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# Focus on Drug Safety Communication & TV DTC Advertising

## A Review of Two New FDA Guidance Documents

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FDA recently published two important guidances that concern the dissemination of drug information to consumers. FDA's Center for Drug Evaluation and Research (CDER) issued guidance regarding how the agency will classify and communicate drug safety information ("Classifying Significant Postmarketing Drug Safety Issues" and "Drug Safety Information—FDA's Communication to the Public"; see http://bit.ly/wGUNCd). FDA's Office of Prescription Drug Promotion (OPDP, formerly DDMAC) issued guidance regarding mandatory review of TV direct-to-consumer (DTC) ads prior to dissemination ("Direct-to-Consumer Television Advertisements—FDAAA DTC Television Ad Pre-Dissemination Review Program"; see http://bit.ly/FO8qRp).

**Safety First**

Let's look at the CDER guidance first.

From approval through post-marketing, CDER provides information about drug risks and benefits to health care professionals and patients, especially when that information has generated a specific concern. In recent years, CDER has begun making information on potential drug risks available to the public earlier—often while the Center is evaluating safety data and determining whether any regulatory action is warranted.

FDA acknowledges the "tension" created by implementting the "dual goals of having people informed as early as possible and having that information thoroughly substantiated. Despite this tension," says the FDA, "we lean toward early communication of emerging drug safety information unless, in our judgment, the information available is not reliable enough to be useful and could mislead the public. We recognize this means that, in some cases, we will have to say that a safety concern 'has not yet been substantiated.'"

**Not All Safety Issues are Urgent**

In 2007, CDER launched a centralized tracking system called DARRTS (Document Archiving, Reporting, and Regulatory Tracking System), which contains "tracked safety issues" or TSIs.

CDER claims that almost 1,000 TSIs have been entered into DARRTS since its inception. "Although all of these issues are considered significant," says CDER in the draft guidance, "all 1,000 TSIs are not, in fact, of the same urgency. Without sufficient resources to manage all TSIs equally, FDA has been prioritizing them on a case-by-case basis, but without an agreed-to priority framework."

**Hazard Assessment**

The guidance specifies that CDER will estimate the hazard posed by a significant tracked safety issue, based on three variables:

(1) the relative seriousness of the issue;
(2) the estimated size of the population exposed to the risk of the drug; and
(3) the suspected frequency of harm to patients exposed to the drug.

"The combination of factors 2 and 3 provides an estimate of population risk; the combination of factors 1 and 3 provides an estimate of personal risk to the patient," says CDER in the guidance.

After assessing the hazard posed by the safety issue, based on the three factors discussed above, CDER staff may consider a range of other modulating factors that have the potential to elevate or, in some circumstances, lower the classification of the safety issue. These factors include the availability of therapeutic alternatives, the clinical setting in which the drug is used, and if there are risks to vulnerable populations such as children, older patients, or pregnant women.

**Social Media Implications**

Brad Pendergraph, Manager, Consumer Digital & Social Engagement at Novartis, posed some questions on his personal blog about the impact of social media on the collection and dissemination of drug safety information (see "FDA Guidance that may... or may not... have anything to do with me"; http://bit.ly/FPOVUh).

NOTE: Brad Pendergraph 's opinions are his own and do not reflect the opinions of his employer.

Pendergraph was concerned about drug safety issues (adverse events) received by CDER that may lack precise and reliable information about the frequency of the adverse event or the increase in risk posed to patients exposed to the drug. "If such information is lacking," says the guidance, "staff will use the existing information on seriousness, and size of the population at risk, and then the modulating factors to classify the TSI."

"What struck me …is the whole 11 page document does not discuss where the information arises from," said Pendergraph. "Is this solely based on reports from physicians? clinical trial outcomes? reports from patients via MedWatch? media outlets? Or... as I'm thinking... does this include trawling Social Media?"

"Patients will discuss their experiences on a drug, and those experiences may include unnecessary positive claims or adverse events," said Pendergraph. "While an actually trackable adverse event is generally few and far between—I've seen 4 in the last 5 years—there may be information being culled from closed platforms, or by integrating other data sources that CDER may have at

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its disposal. For me, this is another wakeup call that we need to expand our listening beyond PR-style KPIs such as 'We got mentioned 1000 times' into much more in-depth sentiment or human language analytics."

**Mission: Correcting Misleading Information**

Pendergraph believes that pharmaceutical companies as well as the FDA have the duty to correct misinformation that consumers may get from mainstream and social media sources.

