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## From Test Tube to Tablet: The FDA Drug Approval Process

With the recent removal of a number of medications from pharmacy shelves, many patients may now be wondering what steps the Food and Drug Administration (FDA) is taking to ensure the introduction of safe and effective medications into the U.S. market. Housed within the FDA, the Center for Drug Evaluation and Research (CDER) is responsible for assuring that drug developers and manufacturers perform rigorous clinical trials and uphold best manufacturing processes to ensure the safety and well-being of the general public.

So, how exactly does a new drug receive approval from the FDA to be used within the United States? Prior to beginning clinical trials with human patients, drug developers are required to submit an Investigational New Drug Application (INDA) to the FDA for review. The INDA highlights the developer's pre-clinical trials, typically in animals, and indicates whether or not the investigational new drug (IND) might be safe for human consumption. If the FDA finds that the IND is reasonably safe, the developer receives permission to begin clinical trials (Phases 1–4) with human subjects to determine the drug's safety and efficacy. At all stages of clinical trials an Investigational Review Board (IRB) is utilized to ensure that all patients have provided consent, been warned of potential risks, and are reasonably protected from harm.



### Clinical Trial Phases

**Phase 1** — The objective of this clinical phase is to prove that the IND is safe for human consumption. Since the purpose of these trials is safety and not efficacy, researchers will typically utilize between 20–80 healthy volunteers with a focus on potential adverse effects and metabolic pathways.

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**On average, it takes 8–10 years for a drug to reach approval status.**

**Phase 2**—Once the safety profile of a new drug has been deemed acceptable, researchers begin testing the IND with patients who possess the disease or condition that the drug is intended to treat. In this clinical phase, patients are typically treated against placebo to highlight the IND's effect. While the focus of Phase 1 clinical trials is safety, Phase 2 trials attempt to highlight the effectiveness of the IND at treating the condition for which it is intended. Although not the main purpose of this phase, safety and adverse effects continue to be monitored. Typically, between 50 and 300 patients are included in these trials.

**Phase 3**—At this stage in the approval process, both the safety and effectiveness of the IND have been verified. The purpose of a Phase 3 clinical trial is to test the IND in

varying patient populations, with different doses and in combination with other agents, to provide a more real-world example of how the IND will be utilized in the general population. Once these trials are completed, the manufacturer is responsible for submitting a New Drug Application (NDA) to the FDA for final approval. Provided that all prerequisites are satisfied, the FDA will review the study results and approve the NDA. At this point, the drug can be introduced into the market as an approved medication. Most INDs will reach FDA approval status in 8–10 years' time, on average.

**Phase 4** (post-marketing)—Although already on the market at this point, the manufacturer of the new medication is required to continue to assess for safety, efficacy, and optimal use.

The process of drug testing and approval is paramount to ensure that patients continue to receive treatment options that are both safe and effective. The FDA regularly informs dispensing pharmacies and the general public of medications that have not met vigorous minimum standards. Rest assured that PMSI continues to be vigilant to communications from the FDA regarding the safety and efficacy of current and future medication therapies. PMSI will continue to monitor FDA announcements and take appropriate actions to ensure that injured workers receive the safest and most effective medications available.

Reference: Food and Drug Administration. "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective." <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> <Accessed April 30, 2009>



## FDA Takes Action on Medications Containing Propoxyphene

The Food and Drug Administration (FDA) has moved to reduce the risk of overdose in injured individuals who take the short-acting analgesic propoxyphene, which has been utilized since 1957 to treat mild to moderate pain. The active ingredient in the popular brand-name medications Darvon® and Darvocet-N® 100 has been under increased scrutiny in recent years from consumer watch groups and the medical community for the drug's lack of efficacy, as well as the increased number of fatal accidental overdose cases. Propoxyphene and its metabolite norpropoxyphene have been shown to accumulate in the body with repetitive dosing, increasing the probability of a toxic overdose. Injured individuals who have impaired renal systems and the elderly are even more susceptible to overdose situations. Toxic doses of propoxyphene can be associated with seizures, coma, respiratory depression, and cardiotoxicity.

