stability

Ensuring stability in pharmaceutical and dietary supplement manufacturing

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This article discusses the costs and consequences of instability in pharmaceuticals and dietary supplements and describes several methods and practices manufacturers can use to ensure the stability of their raw materials and final products.

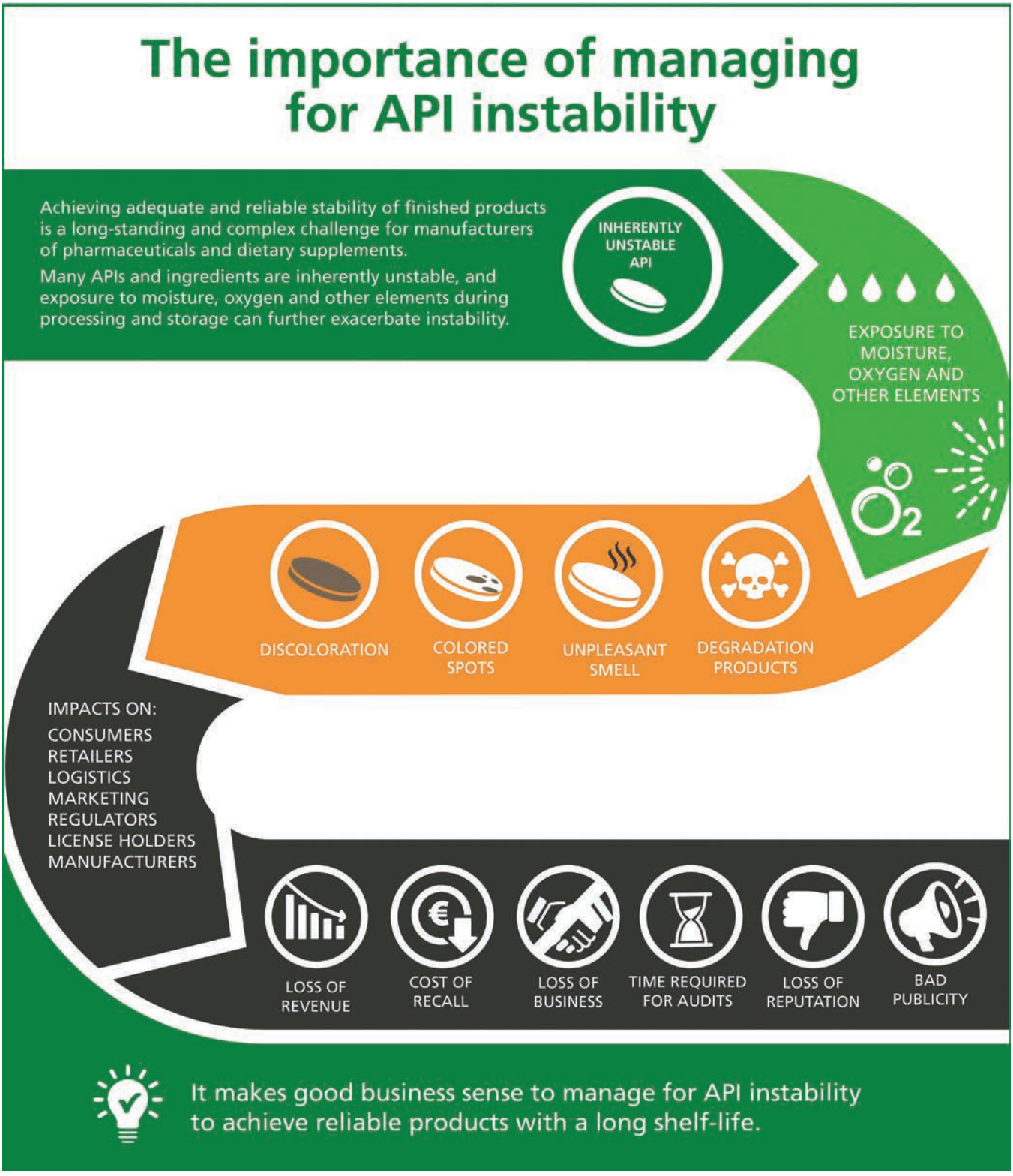
Achieving adequate and reliable stability of finished drug products is a long-standing and complex challenge for manufacturers of pharmaceuticals and dietary supplements. Many active pharmaceutical ingredients (APIs) and other ingredients are inherently unstable, and exposure to moisture, oxygen, and other elements during processing and storage can further exacerbate instability. Unsuitable storage conditions or poor handling of intermediate materials during manufacturing can also have an impact. After manufacturing,

use of the right packaging materials is essential to maintaining the stability of the final product.

