

UPDATE

Food and Drug Law, Regulation and Education



A PUBLICATION OF THE FOOD AND DRUG LAW INSTITUTE

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UPDATE

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letter from the **president & ceo**

Keeping Up with the Food and Drug Law Community

‘**K**eeing up’ may be a universal challenge in today’s world—whether keeping up with regulatory actions and court decisions in our professional lives, keeping up with the deluge of ‘news’ available in traditional outlets and through social media in our professional and personal lives, or, for the adults in my house, keeping up with the laundry. It seems there is always a new development to review, another commentary to consider or another pair of socks to clean.

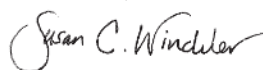
At FDLI, we aspire to be your first resource in ‘keeping up’ with developments in food and drug law. Just one week after President Obama signed the Drug Quality and Security Act into law late last fall, we convened a webinar with a lead Congressional staffer and two private sector experts to explain the nuts-and-bolts of the new law. Recognizing that new statutory authority raises new questions, authors for two issues of our *Food and Drug Policy Forum* provided quick recommendations, in December, regarding the implementation of the pharmacy compounding and supply chain security provisions. And to make sure that the community had access to an up-to-date version of the Federal Food, Drug, and Cosmetic Act, we published the FDCA Statutory Supplement, 2013, before the end of the year.

Keeping up with FDLI activity can be a challenge as well. If Update magazine is your primary connection with our community, you will learn about many activities after-the-fact. (See my prior paragraph, and the write-up of our Enforcement Conference on pages 35, 37, 39, 41, and 44.) This magazine is a great way to keep pace with our major programs, but you will likely miss out on our quickly-convened webinars, the bi-weekly Policy Forum and our one-day conferences. We provide four easy options for staying up-to-date:

- FDLI SmartBrief, a daily collection of news relevant to our community (sign up through www.fdpi.org)
- our weekly e-newsletter (FDLI Weekly, sign up through www.fdpi.org)
- follow us on Twitter (@foodanddruglaw)
- and connect with us on LinkedIn (the Food and Drug Law Institute group).

Our website (www.fdpi.org) is a great repository of our publications, upcoming programs and audio and slides from past events. Let us help you ‘keep up’.

(If you have any ideas about keeping up with the laundry, let me know.)



Susan C. Winckler
President and CEO

Letter from the Editor

As I write this column, I hope you are preparing to attend our Annual Conference April 23-24, in Washington, D.C.

I'm looking forward to seeing many familiar faces and some new ones as well. Indeed, our program this year is a combination of the tried and true with a twist of the novel thrown in for good measure.

So, you'll get to hear top FDA officials because, as usual, we have invited the Commissioner of Food and Drugs, Margaret Hamburg; Michael Taylor, Deputy Commissioner for Foods and Veterinary Medicine; Elizabeth Dickinson, Chief Counsel; and representatives of the six product Centers.

But we've also thrown in a few new wrinkles: We are pleased to announce that the Honorable Samuel Alito, Justice, Supreme Court of the United States, will be the luncheon speaker on April 24. (To our knowledge, this is only the second time a sitting Supreme Court Justice has addressed FDLI attendees at our Annual Conference—Justice Scalia spoke at the meeting several years ago.)

In addition, we have new plenary sessions on the role of non-governmental standards in food and drug law and what food and drug stakeholders need to know about counterfeiting and fraud and as well as the always popular and entertaining Top 20 Cases.

And we'll be hosting one of our popular breakout sessions, career opportunities in food and drug law, at a breakfast before Day 2 begins.

Most of all, we will, as usual, be covering the food and drug law, regulation and policy waterfront when it comes to matters regulated by FDA and other government agencies.

This issue of *Update* reflects that scope of coverage, as you'll see articles on the different areas of interest to food and drug law stakeholders, with such titles as:

FDA Flexes Its Muscles: A Stronger Stance against Trans Fat;

A Primer on Concluding Effective Compliance Investigations;

Fraud Law in Canada — Looking Forward to 2014;

Coloring between the Lines: Key Regulatory Insight from 2013 FDA Warning Letters Issued to Personal Care Product Companies; and

How Pharmaceutical Industry Should Prepare to Address the New Legislative and Regulatory Challenges in the European Union.



Hope to see you at our Annual Conference!

A handwritten signature in black ink that reads "Michael Levin-Epstein". The signature is written in a cursive, flowing style.

Michael Levin-Epstein

Editor-in-Chief



A Primer on Conducting Effective Compliance Investigations

By Gary Messplay and Sharon Bradley

The pharmaceutical and medical device industry is among the most heavily regulated in the U.S., subject to numerous laws, regulations, and guidelines that federal, state, and local government entities and prosecutors are especially eager to enforce. With government enforcement actions against pharmaceutical/device companies regularly resulting in multi-million and even multi-billion dollar settlements, industry's compliance with applicable laws, regulations, and guidelines has never been more critical. As a consequence, companies of all sizes have become increasingly dependent on their internal compliance functions to prevent, detect, investigate, and redress non-com-

pliant behavior before it reaches a magnitude likely to attract government attention. This article offers practical suggestions for conducting internal compliance investigations and addressing detected misconduct in a manner that reduces an organization's overall compliance risk.

Follow Procedure

Pharmaceutical and device companies may receive reports of non-compliant behavior through a variety of channels, including direct reports by employees to management or compliance personnel, anonymous tips submitted to the company's internal compliance hotline, and complaints received from competitors.



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Regardless of the source, every report of non-compliance must be taken seriously and subjected to a prompt, thorough, and objective investigation.

One way to ensure uniform and appropriate handling of all compliance complaints is to establish a formal, written policy that governs the management of all compliance reports and investigations. At a minimum, the policy should require the tracking of all compliance reports, development of an investigation plan, reporting of investigation results, and taking appropriate corrective actions. The policy should also require the investigation to be conducted in a manner that adequately protects the confidentiality of the individuals and information involved.

Document Everything

It is imperative for the company to extensively and accurately document each step of a compliance investigation. By doing so, it creates a record that potentially will be scrutinized by outside parties, such as the government or private litigants. An investigation will be questioned if it is not seen as fair and impartial. The development of an extensive record will assist the company in establishing timeliness, completeness, fairness, and impartiality.

Define and Redefine the Scope

At the outset of a compliance investigation it is important to define the scope of the inquiry, taking into account both the extent and the severity of the alleged misconduct. For example, an investigation into an allegation that a single entry-level employee violated an internal company policy will initially have a much narrower scope than an allegation that the entire sales force is routinely engaging in off-label

promotion at the direction of a member of senior management. That being said, the former type of investigation may uncover evidence of systemic misconduct, thereby necessitating expansion of the investigation's initial parameters. Because the scope of an investigation is inherently dynamic, it should be continually reassessed throughout the course of the investigation.

Have a Plan

After determining the preliminary scope of the investigation, the next essential step is to create a written investigation plan that identifies the potential misconduct, the internal and external resources that will be involved in conducting the investigation, the areas of inquiry to be pursued and the individuals responsible for pursuing them, and each step that will be taken during the course of the investigation. Almost all investigation plans will call for collecting and reviewing documents, as well as conducting interviews.

Document Review. Oftentimes the first step in an investigation is to review the documents of the individual(s) involved in the alleged misconduct. At a minimum, this will include conducting a targeted search of each individual's email, shared files, phone messages, and computer hard drive. Depending on the nature of the allegations, it may also be necessary to review expense reports, call notes, and phone records, among other things.

After this initial review of documents, it is important to reevaluate the investigation plan and determine whether the documents of additional employees should be collected and reviewed.

Interviews. Generally interviews should be conducted after reviewing and analyzing pertinent documents, which often will help with selecting

interviewees. However, in some circumstances there may be time constraints that prohibit the collection and review of all documents prior to conducting interviews. In addition to company employees, it may be necessary and appropriate to interview third parties. The decision whether to interview third parties should take into account the need for confidentiality.

Determining the interview sequence is almost as important as deciding whom to interview; typically interviews should begin with the individuals who are likely to be the most forthcoming (i.e., those who have the least to lose), with the goal of obtaining information that will be useful during interviews of the individuals who have the most at stake and therefore may have an incentive to obfuscate the truth. In this regard, it is imperative to obtain buy-in from the highest levels of the organization; the message from the top should be an expectation of complete cooperation with the investigation. It is equally important to ensure confidentiality so that interviewed employees do not discuss the investigation or their interview with other employees. One way to minimize this risk is to conduct the key interviews in a single day or at least on a compressed timeline.

As with the scope of the investigation, the investigation plan should be continually reexamined and modified as needed.

Bring in Reinforcements When Needed

Both at the beginning of an investigation and throughout its duration, staffing is an important consideration. It is essential that an investigation be conducted in an expeditious, thorough, and objective manner. In some instances, assistance from outside counsel may

be required depending on a number of factors, including the following:

Adequacy of internal resources. If the scope of an investigation exceeds the available internal resources, an outside firm should be brought in to assist with the speed of the investigation. Inadequacy of internal resources does not excuse the company from its obligation to conduct a prompt, thorough, and objective investigation into all compliance complaints. This is particularly important if the non-compliant activity may be ongoing.

Need for demonstrating independence. Seeking assistance from an outside firm is also advisable if the nature of the investigation is one that would call into doubt the objectivity of an internal review. For example, if the alleged misconduct is attributed to one of the company's top sales representatives, third parties including the government may be more likely to give credence to an investigation conducted by outside counsel rather than internal compliance personnel.

Resistance from within. Due to the particularly sensitive nature of some compliance investigations, such as those involving allegations of executive wrongdoing, compliance personnel may face resistance when attempting to conduct the investigation. In such instances, hiring outside counsel to conduct the investigation may be preferable because outsiders are less likely to succumb to internal pressures. In some instances, outside counsel may be retained by a corporate board of directors to bolster the authority of the outside lawyers.

Severity of the misconduct. Minor violations of internal company policies most often can and should be investigated by internal compliance personnel. But if the alleged misconduct is particularly egregious, such as a violation

that could lead to criminal and/or civil penalties, hiring outside counsel to conduct the investigation is likely in the company's best interests.

Extent of the misconduct. Some investigations begin with a single allegation of wrongdoing that, once investigated, leads to the discovery of additional violations that are so pervasive that internal compliance personnel cannot demarcate the wrongdoing—in other words, they cannot identify a boundary within which the misconduct is contained. In such instances, involving outside counsel is particularly advisable.

Need for specialized expertise. Certain types of violations may require specialized expertise that internal compliance personnel do not possess. For example, investigations into potential violations of the Foreign Corrupt Practices Act may require consulting an outside firm to help navigate the nuances of this area of law. Similarly, an issue involving data integrity may require the expertise of an outside law firm.

Privilege. In some instances, the company may want to attempt to conduct the investigation in a manner that is protected by the attorney-client privilege, which is another reason for retaining outside counsel to conduct the investigation.

Government involvement. If the conduct in question is likely to be disclosed to, or discovered by, the government, it may be in the company's best interest to involve outside counsel from the outset.

Report Findings

The company's compliance officer (or equivalent) should report the findings of each compliance investigation to the Chief Executive Officer, the Board of Directors, and/or the Compliance Committee, as appropriate. The report should include the compliance officer's

recommendations regarding corrective measures to be taken, if any.

With respect to the timing of these reports, findings of confirmed wrongdoing should be reported as soon as practicable after concluding the investigation. For investigations that conclude that a violation did not occur, it would be appropriate to deliver such reports on a quarterly basis or during the next scheduled compliance update.

In addition, the results of compliance investigations—either individually or at least in the aggregate—should be reported to the entire organization. By doing so, the company assures employees that if they voice compliance concerns, those concerns will be addressed. Such assurance is essential to building and maintaining a culture of compliance. Conversely, failure to communicate the results of the investigation can lead to a number of unfortunate consequences including the belief that the company permits or even condones non-compliance.

Finally, the company should consider whether to report the misconduct to federal or state authorities and/or make a repayment of any kind to the government or another entity. According to the oft-cited compliance guidance issued by HHS' Office of Inspector General,¹ prompt voluntary reporting demonstrates good faith and will also be considered as a mitigating factor if the company becomes the subject of an OIG investigation. But there are numerous factors to consider before deciding whether to self-report and it is advisable to consult with outside counsel before reporting.

Take Corrective Actions

When an investigation uncovers wrongdoing—and sometimes even when it does not—the final step is to develop and undertake corrective actions. Companies should assume that one day

the government will learn about the misconduct and will inquire about the company's response to the non-compliant activity. How the company addresses misconduct will directly influence the government's response to the situation. An inadequate investigation or insufficient corrective action to redress the misconduct is more likely to result in government enforcement or a more severe government response. In general, corrective actions fall into one of the following five categories: (1) disciplinary actions, (2) training, (3) policy revisions, (4) corrective communications, and (5) culture adjustments.

Disciplinary Action. In almost all cases, some form of disciplinary action should be taken against the wrongdoer. It also may be necessary to take disciplinary action against managers who failed to use reasonable care to detect the misconduct, employees who refused to cooperate with the investigation, supervisors who condoned the malfeasance, or anyone who attempted to retaliate against the reporter of the misconduct.

Disciplinary action can take one or more of the following forms: employee counseling, verbal or written warning, verbal or written reprimand, probation or suspension without pay, demotion, salary decrease, bonus reduction or forfeiture, and/or termination. Every company should have in place a "disciplinary matrix" that guides the determination of which form or forms of discipline to impose. The matrix should take into account the nature and severity of the violation at issue; whether the employee

acted intentionally, recklessly, negligently, or accidentally; whether the employee has committed any prior violations, and if so the nature and severity of those violations; whether the employee voluntarily disclosed the violation; and the extent to which the employee cooperated with the compliance investigation.

Training. In lieu of or in addition to disciplinary action, misconduct often signals the need for additional compliance training, whether for the wrongdoer individually, a specific department within the company, or the organization as a whole.

Even in instances where an investigation into alleged misconduct concludes that no wrongdoing occurred, additional compliance training may be warranted. For example, the allegation of wrongdoing may reflect that the reporter himself does not understand the rules that govern his conduct and therefore needs additional training.