FDA notes that its decisions to communicate about important drug safety issues are affected by information the public has received from sources other than FDA, such as the mainstream media. "In these cases," says FDA, "the safety of a particular drug or drug class may be publicly questioned based on information provided by these other sources that may be incorrect, incomeplete, or misleading. In such cases, FDA may issue a statement or engage in other methods of communication to clarify or correct information and respond to public interest."

Pendergraph contends that "Big Pharma has one of the most comprehensive data sets regarding safety for all of their marketed molecules." He asks, then answers, the question: "what benefit can Big Pharma derive from correcting 'incorrect, incomplete, or misleading' information?"

"The answers to that question move us into the realm of things like trusted partner in providing quality healthcare, acting in the best interest of our business partners, or behaving in a socially responsible manner," says Pendergraph.

"Big Pharma has very highly worded mission statements. I believe that achieving those mission statements is an ROI all to itself," said Pendergraph. "There are a lot of other relatable KPIs that we could tie to this, like the value of a happy customer, influence of eCOLs or eKOLs, rating high in SEO rankings in the areas of our expertise. These are soft measures, for sure, but I'm sure that our ROI calculations involve lots of tangential soft measures like these."

**Preview of TV Ads**

On September 27, 2007, President Bush signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA), which gives FDA the authority to ". . . require the submission of any television advertisement for a drug . . . not later than 45 days before dissemination of the television advertisement." Nearly five years later, on March 12, 2012, the FDA published its "Draft Guidance for Industry Direct-to-Consumer Television Advertisements — FDAAA DTC Television Ad Pre-Dissemination Review Program" in the Federal register (see http://bit.ly/Ag5eEM).

Up until now, the FDA allowed the VOLUNTARY submission of TV ads for review prior to airing, but did not require it.

The draft guidance details which type of TV ads REQUIRE approval prior to "dissemination," how long it will take FDA to review these ads and get back to the sponsor (45 days), and what the sponsor can do if the FDA does NOT meet the 45-day deadline. Of course, it also mentions CRIMINAL and CIVIL MONETARY penalties that may be sought by the FDA for violations.

**Which Ads Will Require "Pre-dissemination" Review?**

FDA intends to require sponsors to submit TV ads for pre-dissemination review in the following categories:

- Category 1: The initial TV ad for any prescription drug or the initial TV ad for a new or expanded approved indication for any prescription drug
- Category 2: All TV ads for prescription drugs subject to a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (see section 505-1(f) of the FD&C Act)
- Category 3: All TV ads for Schedule II controlled substances
- Category 4: The first TV ad for a prescription drug following a safety labeling update that affects the Boxed Warning, Contraindications, or Warnings & Precautions section of its labeling
- Category 5: The first TV ad for a prescription drug following the receipt by the sponsor of an enforcement letter (i.e. a Warning or untitled letter) for that product that either cites a TV ad or causes a TV ad to be discontinued because the TV ad contained violations similar to the ones cited in the enforcement letter
- Category 6: Any TV ad that is otherwise identified by FDA as subject to the pre-dissemination review provision

"Specifically, these categories allow the Agency to review and provide comments on TV ads for prescription drugs with particularly serious risks," says the FDA. Other people, such as Arnie Friede, a former FDA associate chief counsel and a former senior corporate counsel at Pfizer, think FDA will be reviewing ALL ads prior to dissemination. "Now it seems that

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we've got a mandatory program under section 503B that, despite its arguable limitation to high risk DTC TV advertising, seems to mandate submission of virtually all DTC TV advertising in virtually all contexts," said Friede in a Pharmalot Op-Ed piece (http://bit.ly/wxB8Ti).

**The 45-day "Shot Clock"**

Regarding the 45-day review period, FDA says: "Once the 45-day review time has elapsed, there is no specific legal consequence resulting from disseminating the proposed TV ad without waiting for FDA's comments. However, once an ad is disseminated, the sponsor is at risk of enforcement action if the ad violates the FD&C Act and implementing FDA regulations."

That is, if the FDA misses its deadline, the situation reverts back to what is the current practice—air the commercial and perhaps suffer the consequences, which could be nothing more than a warning letter, but may also require the sponsor to air a correction.

"This guidance creates an FDA 'shot clock' that doesn't allow you to take a shot at broadcast marketing for an additional 45 days," said Coalition for Healthcare Communication executive director John Kamp in an MM&M story (see http://bit.ly/yN9g40). "And unfortunately, there's no 'overtime' tacked on at the end of the patent period to recoup the lost sales opportunity."

