reveals whether a traditional excipient development approach is likely to yield a palatable formulation or whether another technology solution such as encapsulation or complexation should be considered at the outset.

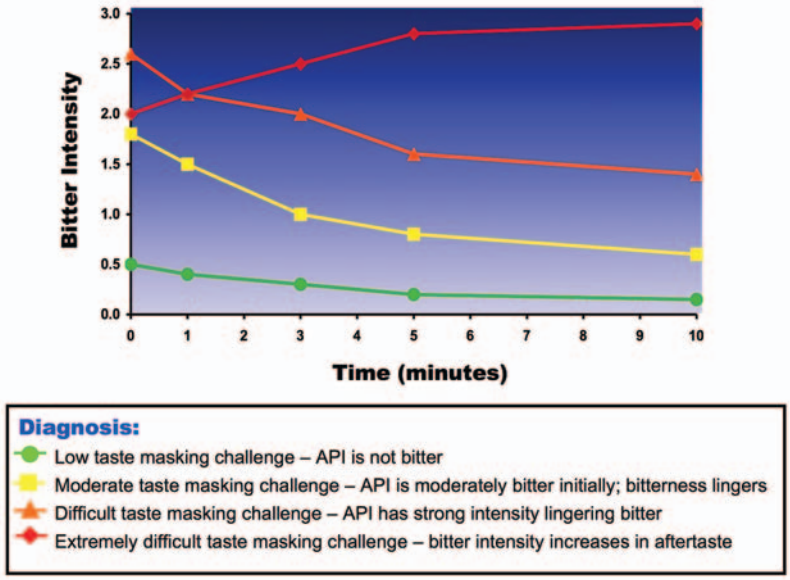
Similarly, answers to a number of important questions regarding the targeted population inform the direction of development of a patient appropriate and palatable drug product. These relate to the condition – acute or chronic, dosage form, dosing frequency and amount, demographics and food effects.

MYTH #2: TASTE IS SUBJECTIVE AND CANNOT BE OBJECTIVELY MEASURED

Optimizing the sensory attributes of products is the top priority of food and beverage companies, while pharma companies appropriately focus on the medical benefits of their products.

The unique selling proposition of these products is so completely different as evidenced by the language used in direct-to-consumer advertising. For drugs it's "effective," "mild side effects," "fast acting" and "long lasting." Contrast this to foods and beverages where it comes down to "great taste," "refreshing,"

Figure 1. **FlavorMetrics℠ Bitterness Profile**



Source: Senopsys LLC

"satisfying," and "convenient."

Just as the pharma industry has developed sophisticated methods for chemical analysis, the food and beverage industries have designed robust sensory analysis techniques. In addition there's little natural interchange between the pharma and food/beverage industries, so it's not surprising that pharmaceutical professionals are generally unaware of the sensory analysis methods available for use in guiding formulation development.

Affective and analytical are two major classifications of sensory tests. Affective tests determine consumer response to products, while analytical tests measure the perceived sensory attributes of products. Affective tests are usually commissioned by market researchers and include preference and hedonic (liking) tests to compare products. These tests support product launch decisions, and product positioning, including advertising claims.

