Minimizing Time to Market: Developing Consumer Health Products under the U.S. OTC Drug Monograph

By Troy Harmon, MS, MBA, Vice President, Business Development

Recent studies have cited the cost of bringing a new prescription drug to market at approximately $1 billion (Adams and Brantner, 2010), although estimates as high as $1.8 billion have been reported (NIH/NIMH). The time and cost involved in this process—which requires submission of a New Drug Application for Food & Drug Administration (FDA) approval—can be significant hurdles in a slow economy with limited financial resources. Development of more convenient dosage forms, by applying novel drug delivery technologies, is a common practice in both the prescription and consumer health industry as a means of broadening market uptake and extending a product’s lifecycle. U.S. retail sales of OTC medicines in 2009 (excluding Wal-Mart) were $16.9 billion. By far the top OTC sales categories for 2009 were cold/cough/allergy-related ($4.2 billion), followed by internal analgesics ($2.5 billion). (The Nielsen Company, 2010.) In addition, many of these OTC products fall under what is called the “OTC Drug Monograph”, a set of regulatory standards set forth by the FDA that dictate how certain active ingredients can be used in OTC medicines. By developing a novel OTC product that complies with an existing OTC Drug Monograph, consumer health companies can often shorten the time—and cost—involves in bringing a new OTC product to market.

The OTC Drug Monograph: How it Works

Drugs considered as “over-the-counter” (OTC) are generally recognized as safe and effective (GRASE) for use by the general public without a prescription. There are more than 80 therapeutic categories of OTC drugs, ranging from acne products to weight control products, and the FDA’s Center for Drug Evaluation and Research (CDER) oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks. (FDA Center for Drug Evaluation and Research, www.fda.gov.)

With the tightening of R&D budgets and increased pressure from financial stakeholders, the pharmaceutical industry faces a great challenge in bringing profitable drug products to market both quickly and efficiently. Specialty pharmaceutical company Eurand maintains that, by choosing to develop new and patient-friendly dosage forms of products conforming to an existing OTC Drug Monograph, companies may be able to reduce the time and cost involved in taking a new product to market. Eurand discusses how the OTC Drug Monograph guidelines work, using Unisom® Sleepmelts™ as a case study to illustrate how innovation and creativity can be used to maximize resources while minimizing time to market.

In addition, established in 1972, the OTC Drug Review Program evaluates the safety and effectiveness of OTC drug products originally marketed in the U.S. prior to May 11, 1972. For such drugs, a three-phase public rulemaking process managed by CDER results in the establishment of standards, known as monographs, for an OTC drug in this category. The monographs outline the conditions under which certain OTC drugs are considered safe and effective—a veritable “recipe book” that includes ingredients, doses, formulation and testing requirements, and labeling standards that are acceptable for the marketing of OTC products containing the “monograph” drugs. Generally, as long as a company can show that its OTC drug product conforms to one of these monographs, it may be marketed without further FDA clearance; those that do not, however, must undergo full review and approval through submission of an NDA, and thus incur the high costs and lengthy approval delays associated with the NDA process.

While it is not required that drug products marketed under an OTC drug monograph receive pre-approval from the FDA, it is quite common for companies to seek guidance in order to ensure that the product they intend to market under the drug monograph is compliant with the regulations. These companies may choose to consult with the Division of Nonprescription Regulation Development (DNRD) prior to going to market. If a drug product is determined not to comply with the drug monograph, then an approved NDA is necessary prior to marketing the product. In any case, consulting with DNRD could aid in avoiding any potential pitfalls and resulting loss of time in the go-to-market process.
Launching Products Utilizing OTC Monograph