Policy Revisions. Sometimes the occurrence of misconduct signifies the need to develop new internal policies and/or to revise existing ones. By way of example, a company policy could be misconstrued by employees to permit the conduct at issue and therefore needs to be revised for clarity to prevent similar behavior in the future.

Corrective Communications. Where the misconduct at issue reaches health-care providers and potentially has a deleterious impact on patient health, it may also be necessary to disseminate corrective communications to affected third parties.

Culture Adjustments. Finally, a compliance investigation might uncover wrongdoing that is attributed, at least in part, to the lack of a "culture of compliance" within the company. In such instances, it is imperative that senior management in the organization work with the compliance department to address these cultural issues. The compliance department cannot be expected to achieve this alone.

The adequacy of a company's corrective action plan depends on the extent to which it addresses the pervasiveness and severity of the improper conduct, and its effectiveness in preventing misconduct in the future. While disciplinary action alone may be sufficient in the case of misconduct by a single rogue employee, systemic problems may warrant all five types of corrective action. In all cases, it is important to subsequently evaluate whether the corrective actions were effective.

Conclusion

In light of the intense scrutiny faced by pharmaceutical and medical device companies, ensuring that allegations of non-compliance are properly investigated and corrected must be a top priority of the compliance function. Following these guidelines will assist companies with this important task.

1. Office of Inspector General, Department of Health and Human Services, [Compliance Program Guidance for Pharmaceutical Manufacturers](#), 68 Fed. Reg. 23731, 23742 (May 5, 2003).



Coloring within the Lines: Key Regulatory Insight from 2013 FDA Warning Letters Issued to Personal Care Product Companies

By Raqiyyah R. Pippins

The past few years have been marked with an increase in scrutiny of personal care products by the Food & Drug Administration (FDA),¹ including FDA efforts to define the regulatory boundaries governing different classes of personal care products and clarify the regulatory distinction between cosmetics and drugs. After hinting to industry in 2011 that it in-



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tended to monitor the category, FDA issued a series of warning letters in 2012 asserting its position that hair removal, anti-aging, and blemish removal claims cross the “line” for cosmetic products and cause products to be drugs under the FDCA.² In 2013, FDA re-affirmed its position regarding the types of beautification claims that it considers to be drug claims, while also highlighting some new-areas for consideration: specifically, the regulatory lines governing beautification devices, personal care products for diseased populations, and third-party contractors.

Reaffirming Past Priorities

Last year, we discussed FDA’s scrutiny of personal care products and the manner in which a personal care product’s regulatory classification can significantly impact the regulatory standards governing the product’s manufacturing, marketing and labeling.³ For example, before being marketed, products

classified as OTC drugs must either receive pre-market approval by FDA or conform to FDA monographs—essentially an FDA-approved formula for a drug product. In contrast, while cosmetic manufacturers are responsible for ensuring product safety, products classified as cosmetics do not need to obtain pre-market FDA approval or conform to a specified pre-approved FDA formula.⁴

How FDA categorizes a personal care product is determined, in part, by what FDA concludes to be the manufacturer’s “intended use” for the product. Among other things, FDA reviews product covers (e.g., advertisements, websites, labeling, and ingredient statements) as evidence of a product’s intended use. Products marketed with drug claims—claims that a product is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or intended to affect the structure or any function of the body”—without pre-market approval by FDA or conforming to FDA monographs are considered “unapproved new drugs” and cannot be legally marketed in the United States.⁵

In 2013, FDA reaffirmed these priorities with more warning letters regarding unapproved anti-aging, blemish removal, and hair-removal product claims that caused the products to be unapproved new drugs. For instance, FDA’s March 2013 warning letter to Keystone Laboratories, Inc.⁶ regarding its personal care products is an example of FDA’s efforts to continue monitoring the category. The letter was largely consistent with previous FDA action challenging the use of claims and/or ingredients that FDA considers to be evidence that a product is intended for use as an unapproved new drug, including allegations that the inclusion of recognized drug ingredients (e.g., hydroquinone 2% and padimate o 1.5%) as

active ingredients and blemish removal claims (e.g., “fades skin discoloration by lightening dark spots such as freckles, age spots, and blemishes”) caused the company’s ULTRA GLOW Fade Cream products to be drugs under the FDCA. However, the letter also serves as a reminder that FDA is monitoring personal care products to ensure that products marketed with claims that are covered by an OTC drug monograph are consistent with the conditions established by the monograph to exempt the company from obtaining additional pre-market approval for promoting the product in the United States.

In its letter to Keystone Laboratories, FDA alleged that the packaging and labeling for Keystone Laboratories’ Long Aid Medicated Hair Revitalizer Anti-Itch Formula indicated that the product is intended for the control of dandruff and microbial use. While the dandruff indication of use is addressed under 21 CFR 348 Subpart H—the OTC monograph covering certain claims for “Drug Products for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis,” FDA alleged that the Long Aid Medicated Hair Revitalizer Anti-Itch Formula product is misbranded because the product also included claims that the shampoo product was intended to control microbial growth. Specifically the letter stated that because this “antibacterial indication... is not included as an indication for use in the OTC Final Monograph for Drug Products for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis... the product is not labeled in accordance with monograph.” Essentially, the inclusion of drug claims that were not covered by the monograph caused Keystone to lose its exemption from obtaining premarket approval for its salicylic acid-based anti-dandruff

shampoo product by causing the product to become a new drug without proper approvals. As noted above, new drugs cannot be legally marketed in the United States without approved applications under Section 505(a) of the FDCA.

Asserting New Priorities: Beautification devices, personal care products for diseased populations, and third-party contractors

Beautification Devices. In 2013, FDA expanded its scrutiny of compliance with pre-market approval exemptions for devices. For example, in a warning letter to Market Technologies, Inc.,⁷ FDA alleged that the company’s Contour Ultra and Starpress devices were being marketed as unapproved medical devices in violation of the FDCA. Notably, this warning letter involved electric therapeutic massagers that can be legally marketed under 21 CFR 890.5660 without premarket notification, provided they are intended for relief of minor muscle aches and pains or to temporarily relieve minor muscular pain or tension caused by fatigue or overexertion. Market Technologies, however, was marketing the product to provide beautification benefits, with claims such as “improves skin quality,” “improves muscle tone in the face and neck,” “visibly reduces wrinkles,” and treats cellulite. FDA considered the claims to be “evidence the [devices are] intended for uses that are different from those legally marketed devices classified under 21 CFR 890.5660,” and therefore required Marketing Technology to obtain premarket approval prior to marketing the products in the United States. Because the claims “exceed[ed] the limitations described in 21 CFR 890(a)” that would have exempted the devices from premarket notification requirements, FDA concluded

that the devices were misbranded and in violation of the FDCA.

Personal care products for disease populations. Given the impact that disease can have on the appearance of the body, some companies have considered marketing personal care products to support the needs of disease populations that are concerned about the impact of their condition on their outward appearance. In 2013, FDA issued warning letters suggesting that FDA may consider such products to be drugs under the FDCA. For example, on July 15, 2013, FDA sent a warning letter to The Magni Group, Inc. regarding claims made for the company's "Diabetic Foot Cream" and "Diabetic Hand & Body Cream" products, alleging that the products are "intended for use in the diagnoses, cure, mitigation, treatment, or prevention of disease and/or intended to affect the structure or any function of the body."⁸ Notably, while most of the highlighted claims were consistent with past claims of concern to FDA, other claims of concern included the product names "Diabetic Foot Cream" and "Diabetic Hand & Body Cream" and the claim, "[O]ne of out of every three people with diabetes will be affected by skin disorders caused by diabetes. Fortunately, most skin conditions can be prevented or easily treated if caught in the early stages. It is important to maintain healthy skin with skin care products specifically developed for people with diabetes." FDA considered these product names and the claim to be evidence that the products were intended for use as drugs and "new drugs" under FDCA section 201(p) "because they are not generally recognized as safe and effective under the conditions prescribed, recommended, or suggested in their labeling." It then concluded that because "a new drug may not be introduced or

delivered or introduction into interstate commerce unless an FDA-approved application is in effect for it," and "there are no FDA-approved applications for these products," "the marketing of these products constitutes a violation of these provision of the [FDCA]."

Contract-based testing laboratories.

In 2013, FDA also asserted its position regarding the use of third party agents to monitor compliance with FDA regulations. In August 2013, FDA sent a warning letter to Jabones Pardo S.A.,⁹ based on an inspection of their manufacturing facility in Madrid, Spain. After determining that many of its personal care products that were to be sold in the United States were out of compliance with FDA regulations, the letter addressed the use of contract testing laboratories, noting the following:

"Although you have agreements with other firms that may delineate specific responsibilities to each party (e.g., quality control testing), you are ultimately responsible for the quality of your products. The Food & Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities (e.g., contract testing laboratories) and regards extramural facilities as an extension of the manufacturer's own facility. Regardless of who performs your operations, or agreements in place, you are required to ensure your products were made in accordance with...the Act so as to provide for their identity, strength, quality, purity, and safety, and are suitable for marketing."

As companies continue to rely on third party laboratories to ensure compliance with FDA regulations, this letter reinforces the importance of actively monitoring the quality and efficiency of the contracted laboratories.

What does this mean for companies marketing personal care products?

FDA activity in 2013 indicates that FDA is continuing to monitor the industry and that care should be taken to ensure that the marketing and manufacture of personal care products account for FDA priorities. It also provides some helpful tips for companies attempting to expand their product portfolios:

- When rebranding products, ensure that new product claims do not fall outside of the scope of the approvals permitting use of the product in the United States. Read both the monographs and the rulemaking records for drugs and devices subject to premarket approval to determine the types of claims that were contemplated by the agency when establishing the OTC monographs or premarket exemptions for the drug or device, and confirm that claims of interest to the marketing team were not rejected by FDA when establishing the monograph or premarket exemption currently applying to the drug or device. It also is helpful to ensure claims of interest to the marketing team that are not well accepted cosmetic claims or included in the monograph or premarket exemption that applies to the company's product are not expressly approved for use to market other drugs or devices. Typically, FDA's inclusion of a claim in a drug approval for another product indicates FDA's position that the representation is a drug claim under the FDCA. Thus applying the claim to a product in commerce as a cosmetic or pursuant to an OTC monograph

or premarket exemption presents high risk of leading FDA to conclude that the new claim causes the product to be an unapproved “new” drug or device;

- Acknowledge the risk of targeting personal care products at diseased populations. To the extent that a company chooses to pursue products targeted at such populations, care should be taken to avoid terms that refer to skin “disorders” and to instead “highlight an intention for the product to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance skin”¹⁰; and
- Closely vet and monitor third-party vendors prior to relying on such entities to ensure compliance with FDA regulations.

For example, companies should ensure that vendors are aware of (and accounting for) FDA’s Draft Guidance for Industry: Cosmetic Good Manufacturing Practices, issued in June 2013.¹¹ Written assurance alone from a third-party vendor that it intends to comply with FDA’s regulations is unlikely to shield a company from liability under the FDCA. In addition, ensure that all contractual agreements with third-party vendors delineate the vendors’ obligations in the event of regulatory enforcement or related action.

Taken together, these steps can help companies to “color within FDA’s regulatory lines” in an effort to minimize the risk of FDA enforcement action regarding the company’s personal care products.

1. For the purposes of this article, “personal care product” is defined to

include any product (including a device) that is topically applied to improve a person’s appearance.

2. Judging a Book by Its Cover: FDA’s Scrutiny of Personal Care Products in 2012, FDLI Update Magazine March/April 2013.
3. Id.
4. In fact, color additives are the only cosmetic ingredients that must be pre-approved by FDA.
5. FDCA section 505(a).
6. FDA Warning Letter to Keystone Laboratories (Mar. 18, 2013)
7. FDA Warning Letter to Market Technologies, Inc. (Dec. 2, 2013).
8. FDA Warning Letter to The Magni Group, Inc. (Jul. 15, 2013).
9. FDA Warning Letter to Jabones Pardo, S.A. (Aug. 22, 2013).
10. FDA Website, “Is it a Cosmetic, Drug, Or Both? (Or is it Soap?)” available at <http://www.fda.gov/cosmetics/guidancecompliance/regulatoryinformation/ucm074201.htm>.
11. FDA Website, “Guidance for Industry: Cosmetic Good Manufacturing Practices” (June 2013) available at <http://fda.gov/Cosmetics/GuidanceCompliance-RegulatoryInformation/GuidanceDocuments/ucm353046.htm>.