Despite recommendations earlier this year from an FDA panel to ban the agent from the market, the FDA has decided to allow propoxyphene to remain available, but with much stricter guidelines; propoxyphene has been banned in the United Kingdom since 2005. The FDA is focusing its strategy on educating prescribers and injured individuals by requiring the manufacturers of propoxyphene-containing products to intensify the labeling regarding the risk of overdose. The makers of propoxyphene-containing products will also be required to provide medication guides to injured individuals underscoring the importance of taking the medication as directed. Future plans include analyzing data from studies that manufacturers must conduct to determine the effects of propoxyphene on the heart when taken in higher-than-recommended doses. The FDA has indicated that it may revisit the idea of removing propoxyphene products from the market, if future studies indicate negative outcomes in injured individuals.

Reference: Food and Drug Administration. "FDA Takes Action on Darvon, Other Pain Medications Containing Propoxyphene." FDA News Release. July 7, 2009. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm170769.htm> <Accessed July 16, 2009>



## Combination Oxycodone-Morphine Analgesic on the Horizon

QRxPharma Limited has announced positive Phase 3 clinical trial results with MoxDuo™ IR, a proprietary combination analgesic containing both oxycodone and morphine for the treatment of moderate to severe pain. Unlike other opioid combination products that are typically combined with non-opioid analgesics (i.e., acetaminophen, ibuprofen), MoxDuo contains both oxycodone and morphine in an effort to provide more effective pain relief while minimizing adverse effects.

The Phase 3 trial was conducted in 197 patients at various U.S. research sites, and compared the combination agent to each component dose (i.e., MoxDuo 12 mg/8 mg versus morphine 12 mg). As would be expected, MoxDuo 12 mg/8 mg provided 80%–100% more pain relief than either oxycodone 8 mg or morphine 12 mg alone. “These data indicate that MoxDuo IR has the potential to provide superior pain relief with a lower frequency and severity of side effects when compared to either morphine or oxycodone,” stated John Holaday MD, Managing Director and CEO for QRxPharma. “The improved tolerability profile should enable pain practitioners to prescribe higher doses of MoxDuo IR to achieve better pain relief with fewer side effects than morphine or oxycodone alone.” Typical side effects observed with opioid analgesics are nausea, constipation, itchiness, and lethargy. Although positive results have been reported thus far, more clinical trials are necessary to determine the true clinical significance of this combination agent.

Reference: “QRxPharma Successfully Completes Comparative Study For Dual-Opioid™ Pain Therapy.” *Medical News Today*. <http://www.medicalnewstoday.com/articles/146741.php> <Accessed May 12, 2009>



## New Latex Material Promises to Reduce the Occurrence of Latex Allergies

Vystar Corp. has announced that it has begun distribution of its revolutionary Vytex™ Natural Rubber Latex (NRL) product through a strategic partnership with Centrotech Minerals & Metals, Inc. and Centrotech Deutschland, GmbH. Manufactured through a patent-protected method, this natural latex derivative possesses all of the characteristics of natural latex; however, does not induce an allergic reaction in those who experience latex allergies.

As early as 1933, latex allergies began to surface worldwide. In the mid- to late-1980s, the allergy problem began to gain momentum, primarily among healthcare workers due to the Occupational Safety and Health Administration’s (OSHA) mandate to use natural rubber latex gloves for protection against diseases such as AIDS and hepatitis. It is estimated that roughly 17% of healthcare workers and 1% of the general population are allergic to latex. Current data indicates that the

risk of developing immediate latex allergies can be as high as 10% for anyone frequently exposed to latex—the general population has a 6% risk of developing sensitivity to latex.

Similar to other latex products, Vytex NRL is manufactured from natural rubber latex; however, special protein binders help to eliminate the specific compounds responsible for most allergic reactions. Currently, there are over 40,000 products made with latex. Vystar Corp. has conducted a variety of clinical studies in an effort to introduce Vytex NRL into a variety of products such as exam gloves and bedding materials. It is estimated that Vytex NRL may become available in current latex-containing healthcare products by 2010.