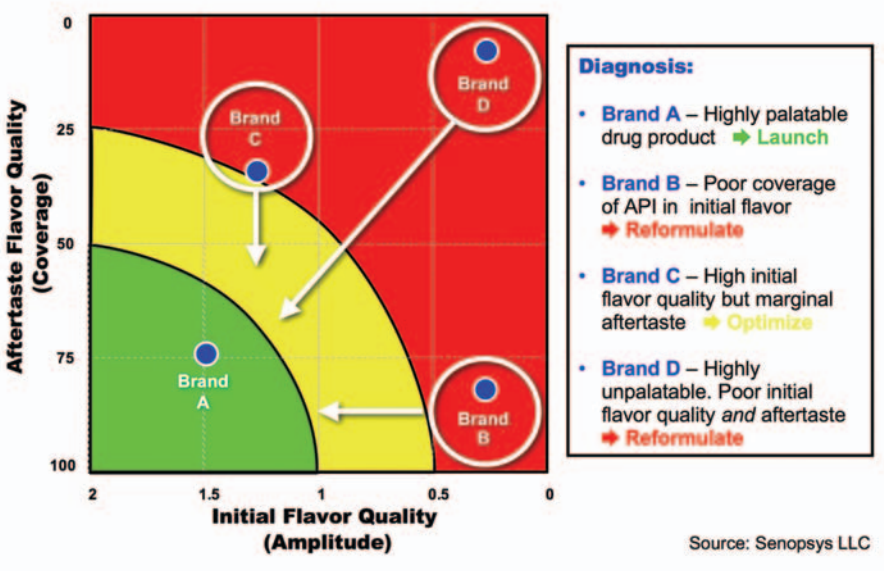
Analytical tests are used in the evaluation of product differences and similarities under controlled laboratory conditions to identify and quantify perceived sensory characteristics. Analytical tests include discrimination tests, grading tests, ratings by expert tasters, and descriptive methods such as the flavor profile. The descriptive methods have the greatest applicability to the development of palatable pharmaceuticals.

The ASTM International Committee E-18 on Sensory Analysis of Products and Materials publishes a set of standard practices, guidelines and methods important references for anyone involved in formulation development. Sensory analysis of pharmaceuticals naturally involves human exposure to drug substances and therefore proper precautions most be taken to ensure the safety and well-being of the evaluators, including Good Clinical Practices for Investigational New Drugs. So called "sip and spit" tasting protocols are recommended to minimize human exposure of drug substances as is the use of Generally Recognized as Safe (GRAS) mimetics or surrogates for the API during the development process. Additionally, *in-vitro* techniques like the "electronic tongue" may be used provided that a correlation has been established between the human taste panel and instrument responses for the specific API, though the current experience base is limited.

MYTH #3: ALL WE NEED IS THE RIGHT FLAVOR

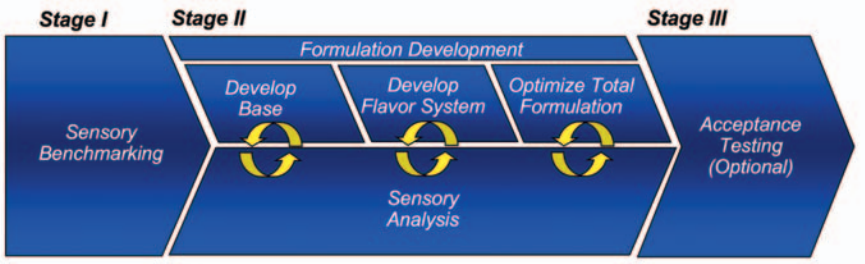
The myth of flavor preferences (#1) inevitably leads to the search for a silver bullet – that elusive flavoring material or other excipient that will effectively mask the bitterness or other negative sensory attribute of the API. The old saying that goes "for every complex problem there's a simple answer" is wrong. Unfortunately, the same is true for most pharmaceutical formulations where palatability is governed by the judicious selection and optimization of all the excipients – not just the flavoring materials. It's the overall sensory quality of the formulation that matters,

Figure 2. **FlavorMetrics℠ Palatability Profile**



Source: Senopsys LLC

Figure 3. **Sensory-Directed Development Process**



- Characterize API
- Quantify taste masking challenge
- Establish flavor quality target

- Develop palatable formulations that meet established target
- Sensory analysis of prototypes is used throughout this step to provide formulation guidance.

- Conduct patient/consumer acceptance testing to:
  - Verify acceptability
  - Select preferred prototype

Source: Senopsys LLC

not the flavor type listed on the label.