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FDA Flexes Its Muscles: A Stronger Stance Against Trans Fats

By Cori Annapolen Goldberg

Desserts and late-night snacks may be forever changed if the U.S. Food and Drug Administration (FDA) has anything to do with it. In an effort to improve public health, the agency is taking a stand against processed foods that contain partially hydrogenated oils (PHOs) such as baked goods, ready-to-use frostings, stick margarine, coffee creamers, microwave popcorn and other snack products, and frozen pizza.¹ That is, FDA published in the Federal Register on November 7, 2013 a preliminary determination that PHOs,

the primary dietary source of trans fats in the processed food supply, are no longer “Generally Recognized As Safe”, or what is known in the industry as GRAS, under any condition of use in food.² According to the agency, it made its preliminary determination to no longer consider PHOs as GRAS because research shows that trans fats have significant adverse health effects and there is therefore no longer a scientific consensus that PHOs are safe for the intended use in food.³

Fatty acids are the chemical compounds that comprise fats.⁴ Trans fatty acids, also known as trans fats, are a “specific type of fat that is formed when liquid oils are turned into solid fats, such as shortening or stick margarine. During this process — called hydrogenation — hydrogen is added to vegetable oil to increase the shelf life and flavor stability of foods. The result of the process is trans fat.”⁵

Trans fats first hit the radar screens of health-conscious Americans when the Center for Science in the Public Interest sent a petition to FDA requesting that trans fats be included in nutrition labeling.⁶ Published human studies had shown that intake of trans fatty acids, similar to the intake of saturated



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fatty acids, increases low-density lipoprotein cholesterol (known commonly as LDL, LDL-C, or “bad cholesterol”) in the blood.⁷ An elevated LDL-C increases the risk of developing coronary heart disease. Research shows that trans fats may also have other adverse health effects, including lowering high-density lipoprotein cholesterol (HDL-C). FDA has stated that, considering only the effects of trans fat from partially hydrogenated oils on levels of LDL-C, the Centers for Disease Control and Prevention (CDC) estimates that eliminating intake of trans fat from PHOs could prevent up to 20,000 cases of coronary heart disease (CHD) and up to 7,000 deaths annually.⁸ Reports published by the Institute of Medicine and the federal government have recommended that Americans limit their intake of trans fats and other cholesterol-raising fats while consuming a nutritionally-adequate diet.⁹

In response to the petition and these studies, on November 17, 1999, the agency issued a proposed rule in the Federal Register, in which it proposed that trans fat content be provided in nutrition labeling in order to educate consumers about the amount of trans fats in the foods that they consume.¹⁰ On July 11, 2003, the agency published a final rule in the Federal Register that amended its regulations on food labeling to require that trans fatty acids be declared in the nutrition label of conventional foods and dietary supplements (68 FR 41434). This rule went into effect on January 1, 2006.¹¹ According to FDA, many foods have been reformulated to remove PHOs and the mean dietary intake of industrially-produced trans fat has decreased significantly since the agency’s estimates provided in July 2003. The agency has said that, despite these reformulations,

there are still many foods on the market that are made with PHOs.¹²

FDA’s most recent action is likely to have a much more significant effect on trans fats than the 2006 food-labeling requirement did. Under section 409 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), any substance that is intentionally added to food is a food additive that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excluded from the definition of a food additive. The agency has defined “safe” as “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use”¹³ “based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food.”¹⁴ FDA’s tentative determination renders PHOs as food additives and subjects them to section 409. Therefore, if the agency’s preliminary determination is finalized, PHOs would become food additives subject to premarket approval by FDA before PHOs can be sold, either directly or as ingredients in another food product. Foods containing unapproved food additives are considered adulterated under U.S. law, meaning that they cannot legally be sold. Removing PHOs from the GRAS list will therefore make it much harder, if not impossible, for food manufacturers to get their products on the shelves if those products contain PHOs. Trans fat would not be completely eliminated, however, because it occurs naturally in small amounts in meat and dairy products and it is also

present at very low levels in other edible oils, such as fully hydrogenated oils, where it is unavoidably produced during the manufacturing process.

FDA is soliciting comments on how such an action would impact small businesses and how to ensure a smooth transition if a final determination is issued. The agency stated that it is seeking comments and scientific data pertaining to the notice, including specific issues such as possible alternative approaches, time needed for reformulation, burden on small businesses, and other technical challenges to removal of PHOs from the food supply. Specifically, the agency wants to know:

1. Should FDA finalize its tentative determination that PHOs are no longer GRAS?
2. Are there data to support other possible approaches to addressing the use of PHOs in food, such as by setting a specification for trans fat levels in food?
3. How long would it take producers to reformulate food products to eliminate PHOs from the food supply? Are there likely to be differences in reformulation time for certain foods or for certain types of businesses?
4. If FDA makes a final determination that PHOs are not GRAS and does not otherwise authorize their use in food, what would be an adequate time period for compliance for producers to reformulate any products as necessary and to minimize market disruption?
5. Are there any special considerations that could be made to reduce the burden on small businesses that would result from removal of PHOs from foods, such as additional time for reformulation? Would those considerations be consistent with a

final determination that PHOs are not GRAS?

6. Are there other challenges regarding the removal of PHOs from foods? Are there products that may not be able to be reformulated? If so, what sorts of products and what challenges are faced?
7. Is there any knowledge of an applicable prior sanction for the use of PHOs in food?¹⁵

Essentially, if FDA makes a final determination that PHOs are not GRAS, the agency and food industry would have to figure out a way to phase out the use of PHOs over time and the Federal Register notice therefore calls for comment on how long it would take the food industry to phase out its use of PHOs. The agency has acknowledged, however, that it may take a while to implement these changes even if a final determination is issued. The agency said originally that it would accept comments for 60 days from November 7. However, on December 17, “in response to numerous stakeholder requests to provide additional time for comments,” FDA extended the comment period to March 8, 2014.

Industry experts should exercise their right to submit comments in an effort to influence FDA’s response, especially because FDA may take similar

action in the future on other ingredients. The agency recently warned Americans about their consumption of French fries, through its issuance of recommendations to growers, manufacturers, and food service operators to reduce in certain foods acrylamide, a chemical that can form in plant-based foods during frying, roasting, and baking.¹⁶ FDA also suggested to consumers that they reduce their consumption of this chemical.¹⁷ Moreover, industry experts have opined that FDA may scrutinize sodium more closely and take similar action in order to protect public health.¹⁸ Other experts have suggested that sugar may also be a likely target.¹⁹ More than likely, food manufacturers will have a lot to say about the agency’s recent actions. In addition to the submission of comments, impacted stakeholders should consider developing strategies and action plans to address the implications of a finalized determination by the agency. Because the changes will not happen right away, food manufacturers will hopefully have enough time to find substitutes for the PHOs in their products so that consumers will not notice much of a difference when they purchase and consume their favorite desserts.

1. <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm372915.htm>.
2. <https://www.federalregister.gov/articles/2013/11/08/2013-26854/tentative-determination-regarding-partially-hydrogenated-oils-request-for-comments-and-for>. While the agency had not listed on the GRAS list the most commonly-used PHOs, they have been used in food for many years based on industry determinations that such use of those PHOs is GRAS. *Id.*
3. *Id.*
4. <http://www.fda.gov/Food/Guidance-Regulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm053479.htm>.
5. <http://www.fda.gov/food/populartopics/ucm292278.htm>.
6. <http://www.fda.gov/Food/Guidance-Regulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm053479.htm>.
7. *Id.*
8. *Id.*
9. *Id.*
10. *Id.*
11. *Id.*
12. *Id.*
13. 21 C.F.R. § 170.3(i).
14. 21 C.F.R. § 170.30(a).
15. *Id.*
16. <http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm151000.htm>.
17. *Id.*
18. See <http://articles.latimes.com/2013/nov/08/science/la-sci-fda-transfat-salt-sugar-regulation-20131107> (last accessed January 2, 2014).
19. *Id.*

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Food Law in Canada: Looking Forward to 2014

By Martha A. Healey and Adrienne M. Blanchard

The year 2013 marked a year of new beginnings and significant change in the area of Canadian food law and policy. The appointment of a new president of the Canadian Food Inspection Agency (CFIA), continuing efforts and outreach in respect of new food safety legislation (not yet in force), a focus on the modernization of Canadian food labeling laws and a re-ordering of the reporting structure of the CFIA from the department of Agriculture and Agri-Food Canada to Health Canada are but a few examples of the areas of change that took place in 2013 and which are expected to continue to unfold over the year 2014. The policy and legislative changes that took hold last year were also matched by an increased emphasis on food recalls and heightened enforcement activities by Canadian food regulators.

Changes within the Canadian Food Inspection Agency – A new President and a new Reporting Structure

In August 2013, Dr. Bruce Archibald was appointed the new President of the CFIA. With a doctorate degree in environmental toxicology, a Master of Science in physiology/biochemistry and a Bachelor of Science in Agriculture, the depth of the new President's credentials in the areas of agriculture and science industries suggest a renewed focus on science-based decision making within the CFIA. Dr. Archibald takes the helm of the CFIA at a time of significant change – both on the legislative front (with the coming into force of the *Safe Food for Canadians Act*) and at a time when the rate of food recalls remains strong and food safety



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issues are assuming an importance; currently, there is public focus and scrutiny on food safety that is unlike any previously experienced. High profile recalls (such as the XL Foods recall of beef products in 2012) is but one example of a large-scale recall; that recall resulted in significant criticism of Canadian food regulators yet there is divided opinion as to whether the recall was necessary given that no illnesses were reported and the issue could have been resolved by cooking the meat. The legacy of such large-scale recalls continues to unfold. The economic consequences of food recalls that may not be strictly necessary from a health and food safety perspective compete against a regulatory concern over public criticism in the event the regulator is perceived as not taking strong enough action. Canadian food regulators continue to have the power to order the recall of a food in cases where those authorities believe, on reasonable grounds, that the food poses a risk to public, animal or plant health.¹

On the heels of the change of CFIA president, in the fall of 2013, Canada also announced that the CFIA would change its reporting structure and would now report to the Minister of Health. Previously, the CFIA had reported to the Minister of Agriculture and Agri-Food. The change was explained by noting that the reorganization would strengthen Canada's food safety system by bringing all three Canadian food safety authorities (the CFIA, the Public Health Agency of Canada and Health Canada itself) under one Minister. It would, said the government, "ensure clear focus, easy collaboration, and timely communication with Canadians when it comes to food safety".²

The Minister of Agriculture and Agri-Food will retain responsibility for the CFIA's non-food safety agricultural activities, such as economic and

trade issues, animal health and plant protection and the CFIA will continue to support the Minister of Agriculture and Agri-Food in such areas of responsibility.³

This change in the reporting structure of the CFIA is also (whether intentionally or not) responsive to criticism levied at the Canadian government since the inception of the CFIA that there existed an inherent conflict of interest in the CFIA reporting to a Minister responsible for the promotion of agriculture. Whether or not the conflict actually existed, the reporting change sends a clear signal that food safety is a priority and creates new opportunity for the CFIA, Health Canada and the Public Health Agency of Canada to streamline and consolidate food safety efforts.

The appointment of a CFIA president with a significant science/agriculture background, the change in the reporting relationship of the CFIA from Agriculture and Agri-food Canada to the Minister of Health and the pending food safety legislation (discussed below) all signal a new era in Canadian food regulation – one of science-based decision-making. The challenge for the food industry will be to ensure that risk-based decision-making remains at the forefront of Canadian food regulatory policy in an era in which public focus and scrutiny are centered on foods and food ingredients which can be confirmed to be 100% free of the risk of any food-borne illness – an unattainable goal, particularly for unprocessed foods.

TO WATCH IN 2014:

- **The new CFIA president establishes his own regulatory approach**
- **The interaction between the CFIA and Health Canada given the new reporting relationship of CFIA to the Minister of Health**

- **Whether an increased focus on science-based regulatory decision-making in the food sector becomes evident**

The Coming into Force and Implementation of the Safe Food for Canadians Act (SFCA)

On July 7, 2013, the Canadian Food Inspection Agency (CFIA) released a discussion document: *A New Regulatory Framework for Federal Food Inspection*⁴ ("Regulatory Framework Document") and asked consumers and food industry stakeholders to comment on elements of the Safe Food for Canadians Action Plan which aim to strengthen and modernize Canada's food safety system. The consultation was designed to provide input into the regulations that are being developed in connection with the SFCA. The SFCA was passed in late 2012 and is expected to come into force mid to late 2014.

The proposed food inspection regulations under the SFCA will be supported by guidance documents, which will provide examples of how required outcomes could be achieved. The proposed regulations will apply to all federally regulated food commodities traded inter-provincially and internationally such as licensing, preventive controls, traceability, record-keeping, and a review mechanism.

The Regulatory Framework Document describes how existing federal licensing requirements would be extended to encompass all parties who import food commodities or prepare them for inter-provincial trade. All importers of food commodities would be required to be licensed. The Document notes that "Canada requires a food safety system capable of continuous improvement that evolves with new food safety practices, technology and other developments in industry to deliver the best possible protection for

Canadians from food safety risks.” It also looks to provide industry with flexibility for food safety approaches within facilities (recognizing that when it comes to food manufacturing, “one-size” does not necessarily fit all) and enables rapid response to emerging food safety risks. Key to the approach described is recognition of the need for alignment between provincial/territorial governments and international trading partners, in particular, the United States, to support greater market access.

It is apparent that there will be new, or more clearly defined, outcome-based requirements in the following areas:

- processes and product controls
- sanitation and pest control
- hygiene and competencies
- equipment design and maintenance
- physical structure and maintenance
- receiving, transportation and storage; and
- recalls, complaints and record-keeping.

With respect to recalls, complaints and record-keeping, for example, the Regulatory Framework Document provides that license holders must:

- develop, implement and maintain written procedures for the recall of food products,
- develop and maintain any product distribution records that are necessary to facilitate the location of products in the event of a product recall,
- review the product recall procedures and to conduct a product recall simulation at least once a year, and
- make available to the inspector, in a readily accessible format and location, a copy of the product recall procedures, the results of

the product recall simulations for the previous year and the product distribution records for at least one year after the expiry date on the label or container or if there is no expiry date, for at least two years after the date of sale.

The Regulatory Framework Document is focused on compliance promotion as well as on industry responsibility for quality systems at all stages of the food manufacturing, distribution and delivery systems.

TO WATCH IN 2014:

- **Implementation framework and timing for the coming into force of the *Safe Food for Canadians Act***
- **Increased licensing and record-keeping requirements for food importers under the SFCA**
- **Likely mandatory obligation to notify food regulators of food safety issues**
- **Continuing focus on voluntary recalls by food manufacturers**
- **Increased need to ensure good manufacturing policies and procedures (such as Hazard Analysis and Critical Control Points systems) are in place**
- **Need for recall policy and procedures for food manufacturers, importers, distributors, and retailers**

Temporary Marketing Authorizations and Marketing Authorizations

The *Food and Drugs Act* was recently amended to provide the Minister of Health with a new authority to issue what will be known as “Marketing Authorizations” (“MAs”). The new authority will permit the Minister to allow the use of specific substances in foods that

are currently not permitted in food in Canada (i.e. certain additives or innovative ingredients). The new authority will also allow the Minister to permit certain health claims for foods. With the new authority also comes the ability to set specific conditions on the approvals. The new approvals will take the form of a regulation made by the Minister of Health and, once the MA has been given, such authorizations may be used by all food manufacturers.

The new MA authority will not take the place of the current ability of Minister to grant Temporary Marketing Authorizations (TMAs) to companies that apply to be exempted from certain provisions of the *Food and Drugs Act* or the *Food and Drug Regulations*. TMAs are limited in scope to the company that applied for the authorization and generally are used to generate information that could lead to an amendment to the *Food and Drug Regulations*.

A second significant change is to allow broader referencing of public documents as part of regulations. This is termed “incorporation by reference”. This amendment would also include documents developed by the department and allows the government to avoid having to amend the regulations, for example, to approve a new additive; rather, new additives can be nominated to a list and thereby become “approved” for use.