Products launched under the OTC monograph often provide patients with the value of a newer, more “patient-friendly” dosage form. While prescription drug products often need to provide a proven therapeutic benefit in order for payers to grant reimbursement—a task that can be more difficult to demonstrate—the value proposition for OTC products can lie in fulfilling a patient need, or providing the appeal of key attributes such as convenience or taste. There is ongoing demand for “improved” dosage forms that make these products easier to swallow, allow for faster dosing, and/or improve organoleptic characteristics by taste, masking the bitterness or chalkiness commonly perceived by patients when taking these drugs. By far the most targeted categories of OTC drug products for the application of these novel dosage forms are the same top-sellers mentioned above: cold/cough/allergy products and internal analgesics (Table 1). Another segment within oral healthcare products that has benefitted from new delivery vehicles is the nighttime sleep aids segment.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Product</th>
<th>Marketed By</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>Benadry® Fastmelt™ Dissolving Tablets</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Benadry® Perfect Measure, Pre-Filled Spoons</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Dextromethorphan HBr, Guaifenesin USP</td>
<td>Robitussin® DM Adult Cough &amp; Chest Congestion To Go</td>
<td>Pfizer/Wyeth</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>Mucinex® Junior Expectorant, Mini-Melts Bubble Gum</td>
<td>Reckitt Benckiser Inc.</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>Mucinex® Kids Mini-Melts</td>
<td>Reckitt Benckiser Inc.</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>Little Colds® Mucus Relief Melt Aways</td>
<td>Prestige Brands</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Children’s Triaminic Thin Strips® Cough &amp; Cold</td>
<td>Novartis</td>
</tr>
<tr>
<td>Diphenhydramine, Phenylephrine HCl</td>
<td>Children’s Triaminic Thin Strips® Cold with Stuffy Nose</td>
<td>Novartis</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Children’s Triaminic Thin Strips® Allergy</td>
<td>Novartis</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Theraflu® Thin Strips® Nighttime Cold &amp; Cough</td>
<td>Novartis</td>
</tr>
<tr>
<td>Acetaminophen, Chlorpheniramime Maleate, Phenylephrine HCl</td>
<td>Alka-Seltzer Plus® Fast Crystal Packs</td>
<td>Bayer</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Bayer® Quick Release Crystals</td>
<td>Bayer</td>
</tr>
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Sources: CHPA’s Pocket Primer on OTC Active Ingredients, www.drugstore.com database
Unisom® SleepMelts™: Success Using the U.S. OTC Drug Monograph

Insomnia is a significant problem in the U.S.—according to a 2009 Sleep in America poll, 64% of adults report experiencing a sleep problem at least a few nights a week (up from 51% in 2001), with 41% reporting problems every night or almost every night, including difficulty initiating sleep, difficulty maintaining sleep, and waking up too early.

Due to the nature of the condition, more convenient dosage forms are appealing for consumers with insomnia; several new dosage forms have been developed for prescription sleep aids, such as Zolpimist™, a lingual spray developed by NovaDel, and Intermezzo®, a sublingual lozenge developed by Transcept and licensed to Purdue, both using the active ingredient zolpidem (Ambien®).

A number of OTC sleep-aids are also available to consumers, including Unisom® SleepMelts™ (a 25mg diphenhydramine ODT), developed by Eurand and launched by Chattem in 2008. Eurand originally formulated a taste-masked orally-disintegrating-tablet (ODT) form of diphenhydramine (containing 12.5 mg) for Pfizer Consumer’s Benadryl® Fastmelt® product line. However, this program was suspended when Pfizer Consumer was divested to GSK Consumer. Through a subsequent product divestment, the Unisom brand was acquired by Chattem, a leading manufacturer of OTC products, toiletries and dietary supplements in the U.S. and abroad. Notable brand names include Icy Hot®, Cortizone-10®, Selsun Blue®, and Gold Bond. OTC products for insomnia—for example, Sominox®, Nytol®, SLEEP-EZE, and Unisom®—usually contain diphenhydramine, an ingredient with a CDER-approved OTC Drug Monograph. Eurand entered into an agreement with Chattem to use taste-masked diphenhydramine for a Unisom line extension that would invigorate the brand. Chattem required a product with differentiating patient benefits: easy to swallow (without water) for quick or middle-of-the-night (MOTN) dosing, and pleasant taste with good mouthfeel and aftertaste. Further, the product had to meet certain minimum commercial and manufacturing criteria, including a product form that was durable for shipping, had acceptable cost-of-goods, and maintained an attractive color for consumer appeal.