But what is flavor quality and how is it measured? To properly address these questions, it's important to review some basic concepts. Flavor is a combination of taste (gustation) and smell (olfaction). Taste is perceived through stimulation of the taste buds on the epithelium of the tongue. Historically, four basic tastes were thought to exist – sweet, sour, salty, and bitter. Recently researchers have advanced the concept of a fifth basic taste, known as "*umami*," which in Japanese means "mouth filling" or savory effects of monosodium glutamate and some amino acids, such as glutamates.

Odors are perceived through stimulation of the olfactory epithelium, which contains receptor cells and the free nerve endings of the trigeminal nerve. The olfactory receptor cells lie in the upper reaches of a small area of the nasal cavity, called the olfactory epithelium. Odors are perceived through two different routes—smelling directly through the nose (orthonasal) or during gustation when the volatile odorous molecules reach the olfactory center through the nasopharyngeal passage (retronasal). Thus when a consumer describes his or her favorite flavor, they are more properly referring to the product's odor or aroma. While it seems like semantics, this has important implications in the development of palatable pharmaceuticals.

To illustrate the concept – try this simple exercise with a Lifesaver or other brand of hard mint. While holding the nostrils closed with one hand, lick the mint held in the other hand. Most consumers will be able to identify a sweet basic taste but will not be able to identify the type of mint, specifically as peppermint, spearmint, double mint (peppermint and spearmint) or wintergreen as the volatile aromatics cannot make their way to the olfactory region. If this exercise is repeated, but this time releasing the nostrils while licking the mint, the volatile aromatics will make their way through the nasopharyngeal passage where they will be perceived and recognized as mint.

So why is the distinction between basic taste and aroma important in pharmaceutical formulation? Many drug substances are bitter and yet as previously described, several of the palatability myths are related to the aromatic flavoring materials that can be added to formulations in an effort to improve palatability (e.g. orange, cherry, grape and mint). Understanding the physiology of taste and smell, one would not expect an aromatic flavoring material to mask a basic taste, bitter or other. Perhaps the greatest myth of all is that taste and smell are the same.

The flavor quality of a drug product is fundamentally related to the perceived blend of the product's sensory characteristics. Many drug substances are bitter and the perceived bitterness "stands out" from the other basic tastes – sweet, sour, salty. If the basic tastes are balanced through the proper selection and use of complementary excipients, then the bitterness of the drug substance will not be distinctly perceived and consequently the drug product will be considered more palatable. The same concept applies to other basic tastes as well as trigeminal effects and odors. The key is to blend away the negative attributes.

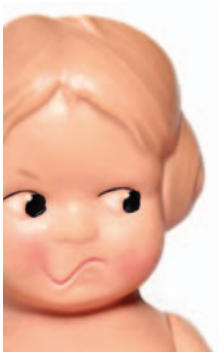
Patient acceptability of drug products is a function of both the initial flavor quality (i.e. first 10 to 20 seconds following ingestion) and the aftertaste (i.e. 1 to 10 minutes following ingestion). Get one of them wrong and palatability suffers.

Palatable pharmaceuticals have a flavor that develops rapidly and is full bodied and well balanced or blended. This requires several compatible elements in the proper proportions, perceived in the proper order, and supported by a complex body of underlying sensory impressions not separately identified. The flavor systems of many oral pharmaceuticals are very simple and thin, providing poor coverage of the active initially and in the aftertaste. Contrast this to Coca-Cola, for example, which is comprised of hundreds of individual flavoring components, but consumers are hard-pressed to be able to describe any of them individually. The components are very well blended. Unlike most foods and beverages, the challenge for pharmaceuticals is to blend away" the negative sensory attributes of the drug substance, while simultaneously minimizing the number of excipients in the formulation. Amplitude, an attribute measured using the flavor profile method, is an integrative measure of balance and fullness. Amplitude is an overall measure of the quality of the initial flavor and has been shown to correlate with patient palatability and acceptance.