TO WATCH IN 2014:

- **Expanded use of MA/TMA approvals**
- **Possible use of MAs for health claims**
- **Swifter regulatory response to new/updated information on currently unapproved food additives or innovative ingredients**
- **Greater use of the TMA procedure as a tool to allow foods to be**

marketed that are not compliant with current food regulation while generating the research and information necessary to support an amendment to the Food and Drug Regulations.

Food Labelling Modernization

The CFIA conducted face-to-face engagement sessions in Canada in October 2013. The purpose of the sessions was to provide the public (consumers, food industry participants and other stakeholders) with an opportunity to raise food-labeling issues and to provide input to the CFIA on the Canadian food labeling modernization initiative that is currently underway. The CFIA also issued a discussion paper relating to the Food Labelling Modernization initiative. A key goal of the engagement sessions was to “collect and prioritize” issues that are important to consumers, industry and other stakeholders. Representatives of both the CFIA and Health Canada were in attendance at the sessions and at the sessions the CFIA updated those in attendance on the status of the Safe Food for Canadians Action Plan and other initiatives being undertaken under that Plan.

The discussion paper⁵ provided a useful framework of what was in/outside of the scope of the Food Labelling Modernization initiative. And, the differences are important: “in scope” were basic (and generally less controversial) food labeling requirements such as ingredient lists, ingredient class names, best before dates, standard of identity, dealer name and address. With consultations now complete, analysis and draft recommendations are expected to follow in 2014 with possible further stakeholder engagement. The CFIA had indicated that it would post its report either in the winter of 2014 or in the spring of 2015.

Regulatory changes arising from the initiative would, therefore, likely take place some time in 2015 (or later).

Importantly, however, “out of scope” (for the initiative at least) were significant labeling issues falling within the purview not of the CFIA but of Health Canada; these include nutrition labeling, health claims, allergen labeling requirements, genetically modified foods, novel foods, food safety related labeling requirements and food additives. It is possible that change may come not in the form of regulatory amendments but rather in the form of increased guidance, particularly in areas such as health claims, an area of significant change and evolution within the North American food industry.

TO WATCH IN 2014:

- Possible further engagement sessions with industry on CFIA labeling initiative
- Increased need for and focus on regulatory food labeling and claims issues within the purview of Health Canada and other federal regulators
- Possible guidance from Health Canada on nutrition and health claims for foods

Food Recalls and Recall Fatigue

The CFIA website reports that in 2012 497 recalls took place. That number dropped only slightly in 2013 – to 442. However, many of these recalls were precautionary in nature – no illness or injury had been reported but the recall nonetheless was actioned because, at least theoretically, the product either did not meet the food quality standards of the manufacturer and/or a theoretical food safety risk had been identified. The quintessential issue, and regulatory/industry conundrum arises: at what point does

over-recalling food (i.e. recalling food in respect of which no health risk exists) actually undermine food safety standards? And, at what point do numerous recall announcements (expanding on the scope of products in announcements previously made) do more harm than good? Such harm could occur if consumers are so accustomed to reading about food recalls, indeed so desensitized to the issue, that they are unable to ascertain whether there is a true food safety issue that could affect their health.

TO WATCH IN 2014:

- Number and extent of “derivative” food recalls (a new recall is announced in respect of a product with a connection to an earlier recall)
- SFCA regulations and possible food safety or recall reporting requirements
- Calls for a limit to food recalls to those where a true food safety issue exists

1. Canadian Food Inspection Agency Act, S.C. 1997, c. 6
2. Health Canada, “Background Information: Canadian Food Inspection Agency Joins Health Canada”.
3. Health Canada, “Background Information: Canadian Food Inspection Agency Joins Health Canada”
4. Canadian Food Inspection Agency: “A New Regulatory Framework for Federal Food Inspection”; Online: <http://www.inspection.gc.ca/food/action-plan/food-safety-regulatory-forum/presentations/discussion-document/eng/1370029593829/1370029641557?chap=18#s17c18>
5. Available online: <http://cspinet.org/canada/pdf/discussionpaper.foodlabelingmodernizationinitiative.2013.pdf>



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- April 22 - FDLI Committee Meetings
- April 23 - General Sessions & Break-outs
- April 24 - General Sessions & Break-outs

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2014 Conference Highlights *(as of 2/6/14 check online for updates)*

Keynote Addresses

The Honorable Samuel A. Alito, Jr., Justice, Supreme Court of the United States

Michael R. Taylor, Deputy Commissioner for Foods and Veterinary Medicine, Office of Foods and Veterinary Medicine, FDA

General Sessions

- The Role of Non-Governmental Standards in Food and Drug Law
- Top 20 Cases in Food and Drug Law in 2013 and Cases to Watch in 2014
- Going Global: What Food and Drug Law Stakeholders Need to Know about Counterfeiting and Fraud

Hear Directly from FDA Product Center Directors

- **Karen Midthun, MD**, Director, Center for Biologics Evaluation and Research, Office of Medical Products and Tobacco, FDA (invited)
- **Jeffrey E. Shuren, MD, JD**, Director, Center for Devices and Radiological Health, OMPT, FDA
- **Janet Woodcock, MD**, Director, Center for Drug Evaluation and Research, OMPT, FDA
- **Michael M. Landa**, Director, Center for Food Safety and Applied Nutrition, Office of Foods and Veterinary Medicine, FDA
- **Mitchell R. Zeller, JD**, Director, Center for Tobacco Products, OMPT, FDA

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- Interchangeability & Pharmacy Substitution: Laws and Regulations in the United States and European Union.
- Full Lifecycle Data Transparency: The Impact of Clinical Trial Transparency, DQSA "Track and Trace" Measures and Post-Market Surveillance
- Mobile Medical Apps and Unique Device Identifiers: Regulatory and Business Challenges
- Protecting our Food Supply: Food Defense Initiatives
- Improving Animal Feed Quality: Proposed Regulations for Pet Food & Animal Feed
- An Update on Tobacco Product Deeming Regulations

Emerging Issues

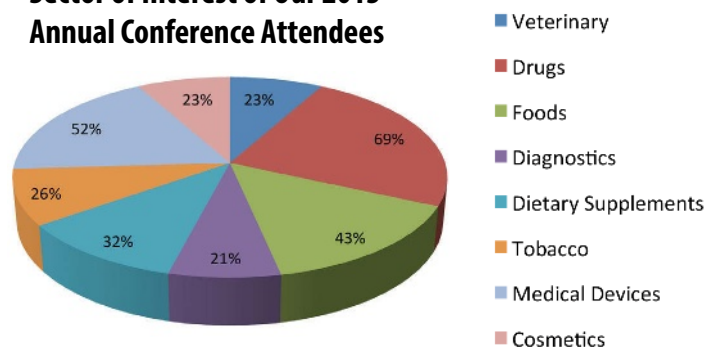
- Ethics (CLE) Liability Under the Park Doctrine: Duties and Pitfalls
- Patent Litigation in the Wake of FTC v. Actavis
- The Complexities of Personalized Medicine: Compliance and Litigation Strategies for Combination Products
- The Future of Food, Cosmetics & Dietary Supplements Labeling: Government Agency Initiatives in 2014
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How the Pharmaceutical Industry Should Prepare to Address the New Legislative and Regulatory Challenges In the European Union

By Vincenzo Salvatore

In less than a couple of years, the European Union has adopted new rules applicable to post-marketing surveillance of medicinal products (“the new pharmacovigilance package”), additional measures to mitigate the risk that falsified medicines are placed into the distribution channels (“the falsified medicines directive”) and new provisions aiming at tightening and making more effective enforcement proce-



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dures (“the Penalty regulation”). In addition, the ordinary legislative procedure concerning a new proposed regulation governing clinical trials and new proposed regulations introducing a mechanism of safety scrutiny and traceability requirements for medical devices is fairly advanced and, at the time of writing this article (January 2014), the concerned regulations are expected to be finally adopted in the next few months. Last but not least, the European Medicines Agency is substantially revising its transparency policy that, although being temporarily delayed due to currently ongoing litigation before the Court of Justice of the European Union, will definitely strengthen the openness approach of the European regulator by granting access to a much broader set of information related to clinical trials. This rapidly evolving scenario requires pharmaceutical and medical devices industry members to thoroughly consider how to best prepare to face

the new challenges and to comply with the new requirements set by the revised legal framework.

The new pharmacovigilance package

A new set of rules applicable to pharmacovigilance activities were set by Regulation EU 1235/2010 and by Directive 2010/84/EU, both applicable as of July 2012, vesting respectively the European Medicines Agency and national competent EU member States regulatory authorities with new responsibilities with regard to post marketing surveillance of medicinal products. This legislation was subsequently amended by provisions applicable as of June and October 2013 (respectively, Regulation 1027/2012/EU and Directive 2012/26/EU) in order to ensure a prompt and accurate exchange of information and timely regulatory actions to be taken at European level in case of failure or inadequacy to act by national competent authorities within the concerned domestic jurisdiction. Should the latter be the case the European Medicines Agency is now empowered to intervene by recommending the European Commission to adopt urgent regulatory actions also with regard to safety concerns related to products authorized at national level, formerly falling outside of the remit of the European regulator. The new system that has been further implemented by the adoption of a Commission regulation (520/2012/EU) defining the scope and the extent of the pharmacovigilance obligations placed upon the marketing authorization holders. It:

(a) imposes tighter obligations as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorized in the European Union;

(b) introduces new requirements to be met in the structure of the risk management plan;

(c), strengthens the transparency of the post-marketing surveillance procedures by making publicly accessible the agenda and the minutes of the activity of the newly established *ad hoc* EMA pharmacovigilance risk assessment committee (PRAC), and

(d) requires EMA to capture all possible signal of safety concerns by requesting the Agency to perform scientific literature monitoring and to duly assess all relevant information that may be received through public hearings or by spontaneous report.

Another significant change is linked to the inherent risk of the concerned medicinal product: the new legislation foresees different rules applicable to different categories of products according to their risk exposure, being they new products or products for which specific safety concerns have been identified. The latter will determine their inclusion in a list of product subject to additional monitoring, according to a principle of proportionality in the imposition of pharmacovigilance obligations.

Other new features of this legislation relates to the possibility to require the marketing authorization holder to perform post authorization safety studies (PASS) and post authorization efficacy studies (PAES). The idea behind that is the continuous benefit-risk assessment approach that should accompany the product during its entire lifecycle: from the very early stage of clinical trials until the product has been removed from the market.

While follow-up measures (FUMs) were often recommended by the EMA scientific Committee for medicinal product for human use (CHMP), PAES are a

brand new tool that may be imposed to prove the efficacy of the product even after it has been licensed. This is somewhat revolutionary as it implies that efficacy should be demonstrated in a much broader context than the usual clinical trials scenario and it will be crucial to understand its full import. An answer will come in the regulation the European Commission must adopt. One aspect that appears to be a recommendation from the Pharmaceutical Committee is that they should not contain comparative assessment requirements.

In order to facilitate compliance with the new requirements set by the revised legislation, the European Medicines Agency has adopted guidance documents in the format of good pharmacovigilance practice (GVP) modules, devoted to selected topics, in order to promote best practices and to provide all the stakeholders with the regulators' interpretation of the relevant provisions of the legislation. Once this exercise is finalized, it is expected that EMA will enforce—and with true consequences. If infringement procedures are requested by the European Commission, by Member States or initiated by EMA, the deterrent is significant: a sanction of up to 5% of the company's European turnover for violations.

The threat of penalties proceedings, which have already been initiated, have led marketing authorization holders to provide new training, to introduce revised and updated standard operating procedures and to get their organization assessed by external experts and consultants through specific and appropriate due diligence exercises.

Towards a new regulation on clinical trials

A new major innovation that will shortly be introduced at the European

level relates to the new Regulation on clinical trials, which is expected to be adopted by April this year. The new regulation will repeal the current directive (2001/20/EC) and introduces a streamlined European procedure for the assessment of the clinical trials application that involves different member States, with the identification of a single reporting member State and a single outcome of the assessment valid for all the concerned EU member States.

A key change is the establishment of a single entry point, a EU portal for all the applications, which will represent the hub through which all the information and communication between the sponsors and the concerned member States will have to be channeled. The objective is to make Europe more attractive for clinical trials by streamlining both the application and the assessment procedure and eliminating the need for sponsors to apply to up to 28 different member States with the uncertainties and the disproportionate costs that come from the disparate regimes. The EU has, over the last few years, become less competitive globally, as demonstrated by the dramatic drop in the number of applications for new clinical trials registered in Europe from 2007 to 2011 (.

The pharmaceutical industry will have not only to become familiar with the new assessment procedure but also get used to a strengthened transparency approach. This goes far beyond the establishment and the updating of the EU clinical trials data base by the European Medicines Agency, as the new legislation also requires publication of a summary of the results of clinical trials within one year of completion and, whenever a clinical

study report is submitted to support an application for a marketing authorization, the concerned report will have to be made publicly available within 30 days from the granting of the marketing authorization (or from the date when the procedure has been otherwise finalized in case the marketing authorization has not been granted or when the applicant voluntarily withdraws).

The issue of transparency of clinical trials related information is particularly sensitive. The European Medicines Agency recently released for public consultation a draft policy new aiming at proactively publishing clinical-trial documents and data, including post-decision clinical-trial reports.. The new policy has not been adopted yet, and there are ongoing legal proceedings pending before the Court of Justice of the European Union triggered by companies challenging the legitimacy of the assumption made by the European Medicines Agency that clinical-trial related documents do not contain commercial confidential information and can therefore be made publicly accessible, providing that patient and other personal information are adequately protected.

The new regulation also includes a different regime for low-intervention clinical trials, sets new and more detailed rules on informed consent, and defines the role and tasks assigned to ethical committees in the authorization process. The possibility of co-sponsorship and the improved conditions for conducting multinational clinical trials are additional incentives that should encourage the pharmaceutical industry to (re-)identify Europe as an attractive place for conducting research.

New rules on safety and traceability of medical devices

Europe is moving from directives to regulations in the medical device space. Recent safety incidents (such as the PIP breast implants affair in France) have demonstrated the need for a revised and harmonized system of assessment of medical devices, until now left to the notified bodies operating in different member States. This has accelerated the legislative process at the EU level in order to better protect patient safety by strengthening supervision of national notified bodies and setting traceability requirements for higher risk medical devices.