Eurand turned to their R&D formulation team to leverage their expertise in developing a customized solution that was optimal to the needs of the partner. They began with their proprietary Microcaps® coacervation tastemasking technology—a technology that involves a process for microencapsulating a drug using phase separation—applied directly to crystals of pure drug substance.

Coacervation is traditionally a 3-step process (Figure 1):

Step 1: Formation of three immiscible (or separated) chemical phases—the drug is dispersed into a vessel containing solvent and a solid coating polymer, and stirred to create the trio of separated phases.

Step 2: Heating the mixture to dissolve the polymer, with subsequent polymer deposition on the drug particles, accomplished by controlled, physical mixing and cooling of the liquids.

Step 3: Rigidizing the coating—as the polymer coating coalesces onto the drug particle, the completed coated drug particles are filtered out, and then washed and dried.

For the development of taste-masked diphenhydramine particles, the traditional Microcaps® process was not deemed completely suitable, due to the micronized particle size of the API which would most likely cause agglomeration during the coacervation process and result in the application of an uneven polymer coating. The R&D team determined that incorporating Eurand’s Diffucaps® technology as an initial process step provided an optimal solution. First, the diphenhydramine drug substance—dissolved in a solution—was sprayed onto spherical, inert cellulose cores, followed by the application of a thin layer of protecting polymer (a “seal coat”). This process was conducted in a fluid bed unit, and produced a diphenhydramine bead with excellent content uniformity and a consistent round particle shape ideal for coacervation. The spherical diphenhydramine particle thus produced was then further coated by the Microcaps® coacervation process, as described above, to ensure complete tastemasking of the diphenhydramine.

Figure 1. Microencapsulation by Phase Separation

![Image of Microencapsulation by Phase Separation]

1. FORMATION OF THREE IMMISCIBLE CHEMICAL PHASES
   (charge, heat, stir)

2. DEPOSITION OF LIQUID POLYMERIC WALL MATERIAL
   (controlled cooling)

3. COAT HARDENING
   (filter, wash, dry)

Induced by a reduction in the total free interfacial energy of the system

Gelation methods: Physical or Chemical

Courtesy of Eurand, Inc.

Figure 2. Diffucaps® technology

![Image of Diffucaps® technology]
The Microcaps® encapsulated diphenhydramine beads were then formulated into an orally disintegrating tablet (ODT) form to meet the patient needs of a convenient/easy to swallow form that could be taken with or without water. Eurand’s AdvaTab® ODT technology (Figure 3) uses Eurand’s rapidly dispersing granulation and tabletting processes to produce a formulation that quickly disintegrates in the mouth without the need to chew or drink liquid. AdvaTab® tablets are designed to meet the FDA guidance regarding ODTs, including a disintegration time of less than 30 seconds. Combining the Microcaps® with the AdvaTab® technologies offers features such as high dose capacity, smooth mouthfeel, and robust tablets that can be packaged in either bottles or blisters.

The Microcaps® diphenhydramine beads were blended with color and flavor/sweeteners to produce a pink color and a cherry flavor prior to tabletting. The final Unisom® SleepMelt™ composition was a 500mg ODT weight containing 25mg of diphenhydramine. Stability testing was conducted in blister packs and bulk drums and in accordance with ICH guidelines, including USP disintegration and dissolution testing, assay testing to measure for degradation of the product, moisture content to test for controlled moisture to ensure tablet integrity, and microbiological testing to establish absence of microbiological organisms. A minimum of three months of stability testing at accelerated conditions was generated before the product was ready for commercial launch.