While challenging, ensuring stability is critical to ensuring a medicine's safety or efficacy and to preventing some dietary supplement products from developing an unappealing smell, taste, or appearance. As shown in Figure 1, manufacturers have many incentives to avoid stability issues, not least of which is that any negative experience, particularly with an over-the-counter (OTC) product, will likely strongly influence a consumer's future purchasing choices.

Given that around half of all consumers experience difficulty swallowing tablets and capsules or simply dislike taking them, demand for alternative dosage forms is increasing. Chewable and effervescent tablets, instant drinks, and orally

Figure 1



disintegrating granules (ODGs), for example, are easy to swallow and convenient to take but can be more prone to stability issues than conventional tablets and capsules, posing a problem for manufacturers. For example, effervescent tablets must dissolve quickly and completely in water so patients can take their medicine without having to swallow a tablet. As a result, they have an inherent sensitivity to moisture that creates a need to control the humidity in their environment during manufacturing and storage.

In addition to responding to patient and consumer preferences and providing a positive experience, manufacturers must also update their approaches to meet regulatory demands. Regulations are becoming increasingly stringent, as evidenced by strict shelf-life specifications and decreasing tolerance levels for unwanted chemicals and impurities that result from a breakdown of intermediate materials or final products (otherwise known as degradation products).

In the face of these collective pressures, investment in improved product stability is not a "necessary evil" but rather a smart business decision that enables pharmaceutical companies to remain competitive. This article will explore some of the many technologies and approaches for overcoming instability issues.

Costs of instability

While safety and efficacy are key priorities for manufacturers, they are not the only reasons for ensuring that products are stable. Poor or variable stability can result in an unappealing product appearance (such as brown spots) or smell, affecting user experience, reducing compliance, and likely impacting future purchasing choices by patients and consumers.

Perhaps more significantly for manufacturers, product instability typically indicates a failure to meet strict regulatory guidelines. Regulatory bodies clearly define acceptable limits for degradation products and are often trying to reduce these limits further. If the amount of degradation product exceeds the strict quantity limits within a product's defined shelf life, the product may be recalled to mitigate the risk to patients or consumers. Manufacturers consider such an event a worst-case scenario, not only because of the potential risk to patients or consumers, but also because of the costs and negative consequences that can occur downstream.

Following a batch or product recall, manufacturers are required to submit their products for stability testing more frequently; specifically, they must test one batch of every product made for stability every year. If any tested products fall out of specification, the company must immediately notify regulatory bodies and evaluate the problem to determine the likelihood of any safety issues. Further batches may be recalled if product quality is deemed to be of sufficient concern.

A company that has experienced a recall event will suffer financial and reputational damage. Immediate costs will result from lost sales of the recalled product as well as from the recall process itself, which includes costs for logistics, destruction of the recalled batch, and labor. In the long term, bad publicity will result in further lost sales as distrusting customers seek alternative products and doctors become reluctant to prescribe the recalled brand. Additional long-term costs may result if the company decides to switch to an alternative outsourcing partner for manufacturing.

Ultimately, extending a product's shelf life is a way to gain a competitive advantage. For practical reasons, a minimum shelf life of two years is required for solid-dose medicines and dietary supplements. However, marketing departments are increasingly seeking shelf lives of three years or longer. For both medicinal and dietary supplement products, logistics, distribution, sales, and retail are all easier to manage when the product has a longer shelf life.