A lively debate characterized the preparatory work on the revised legislation. Requests for introducing a pre-market assessment procedure, similar to the rules applicable for placing medicinal products on to the market, were proposed, as were proposals substantially maintaining the current regulatory framework (i.e., no pre-authorization mechanism) with a closer monitoring of the notified bodies activities. The compromise reached was a scrutiny mechanism at European level for medical devices which presents higher risks for patients.. Additional provisions will aim to introduce a progressive approach towards a common framework for a unique device identification system. This is intended to make high-risk medical devices traceable during their entire lifecycle, which improve incident reporting, facilitate efficient recalls and other field safety corrective actions and prevent abuses in the re-conditioning of medical devices intended for single use.



Crafting Changes for the Future: Increasing the Availability of Nonprescription Drugs

By Debra S. Dunne, RPh, JD and Brian T. Guthrie, PharmD, JD

The availability and use of nonprescription drugs is likely to increase in the near future due to rising health-care costs, patient interest in self-selection and self-treatment, and continued advances in technology. Recently, the Food and Drug Administration (FDA) has shown support for this proposition with its Nonprescription Safe Use Regulatory Expansion (NSURE) Initiative, which seeks to expand patient access to medications by making them available without a prescription.

Since 1951, the dispensing of drug products in the United States has been based on a two-class system: prescription and nonprescription.¹ Under section 503(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a drug must be dispensed by prescription if, “because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug.”² In contrast, a nonprescription or



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over-the-counter (OTC) drug is one that the FDA has determined is safe and effective for consumer OTC use and is generally recognized as having a benefit profile that outweighs its risks, a low potential for misuse and abuse, characteristics that support direct consumer use for self-diagnosed conditions, and an ability to be adequately labeled.

More than 300,000 OTC drug products are currently marketed in the United States.³ U.S. consumers have ready access to these products from a variety of retail settings, including pharmacies, supermarkets and convenience stores, at all hours of the day and night. Notwithstanding the strong U.S. market demand and research addressing the value of OTC drugs in reducing healthcare costs and expanding self-care, the nonprescription drug industry is constrained by an antiquated system of complex regulation and challenges that hamper bringing OTC drugs to market and, in particular, impede prescription-to-OTC switch approvals.

During the past 10 years, very few prescription drugs have switched to OTC status. However, promising signals of an increase in FDA support for prescription drug switches emerged with the rare approvals of two first-in-class prescription-to-OTC switches: *Oxytrol for Women*⁴ and *Nasacort 24HR*. These switch approvals may be a welcomed trend evidencing an agency willing to exercise its latitude to apply conditions of safe use to make a wider range of nonprescription drugs more available to consumers.

Further evidence of a changing regulatory environment for nonprescription drugs is FDA's NSURE Initiative. Under this new paradigm, the agency would approve the nonprescription use of medicines for certain diseases or conditions that otherwise would require

a prescription if certain conditions of safe use are met. Since introducing the paradigm in 2012, FDA has clarified that NSURE is not an effort to establish a third class of drugs, often referred to as "behind the counter" at the pharmacy. Rather, NSURE is aimed at creating flexibilities in how FDA considers a drug's prescription status through conditions of safe use. Under NSURE, these conditions of safe use could include requiring pharmacist intervention to ensure appropriate nonprescription use, involve the use of innovative technologies such as diagnostics for use in the pharmacy or other settings, or moving to a dual-availability system where a medication is available by prescription and OTC.

Innovation in switches and the NSURE Initiative are examples of regulatory game changers that could lead to significant outcomes for the OTC industry and change the OTC landscape as a whole. It seems that the typical barriers to self-diagnosis of a condition, self-selection of treatment and self-management of therapy with nonprescription drugs are slowly coming down in favor of a modern-day revolution with innovative technology and enhanced self-care solutions around an expanded range of nonprescription treatment options for consumers. A look at future considerations for nonprescription drugs with conditions of safe use, as a novel solution for undertreated diseases or conditions, follows.

Prescription-to-OTC Switch

The central approval issue in any prescription-to-OTC switch applications is whether the drug is safe and effective for consumer OTC use. This issue requires consideration of whether the consumer can successfully self-recognize and self-treat the condition and, importantly, whether the drug label indications,

directions and warnings can be understood by the average consumer without the assistance of a learned intermediary, i.e., physician, pharmacist or other health care provider.

A drug manufacturer can initiate a prescription-to-OTC switch by submitting a supplement to an approved new drug application (NDA). If the manufacturer plans to switch the entirety of the drug's indications from prescription to OTC without a change in the previously approved dosage form or route of administration, the manufacturer submits an efficacy supplement to the approved NDA. An NDA 505 (b)(1) should be submitted if the manufacturer is proposing to convert some but not all of the approved prescription indications to OTC marketing status. And, an original NDA (505)(b)(1) or 505(b)(2) is submitted if the sponsor plans to market a new product OTC whose active ingredients, indication or dosage form has not previously been marketed OTC.

Underlying an NDA for a prescription-to-OTC switch are the safety and efficacy data for the original prescription medication, information on adverse events reported in association with prescription use of the drug and, occasionally, information pertaining to OTC use in other countries. Special consumer-behavior research studies such as label-comprehension, self-selection and actual-use studies are often conducted to gain additional insights about consumer understanding and likely behavior in selecting and using the drug in an OTC setting. While these studies are not always required for a switch, consumer-behavior research may provide meaningful data for predicting if a drug can be used safely and effectively according to labeling in the OTC setting.

Drugs that are the first-in-class for a new indication, possess a novel mechanism of action or present unique concerns are designated for review by the Nonprescription Drugs Advisory Committee, which then makes recommendations to FDA. Such was the case in 2012, with the first-in-class FDA approval of *Oxytrol for Women*, a transdermal system indicated for women with overactive bladder. FDA approved another first-in-class prescription-to-OTC switch in July 2013 for the corticosteroid nasal spray *Nasacort*. The OTC-approved version, *Nasacort Allergy 24HR*, is planned for launch in spring 2014. And recently, there have been discussions about the possibility of a switch application for the prescription proton pump inhibitor (PPI) *Nexium*.⁵ A change in prescription status for *Nexium* would follow other PPIs previously switched to OTC, including *Prilosec OTC*, *Zegerid* and *Prevacid*.

Looking forward, FDA's Nonprescription Drugs Advisory Committee is scheduled to meet on February 26, 2014, to discuss data submitted by Armstrong Pharmaceuticals, Inc. in support of an NDA for the OTC marketing of an epinephrine inhalation aerosol under the proposed trade name *Primatene HFA* for temporary relief of intermittent asthma.⁶ This upward trend in switch applications is expected to continue through 2014 and beyond due to factors such as product lifecycle extension strategies, a market-driven health-care environment focused in part on consumer self-care, particularly for common chronic and recurrent diseases and conditions, and, as discussed below, a more welcoming regulatory landscape.

NSURE

Recognizing the impact on public health of under treatment of common diseases and conditions, the FDA is

seeking to address one aspect of the issue, access to appropriate medications, through the NSURE Initiative. One of the most dynamic initiatives to come out of FDA in the drug area, NSURE seeks to allow prescription drug products to become available without a prescription through the use of innovative technologies and other conditions of safe use, such as consultation with pharmacists and other health-care professionals.⁷ To initiate the conversation, the FDA held a public meeting in March 2012 titled "Using Innovative Technologies and Other Conditions of Safe Use to Expand Which Drug Products Can Be Considered Non-Prescription"⁸ and since then has held three workshops in cooperation with the Engelberg Center for Health Care Reform at Brookings, to explore practical considerations in the development of the NSURE Initiative.⁹ Although the conceptual framework for NSURE is still in development, the idea is that identifying the specific risks and safety issues for each drug can inform the development of targeted interventions and technologies that can serve as a condition of safe use in a nonprescription setting.

An interesting segment of the NSURE conversation is focused on the innovative application of technologies to facilitate the safe and effective use of a variety of products in a nonprescription setting. While the use of technology in health-care settings to enhance patient care is certainly not new, NSURE is considering several novel concepts, including (1) how applications developed for the Internet, smart phones, or other electronic devices can assist patients in making complex health-care decisions; (2) how portable and wireless diagnostic technologies that collect health information and transmit the data to

providers and consumers to inform and optimize treatment can be used to address a range of critical barriers to self-care; (3) how technology can serve as a safety tool to allow for new prescription-to-OTC switch pathways; and (4) how technology driven conditions of safe use can be integrated into the practice and workflow of the pharmacist, physician and nurse.¹⁰

Conclusion

The use of nonprescription drugs is likely to proliferate based on advancing technologies, market influences and patient interest in self-treatment. Through the NSURE Initiative, FDA is providing an opportunity for drug manufacturers and other interested parties to propose novel methods and delivery systems to allow prescription medications to be available to patients without a prescription. As Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research (CDER), stated, "We are crafting changes for the future and want to incorporate innovations and new technologies into CDER's regulatory practices....The rules for nonprescription status were established in an age when widespread access to information technology did not exist. The world is evolving. It is clear there are now many interactive mechanisms that can help consumers through the process of self-diagnosis and medication selection in a much more comprehensive manner than a few words on a fact box."¹¹

1. See Durham-Humphrey Drug Prescriptions Act, 82 p.l. 215; 65 Stat. 648; 82 Cong. Ch. 578.
2. 21 U.S.C. § 353(b)(1)(A).
3. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/Over-the-CounterDrugs/default.htm>

4. The NDA was submitted for the partial switch from prescription to OTC of the oxybutynin transdermal system.
5. <http://www.drugstorenews.com/article/pfizer-will-shepherd-otc-nexium-through-switch-process>
6. 79 Fed. Reg. 138, available at <https://federalregister.gov/a/2014-00091>
7. See <http://www.fda.gov/downloads/ForHealthProfessionals/UCM330650.pdf>
8. Using Innovative Technologies and Other Conditions of Safe Use To Expand Which Drug Products Can Be Considered Nonprescription; Public Hearing. Federal Register/Vol. 77, No.39/Tuesday, February 28, 2012/Notices 12059. Retrieved January 21, 2014, <http://www.gpo.gov/fdsys/pkg/FR-2012-02-28/pdf/2012-4597.pdf>.
9. See <http://www.brookings.edu/events/2012/11/08-nsure-initiative-event>; <http://www.brookings.edu/events/2013/11/04-nonprescription-drug-safe-use-regulatory-event>; <http://brookings.edu/events/2013/05/09-innovative-technologies-nonprescription-medications>
10. <http://www.brookings.edu/~media/events/2013/5/09%20innovative%20technologies%20nonprescription%20medicines/09%20innovative%20technologies%20nonprescription%20medicines%20discussion%20guide.pdf>
11. <http://www.fda.gov/Drugs/Resources/ForYou/SpecialFeatures/ucm297128.htm>

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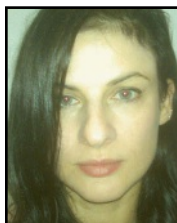
The Scientific Challenges of Toxicant Management in Combustible Cigarettes

By Mr. Gavin Mullard and Dr. Marina Murphy

It is well known that the more one smokes and the longer one is a regular smoker, the higher the risk of a smoking-related-disease – a so-called ‘dose-response relationship’. It is also known that it is the toxicants in cigarette smoke that cause smoking-related diseases. It therefore might make sense that reducing levels of toxicants in cigarette smoke may ultimately reduce smokers’ disease risk. For this reason, some regulators and tobacco companies are studying methods for reducing levels of smoke toxicants. Existing technology enables reductions in levels of certain smoke toxicants under laboratory conditions. But such reductions do not necessarily translate to reduced toxicant

uptake by smokers or necessarily reduce health risks associated with cigarette use. Reasons for this include:

- The lack of scientific consensus as to which smoke toxicants are the greatest contributors to disease;
- The extreme chemical complexity of cigarette smoke;
- The challenge of consistently measuring minute quantities of toxicants that; constantly interact and react with each other;
- The difficulty in distinguishing between differences in smokers’ toxicant uptake due to product changes versus differences caused by variations in smoking behaviour; and



Mr Gavin Mullard and Dr Marina Murphy, Scientific Affairs, British American Tobacco

- The difficulty of creating predictive tests to determine in the short term the risk of developing a disease in the long-term.

Clearly the complexity of cigarette smoke and the wide variability in smoking behaviour makes achieving meaningful toxicant reduction extremely challenging. It may be that substantial progress in the field of reduced-risk tobacco and nicotine products will take place in categories such as e-cigarettes or heat-not-burn products, for which toxicant production is much lower than it is for cigarettes. But reducing smokers' exposure to cigarette smoke toxicants will continue to be an important goal, given the numbers of people who smoke and who are likely to smoke in the foreseeable future. Further research should yield better, more advanced toxicant-reducing technologies. But first, it is essential to identify and agree which toxicants are the greatest contributors to disease and create an internationally accepted regime for measuring and reporting them.

Prioritizing Cigarette-Smoke-Toxicants

Historically, the main focus of toxicant regulation has been the requirement of disclosure and the setting of limits for cigarette emissions of tar, nicotine and carbon dioxide (TNCO). Currently there are more than 80 countries where TNCO disclosure is mandated. However, efforts have been ongoing for years to identify significant toxicants beyond TNCO and to prioritise for study the more than 150 toxicants identified so far. Success has proved elusive.

Priority lists have been created by some regulatory authorities, but they differ. For example, a list of eighteen 'priority' toxicants has been drawn up by the WHO's Study Group on Tobacco Product Regulation (TobReg), of which a

subset of nine have been recommended for mandatory lowering. The US Food and Drug Administration (FDA) has categorised ninety-three toxicants as Harmful and Potentially Harmful Constituents (HPHC). Of these, eighteen have been prioritised, based on the availability of analytical methods and constitute a representative example of the complete HPHC list. There is significant overlap between the FDA abbreviated HPHC list and the eighteen toxicants identified by TobReg, but the two lists are not identical. Meanwhile, Canadian regulators have prioritised forty-one toxicants.