References: “Vystar Corporation Signs Key Agreement with Centrotech Minerals & Metals, Inc. and Centrotech Deutschland, GmbH, to Distribute Vytex™ NRL.” Vystar Corporation. <http://www.reuters.com/article/pressRelease/idUS198345+15-Jan-2009+BW20090115> News Release 2009. <Accessed July 1, 2009>

Vytex™ NRL. American Allergy Latex Association. <http://www.latexallergyresources.org/related/VytexNRL.cfm>. <Accessed July 1, 2009>



## Bone Growth Agent May Lead to Increased Costs Following Spinal Fusion Surgery

A new study indicates that a novel bone stimulation agent known as BMP, or bone-morphogenetic protein, may lead to post-operative complications and increased costs. Utilized for the purposes of stimulating new bone growth during spinal fusion surgeries, the agent appears to be the cause of post-operative swelling, swallowing difficulty, and hoarseness. Although smaller studies have shown that BMP promotes improved healing of spinal bone with fewer repeat surgeries and makes it unnecessary to harvest the patient’s own bone, the agent has been shown to cause bone growth in unwanted areas if used incorrectly.

In 2008, the FDA warned physicians regarding 38 reports of complications when the treatment was used in the neck region of the spine. Elsewhere in the spine, BMP has been shown to lead to no more complications than other spinal fusion treatments. As early as 2005, Medtronic, one of two manufacturers of the product, enhanced its labeling to indicate a potential for complications when BMP was used for neck surgeries. Medtronic is currently conducting clinical trials that may address how BMP could safely be used in the neck area. According to the manufacturer it is recommended that BMP only be utilized for FDA-approved indications, which currently does not include spinal neck fusions.

Reference: “Assessment of Bone Growth Stimulator is Mixed.” *MedicineNet.com*. June 2009. <http://www.medicinenet.com/script/main/art.asp?articlekey=101612>. <Accessed July 1, 2009>

## DRUG AND DME

# update

### New Generic Drug Arrivals

#### Tegretol®-XR (carbamazepine)

*Launched: May 2009*

As of early 2009, Tegretol-XR is now available as the generic equivalent of carbamazepine extended-release tablets. Approved for the treatment of seizures as well as various forms of neuropathic pain, the generic equivalent of Tegretol-XR is available in 100 mg, 200 mg, and 400 mg dosage-strength tablets in limited quantities.

### New Formulation

#### Edluar™ (zolpidem)

*Anticipated Launch Date:*

*Third Quarter 2009*

Approved in early 2009, the FDA has granted Orexo Pharmaceuticals approval to market Edluar, a new sublingual dosage form of the sedative/hypnotic agent, zolpidem. Similar to Ambien®, Orexo's new formulation product is approved for the short-term treatment of insomnia; however, it is unlikely that this sublingual formulation will add significant clinical advantages when compared to currently available generic zolpidem products.

### New Approvals

#### Onsolis™ (fentanyl buccal soluble film)

*Approved: July 2009*

Formerly known as BEMA™ fentanyl, the FDA has approved Onsolis for the treatment of breakthrough pain in cancer patients already tolerant to other opioid pain relievers. Similar to Actiq™ and Fentora™ Onsolis is not indicated for the treatment of non-cancer-related pain and is not interchangeable with other fentanyl products due to its absorption profile. Onsolis will be manufactured as a soluble buccal film to be placed on the inside of the cheek. Once on the market, Onsolis will be available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1200 mcg strength form.

#### Bryan® Cervical Disc

*Approved: May 2009*

Approved by the FDA in May 2009, the Bryan Cervical Disc is now available as a replacement disc following C3-C7 disc removal for the treatment of myelopathy and intractable radiculopathy. It is anticipated that the use of this device will be recommended only if patients are not responsive to six weeks of conventional therapy. It is expected that the Bryan Cervical Disc will become available sometime in 2009.

### New Launches

#### Nucynta™ (tapentadol)

*Launched: June 2009*

As anticipated, Ortho-McNeill-Janssen Pharmaceuticals has launched its newest short-acting partial opioid analgesic agent, Nucynta, after receiving final instruction from the Drug Enforcement Agency (DEA) to categorize it as a C-II controlled analgesic. Similar to tramadol (which is not a controlled substance) Nucynta provides pain relief via a dual mechanism of action. Although currently not on pharmacy shelves, Nucynta will be available in 50 mg, 75 mg, and 100 mg tablets.

### New Product Arrivals

#### Venlafaxine extended-release

*Release date: May 2009*

Approved in May 2008, venlafaxine extended-release tablets were released on the market in May 2009. FDA approved for a number of indications such as anxiety, depression, panic disorder, and neuropathic pain, venlafaxine extended-release tablets are not considered therapeutically equivalent to Effexor XR® capsules. Patients currently utilizing Effexor XR will need a new prescription for venlafaxine extended-release tablets in order to utilize this agent.