The degree of coverage of the "negative" sensory attributes a minute and longer following ingestion is the key measure of the flavor quality of the aftertaste. For many APIs, the aftertaste is most critical as many flavor systems provide adequate coverage in the early aftertaste but these beneficial effects quickly decrease, exposing the API. As a general rule it is easier to mask a strongly bitter API that "fades" quickly (steep decay curve) versus a moderately bitter API initially that lingers well into the

aftertaste (flat decay curve) or worse, an API with bitterness that builds. The challenge for the formulator is to mask the taste of the active throughout the duration of the aftertaste—be it 30 seconds or 30 minutes. The relative challenge of four APIs is illustrated in Figure 1.

As mentioned earlier, patient acceptability of drug products is a function of both the initial flavor quality and the aftertaste. It is critical that both be properly addressed otherwise palatability will suffer. When it does, patient compliance and health outcomes suffer, as do product sales. This concept is illustrated in the drug palatability profile shown in Figure 2, where initial flavor quality (Amplitude) and aftertaste flavor quality (API Coverage) are plotted together. Decision boundaries have been overlaid to translate flavor quality to patient palatability and expected compliance and several examples highlighted. This type of framework is widely used to guide formulation decision making during clinical and commercial development.



In the pharma industry where sensory analysis is not a core competency, it's not surprising to find formulators using a "trial and error" approach to develop palatable formulations. In this approach, formulators source individual flavoring materials, drop them in to the formulation and informally (and unofficially) taste the resulting prototypes. In the absence of proper sensory analysis training, the feedback is typically degree-of-liking ("yuck factor"), with the results from multiple evaluators winding up confused at best and often conflicting.

MYTH #4: THERE IS NO PROCESS FOR DEVELOPING PALATABLE PHARMACEUTICALS

Consumers have little difficulty telling whether they like or dislike a product, or which product they prefer. However, their ability to reliably describe the reason for their likes, dislikes and preferences and more importantly to offer meaningful suggestions for improvement is notoriously poor. In the pharma industry where sensory analysis is not a core competency, it's not surprising to find formulators using a "trial and error" approach to develop palatable formulations. In this approach, formulators source individual flavoring materials, drop them in to the formulation and informally (and unofficially) taste the resulting prototypes. In the absence of proper sensory analysis training, the feedback is typically degree-of-liking ("yuck factor"), with the results from multiple evaluators winding up confused at best and often conflicting. In the food and beverage industries, this is referred to as "cook and look" formulation development, an approach widely regarded as being both ineffective and inefficient. In pharma this approach yields palatable formulations for only the most innocuous APIs.

What then is an appropriate alternative? Developing palatable pharmaceuticals requires a solid understanding of the principles of flavor construction adapted from the food and beverage industries. The sensory-directed process depicted in Figure 3 was honed through decades of experience in the highly competitive food industry where taste is paramount. This approach has been successfully applied to create hundreds of palatable oral pharmaceuticals and could represent "best practice" for the pharma industry. As the name implies, sensory analysis is used throughout the process, taking appropriate measures to minimize human exposure to drug substances as described earlier. The results are interpreted for initial flavor quality and aftertaste flavor quality using the drug palatability profile. It's also worth noting that many companies find it useful to include the results for one or more commercial products of competitive interest on the drug palatability profile to gain insight as to relative flavor quality. This information can be used to support a decision to "finalize" the formulation or gauge the likelihood of developing palatability claims, e.g. 83 percent of children prefer the taste of Brand A to Brand B.

Most pharma companies have only an infrequent need to develop palatable formulations – and when they do, the challenges can seem daunting. Understandably, organizational knowledge of appropriate development approaches, methods of analysis, tools and techniques is diffuse at best and frequently nonexistent. Confounding the situation is the rich mythology of taste masking, whose fiction and half-truths conspire to the development of low flavor quality products with poor acceptability and compliance.

Consumer packaged goods companies have developed scientific processes, methods, and tools for creating products that can be differentiated based on customer-perceived sensory quality. This sensory-directed approach represents a potential "best practice" for pharmaceutical companies faced with overcoming the challenge of reducing the bitterness of medicine. *–PFQ*

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