In a comment to the MM&M piece, Bruce Grant, SVP, Strategic Services at Digitas Health Consulting, disputed the significance of Kamp's "lost sales opportunity" argument. "PhRMA already committed itself to a voluntary DTC waiting period for new drugs (length officially unspecified but in practice 6 months; [see box]). In comparison," noted Grant, "6 weeks seems like small change indeed. And for in-market brands, all this means is that the production cycle needs to begin 45 days earlier to meet the planned air date. In any event, industry seems quite skilled already at extending patent life through a host of 'evegreening' and 'life-cycle management' strategies. I'm guessing that most will find a way to make that 6 weeks back... with interest."

**PhRMA DTC Guiding Principle #6**

In order to foster responsible communication between patients and health care professionals, companies should spend an appropriate amount of time to educate health professionals about a new medicine or a new therapeutic indication and to alert them to the upcoming advertising campaign before commencing the first DTC advertising campaign. In determining what constitutes an appropriate time, companies should take into account the relative importance of informing patients of the availability of a new medicine, the complexity of the risk-benefit profile of that new medicine and health care professionals' knowledge of the condition being treated. Companies are encouraged to consider individually setting specific periods of time, with or without exceptions, to educate health care professionals before launching a branded DTC television or print advertising campaign. Companies should continue to educate health care professionals as additional valid information about a new medicine is obtained from all reliable sources.

**What Exactly Will the FDA Review?**

In the past, FDA has primarily reviewed TV Ad storyboards, which are graphical representations of key scenes in the ad with dialog included. Storyboards are blueprints for production and are created BEFORE any video production has begun. Now, however, FDA requires a video of the TV ad to be submitted to fulfill the submission requirements. Only after the video is submitted will the 45-day review clock start running.

"FDA cannot provide final comments on the acceptability of a TV ad without viewing a final recorded version in its entirety. FDA understands that some sponsors may wish to receive comments from the Agency before producing a final recorded version of the ad. In such situations, sponsors can submit a pre-dissemination review package without a final recorded version of the ad, but once the final recorded version is produced, it will need to be submitted to the Agency for pre-dissemination review."

**Pushing the Envelope May Be Too Costly**

Alexander Gaffney (@AlecGaffney), health wonk and writer of news for @RAPSorg & Regulatory Focus, had some further thoughts regarding FDA's requirement to review videos and not just storyboards. Gaffney said the guidance would likely cut down on "poor marketing" spending, which could be interpreted to mean "pushing the envelope" spending.

In the past, pharma marketers could submit a storyboard (cheap) and run the ad without waiting for comments from the FDA. The ad could push the

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regulatory envelope and run its course on TV before the FDA could issue a warning letter (read, for example, "FDA and YAZ: Is FDA Helping Marketers Work Around Regulations?"; http://bit.ly/ADZdSS). If marketers have to essentially create the entire ad for review prior to dissemination, they may be less likely to "push the envelope" and risk losing money spent on the production side.

**A Possible Loophole**

FDA does not define what exactly it means by "dissemination." Obviously, FDA is focused on television commercials seen by millions of Americans during the nightly news or daily talk shows. But does dissemination also include uploading the video to YouTube? A drug company could upload a video of a pre-approved ad to YouTube at the same time that it submits the video to FDA for "pre-dissemination" review. The video can then be embedded in the drug.com website or promoted via Twitter.

"FDA is, of course, bound by its statutory authority—in this case a new pre-dissemination review power granted it by the FDA Amendment Act (FDAA) of 2007, which specifically refers to 'television advertising'," said Grant in a comment posted to Pharma marketing Blog. "Your point is well taken—and came up almost immediately in our internal discussions and in conversation with clients—but it's genuinely unclear whether the FDAA authorization would stretch to cover media that are not 'television.' I predict many comments on this issue during the 90-day comment period but don't foresee FDA extending the scope of its review in the final guidance."

Would a pharma company want to take advantage of this "loophole?" Maybe, if it does not violate the "letter" of the law; ie, if uploading the video to YouTube is not considered "dissemination." That would let the company off the hook for violating the law, but FDA could still cite the YouTube version as violative (ie, as it does right now). A violative YouTube version of the video, however, would warrant only a warning letter, a mere slap on the wrist. Unless such videos go "viral," which is unlikely to happen, they won't be seen by millions of people. Still…

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