The Unisom® SleepMelts™ product was developed at Eurand’s U.S. facility in Vandalia, Ohio, an integrated site where formulation development, analytical testing, scale-up and clinical/commercial manufacturing are all accomplished under one roof. Process validation, commercial tablet production, and commercial packaging took three months and were conducted in parallel with the stability study. The monograph process saved the substantial time periods usually required for pilot pharmacokinetic (PK) supplies/studies (three months), pivotal PK supplies/studies (four months), and preparation/approval of an NDA (about one year). As a result, the final product reached pharmacy shelves in only nine months after entering into the development agreement with Chattem (Table 2). Today, the product can be found at key retail outlets as well as online outlets throughout the U.S. (Figure 4).

<table>
<thead>
<tr>
<th>Process</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste-masked particle developement</td>
<td>2 Months</td>
</tr>
<tr>
<td>ODT tablet development</td>
<td>2 Months</td>
</tr>
<tr>
<td>Trial packaging</td>
<td>1 Month</td>
</tr>
<tr>
<td>Stability study</td>
<td>3 Months</td>
</tr>
<tr>
<td>Distribution</td>
<td>1 Month</td>
</tr>
</tbody>
</table>

**TOTAL TIME TO MARKET: 9 MONTHS**

Table 2. Timeline to Market for Unisom® SleepMelts™
Building on Expertise in OTC Product Development and Delivery Technologies

With extensive expertise in developing and licensing tastemasked formulations of OTC/monograph drugs, Eurand has developed products for marketing in the U.S. and around the world with multiple partners, including branded as well as private-label products. Examples of currently licensed OTC formulations include:

- **Tastemasked Acetaminophen (Paracetamol)—** contained in GSK Consumer’s Panadol® brand;
- **Tastemasked Ibuprofen—** contained in Chewable Children’s Advil® Tablets marketed by Wyeth Consumer (now Pfizer);
- **Tastemasked Aspirin (Acetylsalicylic acid)—** contained in Cemirit Children’s Aspirin marketed by Bayer.

Other OTC drug categories in which Eurand has developed products include nutrition (Vitamin C sustained-release products) and cold/allergy therapies (taste-masked Pseudoephedrine).

Building on this successful track record in the OTC market with its AdvaTab® technology, Eurand has also developed new ODT formulations for both OTC and prescription products that are available for licensing, including:

- **Acetaminophen (Paracetamol) ODT.** This product has demonstrated bioequivalence to Panadol IR. The product is licensed out in certain European countries, and licensing rights are available in the U.S. and other countries worldwide. Strengths are available that are suitable for both pediatric and adult populations. As this is a USP monograph product, it could be commercialized in the U.S. in 6–12 months.

- **Cetirizine ODT.** In a crossover pilot PK study Eurand demonstrated bioequivalence, versus ZYRTEC® IR (with water) and ZYRTEC® Chewable (without water), of its AdvaTab® formulation both with and without water. This formulation, however, would require an NDA filing in the U.S.; Worldwide license available.

- **Temazepam ODT.** This product contains the active ingredient in the prescription brand sleep aid Restoril®. New formulations are available for out-licensing. This product would require an NDA filing in the U.S.; Worldwide license available.

Always expanding on its technologies, Eurand is building on the AdvaTab® ODT Immediate-Release (IR) franchise with the development of a controlled release version of ODT. More information on out-licensed products, and updates on technologies capabilities, can be found on the Eurand website at www.eurand.com.

Utilizing approved drug monographs is an effective and proven option for broadening market uptake and extending the lifecycle for OTC drugs in the United States, while minimizing a product’s development cost and time to market. However, in order to fully realize the potential of these products and the time-saving benefits of the monograph process, an organization must also demonstrate expertise in drug delivery technology, formulation development, manufacturing, and an understanding of the OTC Drug Monograph guidelines and related regulations. Companies that can tap into the growth potential of the OTC market in this way and develop new formulations of OTC products that address the ongoing and ever-increasing patient demand for convenience and appeal will maximize their potential for success.