For the most part, these lists of priority toxicants have been assembled on the basis of the toxicological properties of individual toxicants when studied in isolation, often in higher concentrations than found in tobacco or tobacco smoke. Although such methods are useful for identifying toxic substances, they are not sufficient for human risk assessment. For risk assessment, it is necessary to consider biologically relevant exposure levels, the potential impact of the complex mixture and many other factors. Cigarette smoke contains thousands of components that may enhance or offset the effects of individual components observed in isolation. Extrapolating the possible toxic effects of an individual compound to estimate the effects of that same compound in a mixture such as cigarette smoke is highly problematic. It is therefore essential that the presence and possible interactions of the thousands of components in cigarette smoke be taken into consideration.

Cigarette Smoke and Complex Mixtures

Lighting the end of a cigarette sets off a series of reactions including oxidation, reduction, addition, condensation, hydrogenation, pyrolysis, decarboxylation and dehydration that result in the

creation of an extremely complex mixture containing thousands of chemicals.

More than 6000 of these chemicals have been identified but there could be many thousands more present at levels too small to be determined using current technology. Indeed, it has been estimated that there could be as many as 100,000 individual components present in smoke¹. Of the 6000 plus chemicals identified so far, more than 150 have been identified as toxicants. These toxicants are part of a swirling mass of chemicals that are constantly interacting and reacting with each other. It is impossible with current technology to predict what happens when the system is perturbed. A reduction in the level of one toxicant can, for example, lead to an increase in the level of another, with unknown effects on health risk. For example, published data indicate that certain technologies that reduce the level of polycyclic aromatic hydrocarbons in cigarette smoke result in an increase in tobacco specific nitrosamines². Therefore, it seems that altering the chemical/toxicological profile of smoke raises concerns over the potential for unknown, adverse consequences, an important consideration when trying to establish and agree which toxicants should ultimately be prioritised as targets for reduction.

Measurement and Reporting

A modern cigarette contains just over half a gram of tobacco. From each cigarette, smokers generally inhale a hundredth of a gram of tar, a thousandth of a gram of nicotine, a few millionths of a gram of formaldehyde, and a few billionths of a gram of benzo[a]pyrene. It is the cumulative effect of years of exposure to minute quantities of smoke toxicants that leads to the onset of smoking-related disease.

Reliably measuring toxicant levels in smoke is difficult, because there are no

internationally validated and agreed analytical test methods to do this. This means that results can vary wildly not only between laboratories but also within laboratories. Identical products can produce vastly different toxicant emission scores, for example, depending on the machine-smoking conditions used for testing. A product under ISO (International Organization for Standardization) conditions can look very different when tested under Health Canada Intensive (HCI) machine-smoking conditions³. Therefore, development of standardised analytical chemistry methods that are robust and reproducible is a must in order to consistently produce data that allows reliable comparisons between products and potential methods for toxicant reduction.

Smoking Behaviour

The aim of reducing toxicant levels in smoke is ultimately to reduce smokers' exposure and uptake. But changing a cigarette may affect the way cigarettes are smoked. Concerns have been raised that the introduction of reduced toxicant combustible products could influence smoking behaviour in a way that increases, rather than decreases the negative health effects of tobacco. This may arise from smoker 'compensation', often exemplified by either increased smoking to maintain accustomed intake of smoke components such as nicotine and tar despite design changes intended to limit smoke uptake or by changes in smoking behaviour caused by subjective perceptions of the redesigned product⁴.

The act of smoking a cigarette is ostensibly very simple but involves a number of separate actions, each of which can vary from smoker to smoker. There are two main stages: Puff and Inhalation. Puffing involves manipulating the soft palate so that air can be drawn through the cigarette while the sealed lips hold the

cigarette and create a pressure drop that draws smoke into the mouth. Puff volume depends on mouth size. The smoke remains in the mouth until inhalation, the volume of which may vary from a shallow inhalation to near maximal inhalation but is typically between 700 and 1000ml⁴. Some smokers do not inhale at all. Others allow a proportion of the puff to drift out of the mouth or nose before inhalation; this is called waste smoke (or spillage). The last component is the breath-hold which usually lasts a fraction of a second.

A smoker can make many conscious and sub-conscious changes to these actions that alter the way the cigarette is smoked and which may affect smoke yield derived from the cigarette. When cigarettes are smoked, there may be substantial variations in number of puffs, time between puffs and number of cigarettes smoked per day. Indeed, smokers can change how they smoke cigarettes and/or their level of consumption in response to varying cigarette designs⁶. As noted, these changes in smoking behaviour can result from compensatory behaviour by the smoker^{5,6,7}, as well as from subjective perception of a new product. The issue here is that some smokers may be lured into a belief that combustible products regulated to be reduced in toxicants are somehow safer than conventional cigarettes⁴ and change their behaviour in response to that.

Quantifying Exposure and Effect

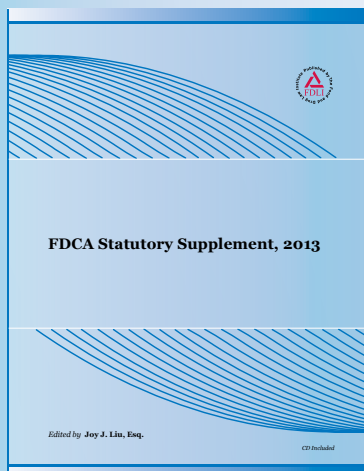
While successfully reducing the levels of toxicants in cigarette smoke is an important goal, it must be acknowledged that what is present in cigarette smoke is not the same as what is delivered to the smoker. It is possible to get a measure of what is delivered to the smoker using biomarkers of exposure — these are chemical compounds found in biological

fluids, such as blood and urine, that may consist of cigarette smoke toxicants or their metabolites. Monitoring such biomarkers during smoking is a technique that has been used to demonstrate that it is possible to reduce smokers' exposure to toxicants over a 6-week period by switching them from conventional cigarettes to a prototype reduced-toxicant cigarette⁸. But it is not known what level of reduction is required to produce a meaningful reduction in health risk, and it remains to be seen whether any reduction can be maintained over the longer term. Assuming that it can, quantifying impact on health risk will require a different set of biomarkers known as biomarkers of effect. These biomarkers of effect are indicators of the body's response to exposure and indicate early sub-clinical changes, which if sustained, may result in disease. Development of reliable, validated biomarkers of effect in relation to smoking-related disease remains a challenging undertaking.

Conclusion

There are serious health consequences associated with cigarette use and a demonstrated relationship between exposure to toxicants in tobacco smoke and smoking-related disease. To date, it has not proved possible to demonstrate that selective removal of specific toxicants from tobacco smoke will have any public health benefit, but seeking to identify the toxicants that are the greatest contributors to disease should continue to be an important research objective. However, it may be that reduction in health risks of tobacco use cannot be achieved by focusing only on combustible products such as cigarettes. Progress in the field of reduced-risk products will likely occur in non-combustible categories, such as electronic cigarettes, heat-not-burn and smokeless tobacco, especially in the shorter term

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FDCA Statutory Supplement, 2013

Edited by Joy Liu, Esq

Why spend countless hours trying to piece together recent amendments to the Federal Food, Drug, and Cosmetic Act (FDCA)? We've done the work of highlighting the 2013 changes for you in the latest issue of Statutory Supplement. The Drug Quality and Security Act amends the FDCA in some very important ways, including: explicitly exempting some compounded drugs from certain requirements; establishing annual registration and reporting requirements for outsourcing facilities; establishing "track and trace" requirements, and

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Summary of the Keynote Address at FDLI's 2013 Enforcement Conference: HHS OIG's Prescription Drug Diversion Enforcement Efforts

By Davina Rosen Marano, Esq.



Gary Cantrell, Deputy Inspector General, OIG, HHS speaking at FDLI's 2013 Enforcement, Litigation and Compliance Conference. Photography from FDLI's 2013 Enforcement, Litigation and Compliance Conference. Photography by Valter Schleder.

The statement that “[g]reed has motivated, unfortunately, too many of our healthcare providers to commit fraud” punctuated the Keynote Address presented by Gary Cantrell, Deputy Inspector General for Investigations in the Office of Inspector General of the U.S. Department of Health and Human Services (HHS). Cantrell opened FDLI's 2013 Enforcement, Litigation and Compliance Conference by reminding attendees that “[h]ealthcare fraud is real,” as evidenced by 2013's 960 related criminal convictions and nearly 500 civil actions.

In advancing the Office of Inspector General (OIG's) articulated mission of protecting “the integrity” of HHS programs

and its beneficiaries, Cantrell explained that OIG is tasked with conducting criminal, civil and administrative investigations of prescription drug diversion, abuse and fraud of Medicare and Medicaid programs. Investigations that suggest fraud are then referred for prosecution, a process that Cantrell said ultimately results in the exclusion of over 3,000 healthcare entities annually from participation in federal healthcare programs.

The typical fraud scheme, according to Cantrell, illustrates that the trust Americans place in physicians and pharmacists “isn't always deserved.” These schemes usually involve a “dirty” physician and pharmacist; the physician writes a fake

prescription, which the pharmacist then files with CMS for reimbursement. The scheming physician, known as a “pill mill,” then receives financial kickback from the dirty pharmacist. Cantrell identified Detroit, Michigan as a “hot spot” and South Florida as an “epicenter” for prescription drug fraud.

Cantrell also illuminated how advancements in technology have made fraud and abuse investigations much more efficient; fraud cases frequently took up to five years of intensive review when he joined OIG sixteen years ago. The vast reduction in processing time comes in part from access to national Medicare claims data, explained Cantrell. OIG can see national billing trends in order to identify, for example, spikes in billing and higher per capital billing in certain areas.

According to Cantrell, “the best example” of OIG’s current investigative efforts is the Medicare Fraud Strike Force. These are collaborative task forces between OIG, the Federal Bureau of Investigation, the Centers for Medicare & Medicaid Services, and the United States Department of Justice that operate in

nine cities nationwide. Cantrell presented their staggering success rates: \$5 billion in fraudulent billing to Medicaid exposed and over 1500 individuals charged.

OIG currently puts most of its effort into fraud and abuse cases because it is mandated by the Healthcare Fraud and Abuse Act; roughly 80% of resources must go toward CMS investigations. Cantrell advised that investigations into food and related sectors will be a “small part of [OIG’s] portfolio until the funding streams change.” OIG does, however, publish a workplan every year informing the sectors of how its efforts will be divided.

Cantrell concluded his speech by stressing that efforts to educate players in healthcare fraud schemes are aimed at preventing future wrongdoing. “Prevention [through education] is really the solution,” he opined. Cantrell reminded the audience that “[t]here is not just a financial impact [of fraud], which affects all of us as taxpayers. There is also a human impact where we [see] the overprescribing of pain medication [when] they are not necessary, resulting in overdoses and sometimes deaths.” ▲

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A Look Back at FDLI's Annual Enforcement, Litigation & Compliance Conference: Highlights from "Compliance Central with FDA Center Compliance Directors (Part I)"

By Rachael A. Vieder, Esq., Manager, Medical Devices/Drugs Portfolio; Editor



Photography from FDLI's 2013 Enforcement, Litigation and Compliance Conference. Photography by Valter Schleder.

ce, snow and a government shutdown could not stop the Enforcement show from going on. Lewis Grossman, Professor at American University Washington College of Law and FDLI Director, aided by Susan Winckler, President and CEO of FDLI, led our FDA panelists, Ilisa Bernstein, Deputy Director, Office of Compliance, CDER; Daniel McChesney, Director, Office of Surveillance and Compliance, CVM; and Jennifer Thomas, Director, Division of Enforce-

ment, Office of Compliance, CFSAN in a discussion covering compliance issues and goals for 2014.

Jennifer Thomas focused on FSMA implementation, including a discussion on FSMA enforcement tools, and food facility registration. Thomas stated that FSMA implementation is a priority and the center is gearing up to shift from the implementation stage to the operations phase of FSMA. Thomas said that CFSAN has used all of their new tools so far, including

suspension of registration, administrative detention, and mandatory recall. Thomas also mentioned that, to avoid being too harsh, CFSAN has the discretion to give the company an opportunity to do a voluntary recall before imposing a mandatory recall. An audience member asked Thomas if she ever imagined having to use the mandatory recall power. Thomas responded that CFSAN would most likely use it in an untraditional situation rather than a normal occurrence.

Ilisa Bernstein spoke next and covered quality initiatives, FDASIA implementation and the new Drug Supply Chain Security Act. Bernstein discussed CDER's new Office of Pharmaceutical Quality (OPQ). Bernstein said that this office is still under development, but that it is moving forward. Bernstein further elaborated and said that this new office is meant to help fulfill the vision of ensuring there are clinically relevant standards across the products and giving more transparency to the center. Addressing the Drug Supply Chain Security Act, Bernstein discussed the secure supply chain pilot, which she said will enable up to 100 qualified firms to expedite the importation of APIs and drug products into the US. Bernstein also

briefly touched on the counterfeit and unapproved drug and said that CDER sent letters to over 1,500 medical clinics/doctors to educate them on avoiding counterfeit and unapproved drug purchases.

Daniel McChesney rounded out the panel and reflected on CVM's 2013 priorities and addressed its 2014 priorities. McChesney noted that CVM's previous priorities included antibiotic resistance issues, drug shortages and safety matters, compounding and unapproved animal drugs and pharmacovigilance. McChesney said that CVM's 2014 priorities include eliminating the FOIA backlog, improving Section 105 backlog and transparency, and identifying path(s) to legal status for unapproved animal drugs. The panel ended on a light note, with McChesney briefly discussing the dangers of having a small turtle as a pet (small turtles carry risks of salmonellosis).

A similar theme running through all of the presentations is that in 2014, we can look forward to CFSAN, CDER, and CVM's compliance offices to strive to correct existing issues and work to implement new strategies for smoother operations in the coming year. ▲



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Hyman, Phelps & McNamara, P.C., the largest dedicated food and drug law firm in the country, is proud to announce that Jim Shehan has joined as Of Counsel. Mr. Shehan comes with more than 25 years of pharma experience, 19 of those serving as Novo Nordisk Inc.'s General Counsel and Corporate Vice President of Legal, Government, and Quality. Mr. Shehan began his career at FDA as Regulatory Counsel in the Office of the Associate Commissioner of Health in 1985-1986, and later went on to advise Pfizer as a regulatory attorney. He has particular expertise in pharmaceutical product lifecycle strategy, including Hatch-Waxman litigation; the emerging field of biosimilar regulation and policy; and orphan drug regulation and exclusivity. His experiences in government, industry, and private legal practice allow him to share with clients a broad perspective on a variety of issues.