Increasing stringency even in the absence of safety risk

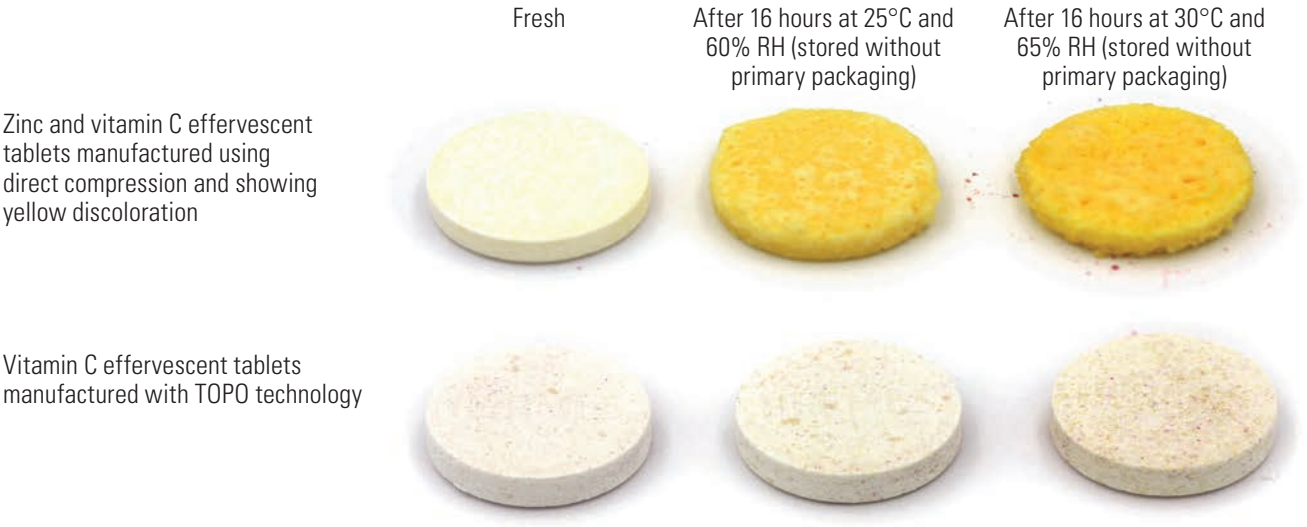
The need to test for and measure degradation products and impurities that may compromise product safety or efficacy is unquestionable. For instance, some degradation products resulting from poor stability may be associated with detrimental effects and should, therefore, be limited. However, not all degradation products are regulated using the same rationale. Manufacturers are required to specify and limit the amounts of all degradation products present—even those that don't pose a safety risk. For example, the degradation products of caffeine are harmless and exist naturally in the cups of coffee that people consume constantly on a global scale. However, for an oral dosage product that incorporates caffeine as an active ingredient, such as a pain reliever with aspirin, regulatory authorities tolerate only very small amounts of caffeine degradation products despite the absence of a safety risk.

Atmosphere filling is an established method that significantly increases omega-3 stability and creates a product with an improved shelf life more suitable for the market.

If tightening regulatory guidelines are any indication, stability is likely to become a more important consideration in the future. Regulatory bodies are becoming less tolerant of impurities and degradation products, even in well-established products such as aspirin, where manufacturing methods might be assumed to be fixed. Consequently, regulators often ask companies to tighten their acceptance criteria for impurities when evaluating new product registrations. Addressing such requirements requires significant time and resources and can be a source of frustration when the rules seem irrational or ambiguous. To minimize impurities and meet strict requirements, manufacturers must establish even

Figure 2

Comparison of effervescent tablets manufactured using direct compression versus TOPO granulation when stored unprotected under different conditions



more sensitive and specific analytical tests, which create additional analytical challenges.

Controlling the atmosphere to minimize instability

Many consumers regularly take dietary supplements to improve their health and wellbeing, but such habits can be quickly broken by a negative experience. Omega-3 fatty acid supplementation in the form of fish oil (or algal oil for vegetarians) is common for both adults and children. Omega-3 fatty acids are composed of alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), all of which are considered essential fatty acids integral to many critical functions [1].

Inconveniently, omega-3 fatty acids are prone to releasing a fishy, rancid smell when exposed to and degraded by oxygen or light; even the slightest amount of degradation can result in the unpleasant odor. Children in particular are sensitive to tastes and smells, so such degradation is problematic. Omega-3 consumption is also associated with "fishy burps," which can occur after swallowing the supplement in capsule form. Such an experience is unwelcome, particularly as many consumers dislike swallowing large capsules in the first place.

Manufacturers can avoid the occurrence of these unpleasant experiences by producing omega-3 supplements in a user-friendly dosage form. ODGs packaged in a small sachet provide a more user-friendly experience for the consumer, but they also represent a novel challenge for manufacturers navigating how to minimize degradation across a range of product forms.

Controlling the manufacturing atmosphere is key to improving the stability of omega-3 ODGs. In an approach known as atmosphere filling, oxygen-sensitive APIs, such as omega-3s, are manufactured in an inert, nitrogen-filled atmosphere free from oxygen. Atmosphere filling is an established method that significantly increases omega-3 stability and creates a product with an improved shelf life more suitable for the market.

A stability study at pharmaceutical standards (36 months at long-term conditions of 25°C/60% relative humidity (RH), 12 months at intermediate conditions of 30°C/65% RH, and 6 months at accelerated conditions of 40°C/75% RH) was conducted with an ODG containing omega-3 acids (sum of EPA and DHA: 100 milligrams) manufactured using inert atmosphere filling. The study showed that the product was stable under all conditions over the entire length of the investigated time span. In contrast, the same product manufactured under normal atmosphere (in the presence of oxygen) became appalling in terms of taste and odor within weeks, even when stored at long-term conditions.

Companies considering outsourcing the manufacture of products requiring inert atmosphere filling must ask the following questions when selecting an outsourcing partner:

- Is the potential manufacturing partner experienced in handling nitrogen?
- If not, do they know how to modify their equipment and processes to make this possible while also securing staff safety?
- Are they aware of the special handling considerations required for oxygen-sensitive raw materials?