### Anticipated Approvals

#### New Wound Measurement Camera

*Anticipated Approval: undetermined*

Researchers at the Shepherd Center in Atlanta, Georgia, are currently testing a prototype wound measurement camera used in the assessment of wound progression and healing. Utilizing proprietary software, the camera will be able to provide accurate and repeatable documentation of wound boundaries, which can be used periodically during the healing phases to determine if treatment therapies are having positive outcomes. An anticipated release date has yet to be determined.



# FDA MedWatch Reports

## Highlighting Important Safety Issues from the FDA

### Boxed Warning Added to Testosterone Topical Products

*Posted: May 7, 2009*—FDA notified healthcare professionals that it will require two prescription topical testosterone gel products, AndroGel 1% and Testim® 1%, to include a boxed warning on the products' labels after receiving reports of adverse effects in children who were inadvertently exposed to testosterone through contact with another person being treated with these products. Despite the currently labeled precautions, FDA has received reports of eight cases of secondary exposure to testosterone in children ranging in age from nine months to five years. Since that time, additional reports of secondary exposure have been received by the agency and are presently under review. Of the fully reviewed cases, adverse events reported in these children included inappropriate enlargement of the genitalia, premature development of pubic hair, advanced bone age, increased libido and aggressive behavior. The gels are approved for the treatment of hypogonadism and erectile dysfunction in men who either no longer produce testosterone or produce it in very low amounts, such as which are evident following chronic opioid use. Both products are applied once daily to the shoulders or upper arms. FDA has provided recommendations and precautions to minimize the potential for secondary exposure.

Reference: FDA MedWatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlerts-forHumanMedicalProducts/ucm149346.htm>  
<Accessed May 7, 2009>

### Concentrated Acetaminophen Drops Voluntarily Recalled

*Posted: July 15, 2009*—Brookstone Pharmaceuticals and the FDA notified healthcare professionals and consumers of a nationwide voluntary recall of all lots of Concentrated Acetaminophen Drops (NDC#42192-504-16) in 16 oz (473 ml) bulk containers. The recalled drops were manufactured by Pharmaceutical Associates, Inc. This 16 oz container is comparable to the size generally used to package regular strength acetaminophen liquid preparations. This aspect of the product coupled with the absence of an integrated dosage delivery device is a contributing factor to possible dosing errors, especially inadvertent overdosing.

Acetaminophen, commonly known by the brand name Tylenol®, is indicated for the treatment of mild pain conditions and can be used as a fever-reducing agent. Overdosage of acetaminophen may result in liver toxicity, kidney damage, and blood disorders. The firm is recalling its product at the consumer level as a cautionary measure to minimize any confusion and potential risk to patients from dosing errors.

Reference: FDA MedWatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlerts-forHumanMedicalProducts/ucm172252.htm>  
<Accessed July 16, 2009>

### Botulinum Toxin Type A and B

*Posted: April 30, 2009*—The FDA notified healthcare professionals that after an ongoing safety review initiated in February 2008, the manufacturers of licensed botulinum toxin products will be required by the FDA to strengthen warnings in product labeling and add a boxed warning regarding the risk of adverse events when the effects of the toxin spread beyond the site where it was injected. Botulinum toxin products are utilized for a number of conditions such as neurogenic bladder, spasticity, and cervical dystonia.

The FDA will also require manufacturers to develop and implement a Risk Evaluation and Mitigation Strategy (REMS), including a communication plan to provide more information regarding the risk for distant spread of botulinum toxin effects after local injection, as well as information to explain that botulinum toxin products cannot be interchanged. The REMS would also include a Medication Guide that explains the risks to patients, their families, and caregivers. The FDA is requiring the manufacturers to submit safety data after multiple administrations of the product in a specified number of children and adults with spasticity to assess the risk of serious adverse reactions associated with the distant spread of the toxin throughout the body.

The FDA's evaluation of the data continues to support the recommendations made in the 2008 communication.

Reference: FDA MedWatch. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlerts-forHumanMedicalProducts/ucm164255.htm>  
<Accessed April 30, 2009>



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