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A Look Back at FDLI's Annual Enforcement, Litigation & Compliance Conference: Highlights from "Compliance Central with FDA Center Compliance Directors (Part II)"

By Rachael A. Vieder, Esq., Manager, Medical Devices/Drugs Portfolio; Editor



Photography from FDLI's 2013 Enforcement, Litigation and Compliance Conference. Photography by Valter Schleder.

After a brief break from our Compliance Central Part I panel, Lewis Grossman, Professor at American University Washington College of Law and FDLI Director, aided by Susan Winckler, President and CEO of FDLI, followed on with our second panel, Mary A. Malarkey, Director, Office of Compliance and Biologics Quality, CBER; Steven D. Silverman, Director, Office of Compliance, CDRH; and Ann L. Simoneau, Director, Office of Compliance and Enforcement, CTP, in a discussion covering compliance issues and goals for 2014.

Beginning with Steven Silverman of CDRH, Silverman covered CDRH's reorganization, reviewed the Case for Quality initiative, and addressed the Voluntary Compliance Improvement Program (VCIP) pilot program. Silverman discussed the reason for the reorganization, noting that certain important compliance activities had been historically underserved and the reorganization allowed for more attention to go to those previously underserved activities. The reorganization will also free up Office of Compliance's front office to focus on cross-cutting

issues, said Silverman. Silverman then touched on the Case for Quality Initiative and discussed its three pillars: Focus on Quality, Enhanced Transparency, and Stakeholder Engagement. Silverman closed out his presentation with a discussion about the Voluntary Compliance Improvement Pilot (VCIP). Silverman said this program allows participants to self-correct problems instead of undergoing FDA inspection. Silverman also said that right now, they are focused on having participants who manufacture devices that contain batteries.

Mary Malarkey followed and gave an overview of the office structure and priorities. CBER's current priorities include FDASIA implementation, preparing for the office's move to White Oak and flu season preparedness, Malarkey noted. Malarkey detailed what key portions of FDASIA does, including expanding reporting requirements for permanent discontinuances or interruptions in manufacturing and requiring annual reporting to Congress on drug shortages. Malarkey also listed some of CBER's accomplishments during FDASIA's implementation, like the release of its strategic plan and a proposed rule requiring all manufacturers to notify FDA of a permanent discontinuance or interruption in manufacturing. Malarkey also said that current compliance initiatives include the continuing expansion of the electronic lot release system, completing the implementation of the Direct Recall Classification (DRC) System for all CBER-regulated products and launching

the Biologics Export Certification Application and Tracking System (BECATS). Malarkey finished her presentation by outlining CBER's vision for the office – their ultimate goal being to advance public health through innovative technology.

Ann Simoneau ended the panel with a discussion of CTP's office structure and its compliance activities. Simoneau touched on the office's tobacco marketing surveillance and said that the office conducts routine monitoring and surveillance of websites and publications that sell, distribute, promote, or advertise regulated tobacco products. Simoneau included an interesting graphic that showed that the most internet and print marketing violations are committed by companies marketing flavored tobacco, followed by "low," "light" or "mild" tobacco products. Simoneau also stated that CTP's compliance office issued nine warning letters as of September 2013 for smokeless tobacco products without their required warnings. After discussing more warning letters, Simoneau ended the discussion with listing the top five violations found during tobacco retailer inspections. Those five violations are: selling tobacco products to minors, failing to verify the age of a person purchasing tobacco products by means of photographic identification, selling through impersonal modes, selling tobacco products in a quantity that is smaller than the smallest package distributed by the manufacturer for individual consumer use and adulterating flavored cigarettes, according to Simoneau. ▲

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The Inaugural Eric M. Blumberg Memorial Lecture

Comments from Annamarie Kempic, Deputy Chief Counsel for Litigation, Office of Chief Counsel

By Elizabeth Stevulak, Manager, Tobacco and Drugs Portfolio; Editor



Annamarie Kempic, Deputy Chief Counsel for Litigation, OCC, FDA speaking at FDLI's 2013 Enforcement, Litigation and Compliance Conference.

Photography from FDLI's 2013 Enforcement, Litigation and Compliance Conference. Photography by Valter Schleder.

Frederick H. Degnan, Partner, King & Spalding LLP, introduced the Inaugural Eric M. Blumberg Memorial Lecture and lecturer, Annamarie Kempic, Deputy Chief Counsel for Litigation, Office of Chief Counsel, FDA during FDLI's Enforcement Litigation and Compliance Conference. This lecture is a new and permanent addition to FDLI's annual Enforcement Conference and was established

after Blumberg in honor of his many years of service with the FDA. Prior to introducing Kempic, Degnan commented on Blumberg's extraordinary career and accomplishments which included a role in shaping FDA's policy on holding individuals responsible in enforcement cases.

Degnan cited a speech given by Blumberg at FDLI's December, 1999 meeting in which Blumberg noted that individuals

are held responsible for the “Practical reason that FDA cannot be in every factory less monitor every decision made every day the affects the quality of our foods, our drugs, our devices and our cosmetics.”

Kempic spoke to attendees on the special relationship between industry and consumers, specifically regarding how enforcement affects the public health. Kempic noted that consumer protection is a fitting topic because Blumberg saw himself, first and foremost, as an advocate for, and protector of, the public from products that could be harmful.

The burden of protecting the public health falls partially to FDA. “The public has a great stake in the compliance decisions manufacturers make,” observed Kempic, and pointed out that “the products that the agency regulates account for \$.25 of every consumer dollar spent.” She added that, “people want to know that the products that you make, that the agency regulates, will do what they say they will do and at a minimum that they won’t be harmed.”

Enforcement is important because foods and medical products are critical to the public health. Kempic quoted a relevant Supreme Court decision to illustrate the need for enforcement to ensure public health which states, “Products touch phases in the lives and health of people, which in the circumstances of modern industrialism, are largely beyond self-protection.”

In an effort to self-regulate and protect the public consumer, Kempic observed that, “a good percentage of the industry is self-motivated... but enforcement looks at the folks that are just not quite sure or need some additional convincing.”

There are three things that FDA aims to do though enforcement to motivate compliance. The FDA protects the public from products that are illegal and could be harmful, they try to intervene in an attempt to compel compliance or stop violations, and they initiate action to make sure that unacceptable activity is addressed.

An example of the first category is FDA’s ability to seizures. Items seized will be held until the product is brought into compliance or until it is destroyed. This is an important step in enforcement to protect the public and stop distribution of products.

Kempic commented that the agency has some new tools at its disposal, including administrative detention authority over foods drugs devices and tobacco. “In each action The goal is to protect the public from products that they would have no reason to suspect could harm them or in some cases are purely fraudulent.” Kempic added that when more enduring results are required to prevent ongoing violation, the agency will seek a court order, such as an injunction. New tools include registration suspension or debarment for some drug or food importation violations. “Industries are regulated for a reason,” stated Kempic, “and the costs are so high to the public, the folks in the industries can at least know what goes on behind the scenes and can take measures to protect and prevent violations – the public cannot.”

“The agency works closely with DOJ to make sure that egregious violators, those responsible for jeopardizing the lives, health and wellbeing of American consumers will be prosecuted. “As an example, Kempic cited the case where two individuals were prosecuted for introducing tainted cantaloupe into the market. The cantaloupe, containing listeria, was distributed widely in at least 28 states and was estimated to have caused at least 33 deaths.

In closing, Kempic asked attendees to reflect on the important role manufacturers, distributors and the FDA plays in protecting the health and wellbeing of consumers. Kempic encouraged each industry to create and maintain a corporate culture committed to compliance. ▲

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EU Health Claims: An FDLI Webinar

By Stephanie Barnes, Esq., Senior Manager, Foods and Global Portfolio, FDLI

On November 20, 2013 FDLI hosted the EU Health Claims Webinar, providing an overview of health related claims for foods in the European Union (EU) and U.S. as well as recent developments involving health and nutrition claims and what to expect in the future. Ricardo Carvajal, Director at Hyman Phelps & McNamara, P.C., laid the framework for the discussion by describing the different types of health claims available in the U.S. including structure function claims, qualified health claims, and nutrient content claims.

In contrast to the U.S. requirements, manufacturers marketing products in the EU must prove nutrition and health claims before making such representations in the market. Vicente Rodriguez, Attorney at Law Legal Agrifood Abogados, explained that as of December 2006, the Regulation on nutrition and health claims made on foods was adopted by the Council and Parliament. For the first time, this Regulation lays down harmonized rules across the European Union for the use of nutrition claims such as “low fat”, “high fiber” or health claims such as “reducing blood cholesterol”, explained Rodriguez. He noted that the EU is attempting to harmonize these rules for all member nations and as of December 2012, more than 200 health claims have been approved. This Regulation foresees implementing measures to ensure that any claim made on foods’ labelling, presentation or marketing in the European Union is clear, accurate and based on evidence accepted by the whole

scientific community. In addition, in order to bear claims, foods will have to have appropriate nutrient profiles which will be set, thus enhancing consumers’ ability to make informed and meaningful choices, stated Rodriguez.

Attendees from both the EU and the U.S. posed many questions as to the similarities and differences of health claims regulations in both countries. Carvajal and Rodriguez closed the webinar with a discussion of what’s to come in health claim regulation in both countries. Recent years have seen an explosion in litigation that targets food products alleged to make fraudulent claims in the U.S. and it doesn’t appear to be slowing down, explained Carvajal. Litigation can be triggered by an FDA warning letter that takes issue with a claim or a Federal Trade Commission action. We’ve also seen dampened enthusiasm with health claim petitions due to the work and expense, along with lack of exclusivity, he observed.

Finishing the list of health claims and finalizing the definition of nutrient profiles are among the current priorities in the EU. Nutrient profiles should be established as a limit to health and nutrition claims to avoid claims that mask the overall nutritional status of the food product, stated Rodriguez. The concept of nutrient profiles is quite controversial and has not been established by the European Commission, but will be forthcoming, he concluded. Δ

Interagency Enforcement Action: An Inside Look

By Elizabeth Stevulak, Manager, Tobacco and Drugs Portfolio; Editor



Photography from FDLI's 2013 Enforcement, Litigation and Compliance Conference. Photography by Valter Schleder.

On December 11, 2013 attendees of the Enforcement, Litigation and Compliance conference got an inside look at interagency enforcement actions in Washington, DC. Moderator Eugene M. Thirolf, an independent consultant, began the discussion by suggesting a common theme of interagency cooperation despite budget and resource constraints. Thirolf noted, “due to budget constraints, and in the wake of hiring freezes, agencies must continue to work together in order to amplify whatever is out there.”

Attendees heard from speakers Jill Furman, Deputy Director, Consumer Protection Branch, Department of Justice (DOJ), Beth P. Weinman, Associate Chief Counsel for Enforcement, Food & Drug Division, Health and Human Services (HHS) Office of the General Counsel, and Mary E. Riordan, Senior Counsel, Office of Counsel, Office of the Inspector General, HHS on their coordination and cooperation with pharmaceutical and medical device enforcement actions, and with each

other. Jill Furman, spoke on the involvement of the consumer protection branch, formerly known as the Office of Consumer Litigation, in enforcement efforts. The DOJ's civil division has civil and criminal authority to handle all litigation arising under the food drug and cosmetic act. The Consumer Protection branch began a formal collaboration in 2009 between HHS and DOJ known as the “Healthcare Enforcement Action Team” (HEAT). “Both the attorney general and secretary of HHS have established that health care fraud is a priority for both departments, and the partnership has been strong and is growing stronger each year.” Beth Weinman also commented on the collaboration between agencies by explaining her role as associate Chief Counsel in FDA's Office of the Chief Counsel. Weinman explained the office contains a group of attorneys that is authorized to provide legal counsel to the agency. The Civil litigators defend the FDA and work on civil enforcement cases, whereas criminal litigators serve as counsel to the office of criminal

investigations. Weinman's office counsels the Office of Criminal Investigations (OCI) on their investigations and serves with attorneys in Furman's office as subject matter experts on the FDC act. On the topic of budget cuts, Weinman stated "The work we do involves folks from agencies across the government. The false claims act may affect money paid out across many different federal programs. These cases require that we work together. With less money we need to work together smarter. With limited resources we need to be investigating smartly, closing cases quickly and focusing on cases that have the most 'bang for their buck' both in regard to public health protection and recovering money for the government."

Mary Riordan, in reference to her position in the Office of the Inspector General reminded attendees that, "By statute and by operation and structure, we are supposed to be separate and independent from the rest of HHS. This is due to our mission – to prevent and detect fraud and abuse in HHS programs. (Ex: Medicaid and Medicare). We also try to improve efficiency and effectiveness in those programs." Riordan's office often assigns agents to investigations on the ground level; however she commented that due to budget constraints, "We try to be smart about using our resources and will often partner with other agencies." Riordan added that, "There are really two components in the resolution of a civil false claims act case. One involves the money and the other involves a resolution of the OIG's administrative exclusion authorities." OIG has exclusion authority which is a prospective remedy that essentially prohibits the payment by federal health care programs for items or services that are furnished by an excluded individual or entity. Practically speaking, what this means for drug and device companies is if a drug or device entity is excluded in participating in fed health care programs Medicare and Medicaid are not going to pay for items produced by that manufacturer.

Robert L. Hill, Executive Assistant, Office of Diversion Control, Drug Enforcement Agency (DEA), gave a prescription drug focused presentation to attendees and addressed enforcement on a national level. The main mission of the Office of Diversion Control is to neutralize individuals and organizations that are involved in the illegal distribution of controlled pharmaceuticals and list 1 chemicals. Hill emphasized that, "Prescription drug abuse is the fastest growing drug problem currently in the US and it has been labeled an epidemic by the Centers for Disease Control and Prevention" making enforcement an increasingly difficult and important venture.

Dora Hughes, Senior Policy Advisor, Sidley Austin LLP; former Counselor for Science and Public Health to Secretary

Kathleen Sebelius, also joined the panel to discuss how politics can influence inter agency collaboration regarding enforcement. Hughes first indicated that the people within each agency are the most important part of effective enforcement. Hughes opined that "there has been a continuous uptick of enforcement actions. Despite the strained resources, we are seeing more enforcement by FDA." As she looks forward to collaborations to come she shared key elements required for interagency collaboration success. "Success requires political leadership and commitment by those at the very top... a need to have a significant public health impact and, cross agency involvement of resources and authorities."