Handling omega-3 raw materials immediately or soon after opening is important, but this requirement can be overcome by using precautionary measures, such as creating a nitrogen "seal" to exclude oxygen once drums have been opened. Partnering with a contract manufacturer that is confident about nitrogen filling and about working with nitrogen in general can help avoid costly and avoidable product degradation.

Harnessing technology to stabilize ingredients and APIs

Effervescent aspirin tablets are another example of a user-friendly product with inherent production challenges. Aspirin in any form is highly sensitive to moisture and, as previously mentioned, the same can be said for effervescent tablets. The degradation products of aspirin are salicylic acid and acetic acid—the latter of which is known for its sharp and undesirable vinegar smell. Effervescent aspirin tablets present particular stability challenges and require tailored technologies to prevent customers from encountering aspirin products that smell like vinegar.

Specialized wet granulation methods can ensure the stability of effervescent tablets by enabling the production of more stable effervescent bases compared to other common tableting techniques such as direct compression. For example, Hermes Pharma's proprietary TOPO granulation method uses a vacuum granulation step to produce a homogeneous, moisture-resistant granulate, which can be easily processed into a tablet form.

Such methods not only improve the stability of effervescent aspirin tablets—as assessed by testing of products under long-term and accelerated conditions—but also enable the stable production of other medicines that could not be achieved in effervescent form otherwise, such as cimetidine, ranitidine, ambroxol, and acetylcysteine. Specialized granulation techniques have also enabled the production of tablets free from discoloration, a common moisture-related problem encountered with effervescent tablets produced using direct compression. Brown spots are a disconcerting sight on tablets, so their absence is welcomed by manufacturers and consumers alike (Figure 2).

For dosage forms such as ODGs, hot melt coating is a key technique for improving the stability of products prone to unwanted discoloration. For example, when exposed to oxygen, ascorbic acid (vitamin C) ODGs become covered in brown spots. Hot melt coating prevents such discoloration because the coating material is melted prior to its application and forms a lipid layer around the ascorbic acid particles, protecting them from environmental oxygen.

Creating the right environment

Managing the environmental conditions within a manufacturing facility is important for minimizing potential instability issues as well as for optimizing efficiency. For example, applying UV filters to glass windows can help protect UV-sensitive APIs. Air conditioning is also critical for maintaining a low humidity level for moisture-sensitive APIs and ingredients.

Packaging is another important consideration for maintaining the stability of certain products during transport and storage. Such packaging should minimize exposure to moisture, oxygen, and/or UV light as needed, and it may be necessary to package each dose in isolation. Optimizing packaging involves choosing the right material, such as polypropylene or aluminum tubes, PET, or paper aluminum foil, and considering additional features, such as tubes with stoppers that contain a water-absorbing molecular sieve. Many packaging options are available that both optimize product stability and provide user-friendly features, making the product convenient and easy to open.

Optimizing logistics and quality control

When dealing with raw materials, intermediate ingredients, or final products that are easily degraded upon exposure to certain physical conditions, it is necessary to take logistical considerations into account. Planning is key to reducing the amount of time materials are exposed to moisture, light, and oxygen, for example. The goal is to minimize exposure time between weighing raw materials and blending as well as between blending and filling.

To minimize exposure time, consider the ingredients' bulk-holding periods when booking time slots for equipment. Raw materials typically must be used within weeks or months of opening, but this time frame can be significantly shorter for sensitive APIs. For instance, bulk holding times for omega-3s should not exceed one to two days. Effective production planning is critical to avoid wasting material. Timing is also important when ordering new raw materials for a campaign.

Where possible, use internal quality control checks to further improve the chance of success. For example, using accelerated stability tests ensures confidence in product stability, particularly for products that are highly sensitive to moisture and other elements.

Laying a foundation for success

As consumers demand greater levels of convenience in all aspects of their lives, pharmaceutical and dietary supplement manufacturers face increasing pressure to deliver easily consumable, user-friendly products. But delivering these products to the market requires effective stabilization strategies. Approaches to ensuring stability vary widely depending on the APIs, the ingredients being used in the manufacturing process, and the selected dosage form. ODGs, effervescent tablets, and instant drinks are just a few examples of user-friendly alternatives to conventional tablets and capsules, but each has its own production challenges. Product stability has always been and will always be a challenge, but prioritizing stability is a smart business decision and can be greatly complemented by the application of expert knowledge and appropriate technology during process development or improvement. With this combination, consistent,

high-quality production is within reach, enabling consumers and regulatory bodies to trust your product and processes, which is key for ongoing commercial success. *T&C*

Reference

1. National Institutes of Health, Office of Dietary Supplements. "Omega-3 Fatty Acids: Fact Sheet for Health Professionals." 2017. Accessed October 30, 2020. ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/.

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