Jarilyn Dupont, Director of Regulatory Policy, Office of Policy, OC, FDA shared developments surrounding "Clinicaltrials.gov" and the pilot enforcement project. Clinicaltrials.gov does have compliance and enforcement activities and FDA is responsible for them." She shared that, "It's a very long process with respect to enforcement and compliance because we are still operating without a final rule." Dupont explained that NIH has the implementation responsibility for the clinical trials.gov databank but because there is not yet a rule making it is making it hard for industry to focus on the requirements surrounding clinical trials. As enforcement procedures expand, the FDA is attempting to clarify procedures for reporting and penalties surrounding noncompliance. Dupont commented on the civil penalties that can be assessed after a notice of noncompliance is sent to a noncomplying party. These letters, in conjunction with compliance on clinicaltrials.gov, are being produced with the help of other agencies. Particularly, the counselors and litigation section of the Office of the Chief Counsel (as Weinman explained) also been very involved with the centers of FDA on a long term plan. The results of the pilot enforcement program will help consideration of a permanent program. Additionally a rule making from NIH will help clarify provisions in the statute. Dupont clearly explained that "We [the Office of Policy] have to cooperate with NIH on this because they have the data, and we have the enforcement. We will not be able to do any of these enforcement actions without ensuring the data they have is accurate."

All speakers emphasized the need for collaboration moving forward in the face of budgetary, personnel, and technology barriers facing enforcement efforts across the country. ▲

A Look Back at FDLI's Annual Enforcement, Litigation & Compliance Conference: Highlights from "Hot Topics in Enforcement: Lessons Learned (Part I)"

By Stephanie Barnes, Esq., Senior Manager, Foods Portfolio and Global Programs



Photography from FDLI's 2013 Enforcement, Litigation and Compliance Conference. Photography by Valter Schleder.

The Hot Topics sessions at FDLI's 2013 Enforcement Conference encompassed two separate panels addressing a variety of issues including pharmacy compounding, the Bottomley case, food importation and privacy issues in social media. Mara V.J. Senn, Partner, Arnold & Porter LLP, began the first session with a discussion of counterfeit drugs. As the global economy becomes more integrated, counterfeit drugs have become a much greater problem, asserted Senn. She noted that approximately 80% of the counterfeit drugs in the U.S. come from overseas, primarily India and China. Senn explained that as international enforcers cooperate more closely there may be increased international enforcement.

John Roth, Director, Office of Criminal Investigation, FDA, followed by elaborating on the severe penalties for counterfeit, unapproved, and mislabeled medical products. According to Roth, securing the legitimacy of the supply chain is a top priority for FDA with a focus on enforcement of foreign unapproved medical products. Roth highlighted three key vulnerabilities to a legitimate supply chain: foreign/unapproved medical products; drug diversion schemes; and direct-to-consumer (internet) sales.

The Bottomley Case and conviction is just one of several convictions in authorities' fight to keep counterfeit drugs out of American borders. In this case, Bottomley's company MHCS imported and distributed misbranded and unapproved drugs

from foreign countries to American physicians, stated Roth. Lab analysis of the products determined the drug to be counterfeit - the substance seized and tested did not contain any of the active drug ingredient that is found in legitimate versions. Prosecutors asked for a one-year prison sentence for Bottomey's conduct, but he was ultimately sentenced to six months of house arrest and five years' probation.

The second portion of the Hot Topics session explored lessons learned from the interaction among the Executive, Legislative and Judicial Branches with a focus on the legislative intricacies of pharmacy compounding and related enforcement concerns. Rachael G. Pontikes, Partner, Duane Morris LLP, began with a review of how pharmacy compounding regulation has developed and how it has changed with the passage of The Drug Quality and Security Act (DQSA) on November 27, 2013. The DQSA, among other things, creates outsourcing facilities, amends and reinstates 503A, creates penalties and requires enhanced communication between FDA and State Boards of Pharmacy. Section 503A describes the conditions under which certain compounded human drug products are entitled to

exemptions from three sections of the FDCA requiring: compliance with current good manufacturing practices (cGMP); labeling with adequate directions for use and FDA approval prior to marketing. In addition, the new law creates a new section 503B in the FDCA, explained Pontikes. Under section 503B, a compounder can become an "outsourcing facility." Although the DQSA clarifies the regulation of pharmacy compounding, many questions remain, opined Pontikes. For example; when does compounding cross the line into manufacturing?

Looking forward, it's difficult to see if FDA's implementation will change significantly under DQSA, asserted Sarah Sorscher, Attorney, Public Citizen. Sorscher remained doubtful that outsources will be able to come up to new cGMP standards without undergoing new drug approval and acknowledged that many questions remain as to the implementation of the DQSA, namely: Whether companies will be registering as outsourcing facilities; Whether FDA will allow manufacturers to use bulk ingredients from a broad list of ingredients or if they will limit it to those on the drug shortages list. ▲

A Look Back at FDLI's Annual Enforcement, Litigation & Compliance Conference: Highlights from "Hot Topics in Enforcement: Lessons Learned (Part II)"

By Stephanie Barnes, Esq., Senior Manager, Foods and Global Portfolio

The Hot Topics in Enforcement (Part II) began with a discussion of lessons learned from recent food importation alerts, proposed regulations under the Food Safety Modernization Act (FSMA), and other importation actions. FSMA has significantly increased the responsibilities of companies who import food into the U.S., placing the primary responsibility on industry, explained Gale Prince, President, Sage Food Safety Consultants. Lucinda J. Bach, Partner, DLA Piper US LLP, narrowed in on two key proposed rules under FSMA, the Foreign Supplier Verification Program (FSVP) and Third-Party Accreditation. The latter is a framework allowing FDA to accredit third parties to audit foreign food facilities to certify they're safe and in compliance with domestic laws. Bach also highlighted key parts of FSVP, which requires importers of food to develop and follow an FSVP that includes a review of a foreign supplier's compliance history, an analysis of hazards reasonably likely to occur as well as the severity of illness or injury that hazard might cause and a verification that those hazards are being controlled. One issue in the proposed rule is the 2 options available for foreign supplier controlled hazards. Option 1 would require an onsite audit of foreign facilities for hazards reasonably likely to lead to serious adverse health consequences or death. Under option 2, regardless of the hazard or seriousness of a potential illness, an importer can choose how they intend to verify safety, stated Bach.

One issue Bach noted in closing was the very small supplier exemption under the proposed rules. She explained that

companies who qualify for the exemption will be relieved of the obligation to verify compliance with food safety laws and will only have to obtain assurance and a list of suppliers. Currently a company with annual food sales \$500,000 or less qualifies, but FDA has stated that 59% of processed food suppliers and 92% of raw produce suppliers fall within this definition, creating a gaping hole.

The Hot Topics panel ended with an overview of privacy issues and lessons learned from mobile medical apps and other emerging technology. Panelists Marta Villarraga, PhD, Principal, Exponent, Inc.; Mary L. Gerdes, Senior Counsel, BD and Adam Solander, Associate, Epstein, Becker & Green, P.C. used a hypothetical mobile app to highlight the differences between older and newer smartphones to show how hackers can reverse engineer apps to extract information in addition to other potential disclosure issues. Villarraga and Solander also provided an update on mobile medical apps regulation in light of FDA's new guidance on mobile medical apps and how law firms can help companies move through the approval process. According to industry experts, 500 million smartphone users worldwide will be using mobile health applications by 2013, stated Villarraga. In light of the increasing prevalence of mobile medical apps, Solander elaborated on the importance of risk management and threats from a security perspective. Companies not only compete on functionality, but also on the security they're providing. As information becomes more readily available through mobile medical apps we'll likely see a switch from a compliance standpoint to enforcement, asserted Solander. ▲

Litigation & Settlements at FDLI's 2013 Enforcement Conference

By Davina Rosen Marano, Esq. Director, Product Development



Photography from FDLI's 2013 Enforcement, Litigation and Compliance Conference. Photography by Valter Schleder.

The session on litigation and settlements at 2013's Enforcement Conference kicked off with an analysis of how FDA uses the regulatory tools at its disposal under the Food and Drug Administration Safety and Innovation Act (FDASIA). FDA's enforcement discretion is an important and timely issue due to drug shortages, asserted Jennifer Zachary, Partner at Covington & Burling LLP. Zachary explained that drug shortages began in 2007 and peaked in 2011 to 2012. In the time leading up to the shortages, FDA had issued warning letters and/or 483s to the top three manufacturers of sterile injectable drugs. These

companies ultimately shut down or limited their production, leading to speculation that FDA enforcement was to blame for the shortages.

According to Zachary, Congress addressed concerns by including a provision in FDASIA that now requires manufacturers to report shortages. It also gave FDA several regulatory tools, while providing that the Agency may use "regulatory flexibility in its discretion." In fact, FDA has become more conscientious in exercising its discretion in the face of drug shortages, Zachary asserted. She cited FDA's Consent Decree with Ben Venue Laboratories as a "creative" and "flexible" use

of enforcement tools, which accomplished the dual goals of bringing Ben Venue into manufacturing compliance and meeting patient needs. Zachary concluded that “FDA’s use of its regulatory . . . and . . . enforcement tools are resulting in much fewer drug shortages.”

Reuben Guttman, Director at Grant & Eisenhofer P.C., responded to each presentation with the plaintiff’s perspective. He warned that when FDA acts with a mind toward preventing drug shortages, the Agency is “held hostage by a bunch of companies.” Guttman suggested that competitors must “pick up the slack” when a manufacturer is removed from the market by FDA action.

In the area of international manufacturing, James R. Johnson, Associate at Hogan Lovells US LLP, stated that “FDA’s tools remain the same.” Johnson explained that the Agency continues to use inspections as a way of holding “the keys to the US,” along with import refusals, guarding of the borders through U.S. Customs and Border Patrol, and control of marketing applications.

Johnson highlighted the Ranbaxy case as an example of an “extremely serious” violation of FDA regulations. The Agency used all its traditional enforcement tools, creating a “roadmap for what to expect” from FDA if a similar situation occurs internationally, Johnson explained. FDA also handled the Ranbaxy case with “an incredibly powerful tool,” according to Johnson: an expanded Consent Decree which gave FDA the power to bring another facility under the agreement based on inspectional findings. The Consent Decree also included the names of non-U.S. executive officers, demonstrating that FDA will hold even international individuals liable.

Moderator Barbara A. Binzak Blumenfeld, Counsel at Buchanan Ingersoll & Rooney PC and FDLI Director, raised the concern that the new compressed timelines at FDA may be insufficient for manufacturers to address “company-wide systemic problems.” Johnson opined that FDA has traditionally been good at giving warnings, which gives sufficient time for manufacturers to respond. He also asserted that, above all else, “FDA wants to see voluntary corrective action;

it is more efficient than going around seizing products all over the country.”

There are, however, ways to challenge FDA for an unreasonable delay. Daniel G. Jarcho, Partner at McKenna Long & Aldridge LLP, explained that the Administrative Procedures Act provides a cause of action to sue when FDA actions have been “unlawfully held” or “unreasonably delayed.” Although the cause of action seems straightforward, Jarcho pointed out that matters are complicated when Congress mandates FDA to perform a specific action, but does not allocate the resources needed for FDA to meet that deadline. Or, Congress may give a specific deadline, but FDA has more pressing matters. Jarcho explained that in light of these tensions, a court often refuses to compel Agency action, but will give a stern warning to try to move action along.

The case of *Center for Food Safety v. Hamburg* (Case No. 12-cv-4529, N.D. Cal.) illustrates how FDA sometimes cannot meet its statutory mandates, according to Jarcho. The Food Safety Modernization Act (FSMA) contained seven sets of complex, specific regulations that FDA failed to meet. The Court in this case acknowledged that FDA is the expert in implementing new food regimes, but that it also plainly failed to meet the statutory requirements. The Court applied a hard-line test in granting declaratory judgment for the plaintiff, Jarcho explained, but then asked the parties to provide input for a reasonable timetable. Guttman declared this type of litigation to be “clever,” and that the Court’s compromise in its holding was “terrific.”

An attendee posed the critical question of how FDA weighs the magnitude of its current good manufacturing practices (cGMP) violations in making enforcement decisions and using its discretionary tools. Zachary explained that FDA begins by considering the impact on patients who will take these drugs. She concluded that, ultimately, where “FDA has a choice between an unsafe product and no product . . . FDA would probably go with no product.” ▲

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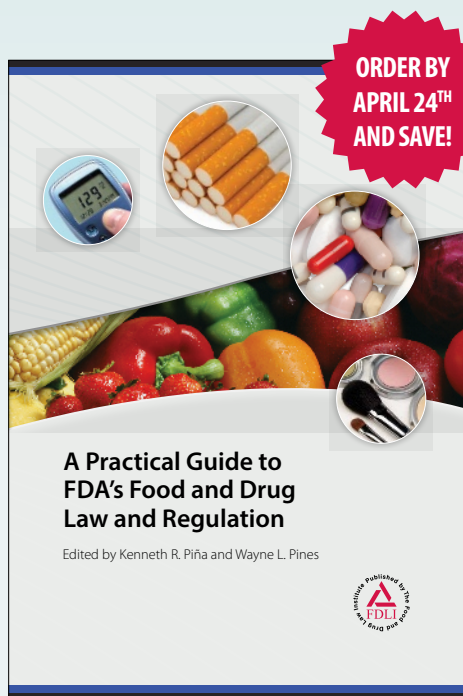
CONFERENCES

- Introduction to Drug Law and Regulation | April, 2 - 3 | Washington, DC
- 2014 Annual Conference | April 23-24 | Washington, DC
- Introduction to Medical Device Law and Regulation | May 6 - 7 | Washington, DC
- Food Advertising, Claims, Litigation and Strategies | September, Date TBA | New York City, NY
- Advertising & Promotion Conference (medical products) | September 29-30 | Washington, DC
- FDA Regulation of Tobacco Products | October, Date TBA | Washington, DC
- Enforcement, Litigation and Compliance | December, Date TBA | Washington, DC

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