Public Dissemination of Information About Investigational Products

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General Overview of the Law

- FDA prohibits sponsors or investigators, or those acting on their behalf, from representing investigational products as safe or effective, or otherwise promoting the products.
- Through its authority over “labeling,” FDA also prohibits investigational products from being represented as safe or effective for the purposes for which they are being investigated.
  - “Labeling” is defined broadly, to include all written, printed, or graphic material having any physical or textual relationship to product.
- See 21 CFR 312.6(b), 312.7(a), 812.5(b), 812.7(d)
General Overview of the Law

- FDA does not preclude sponsors or investigators from communicating truthful and non-misleading information about their products, so long as those communications constitute what is referred to as “scientific exchange”:
  - A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
- 21 CFR 312.7(a) (emphases added)

Permitted Promotional Practices

- FDA does allow two types of pre-approval promotion:
  1. “Institutional Advertisements” may state that the company is conducting research in a certain therapeutic area, but may not suggest that a drug will soon be approved for any specific use.
  2. “Coming Soon Advertisements” may announce the name of a product that will be available soon, but may not make any written, verbal, or graphic representations about the use of the product.
- Analogous to “disease awareness” and “reminder ads” in post-approval context, thus cannot be used in tandem.
- FDA has interpreted these very narrowly, objecting to:
  - An institutional ad describing research into platelet aggregation, where a drug inhibiting aggregation “should diminish mortality”
  - A coming soon ad promoting the drug’s “once-a-day dosage”
Agency Enforcement Actions

- FDA enforces its policies through routine surveillance and attendance at scientific meetings and conferences
- Has issued ~55 Notice of Violation (Untitled) Letters, ~1 Warning Letter since 1991 on pre-approval promotion
- Promotional materials cited include:
  * Press releases
  * Direct mailings
  * Formulary kits
  * Teleconferences
  * Journal ads
  * Sales aids
  * Abstracts
  * Booth panels
  * Videotapes
  * Oral statements
  * Websites
  * Posters
  * Reprints
  * Slide kits

Consequences of Receiving Letter

- Company will be required to cease making similar claims
  - May be required to provide a list of all materials containing claims
- Company may be required to issue corrective messages
  - Issue a “Dear Healthcare Provider” letter
  - Place an advertisement in same journal
  - Include a disclaimer on all future materials
- Company may be asked to pre-clear all future materials
- Company may receive negative trade, lay press attention
- Company at risk of additional FDA enforcement action
Key Drivers of Enforcement

• Most commonly cited violations include:
  – Conclusory statements of “safety” or “effectiveness”
  – Descriptions of MOA that imply safety or effectiveness
  – Claims unsupported by appropriate clinical studies
  – Failure to disclose risks and provide fair balance

• No formal distinction between scientific, investor audiences
  – As a matter of enforcement priorities, however, FDA focuses much more (if not exclusively) on scientific and clinical communications

• The distance of a product from the market is a key factor
  – How far are physicians from being able to prescribe the product?
  – Has the product received a “Not approvable” letter?
  – Is the product approved for one use, being studied for another?

Conclusory Statements

• In May 2001, FDA sent an Untitled Letter to Maxim regarding the company’s exhibit booth activities. FDA objected to the following statements by representatives:
  – “Side effects are transient and will pass in an hour or two.”
  – “You see less side effects of IL-2 when used with histamine dihydrochloride [the investigational drug].”
  – “You can save on costs by using histamine dihydrochloride in combination with IL-2 because you can send patients home earlier and they can inject themselves.”
  – “Phase III studies are showing a doubling of survival. I would love to tell you more but I can’t in case your [sic] with the FDA.”

• This company had also received an earlier Untitled Letter for pre-approval promotion and a not approvable letter
Mechanism of Action

- In July 2001, FDA sent an Untitled Letter to AstraZeneca regarding its exhibit booth materials. FDA objected to the following claims, among others:
  - “Orally administered ZD1839 is active against central nervous system tumors with limited or no systemic toxicity.”
  - “[ZD1694 is a] [s]pecific TS inhibitor active in a range of malignancies.”
  - “There was evidence of antitumor activity [with ZD0473] in ovarian cancer patients.”
- These were two of the many letters issued after the 2001 ASCO meeting.

Unsupported Claims

- In May 1998, FDA sent an Untitled Letter to Anesta for several press releases concerning the drug Actiq. FDA objected to the following:
  - A claim that Actiq provided statistically significantly better pain relief scores than patients' previous medication
  - “Actiq remained effective over time and patients safely used the product in multiple stages of disease progression.”
- FDA objected that the claims were based on open-label, dose-ranging, tolerability studies that were not designed to evaluate safety or efficacy.
Fair Balance

• In April 2000, FDA sent an Untitled Letter to TAP over its issuance of a press release after Advisory Committee review of its drug, Uprima. FDA objected to the following:
  – “The most commonly reported side effect was nausea. Of the nausea reported in the NDA clinical studies, most incidences were mild to moderate in severity.”
• FDA objected that this was the full extent of the safety information in the release
• The press release also failed to disclose the significant risk of syncope and severe hypotension, which prompted the Advisory Committee to recommend contraindications and a boxed warning

Current Enforcement Climate

• Enforcement has never been transparent or consistent
• The number of Untitled and Warning Letters is down
• But outside of FDA, overall enforcement is very high
  – In 2004, FDA entered into a cooperative agreement with SEC, allowing FDA to refer to SEC potentially false or misleading statements, and for SEC to request non-public information
    • This agreement has resulted in several civil actions and investigations regarding investigational products
  – Where a product is approved for one use and being investigated for another, “pre-approval promotion” equals “off-label promotion”
    • $37MM InterMune settlement triggered by a press release describing results of Phase III study for unapproved use
“Do’s”

- Do disseminate accurate, balanced, scientific information regarding your investigational product
- Do include all appropriate qualifiers and disclaimers, and put all information in its proper context
- Do make clear that your product is investigational, and indicate the actions still needed to gain FDA approval
- Do present data whenever possible, and not conclusions about those data
- Do provide a balanced portrayal of the risks of your product, including side effects or adverse events

“Don’ts”

- Don’t describe clinical trial results as established facts, or state or imply that your product is “safe” or “effective"
- Don’t make promotional statements, or use inflammatory words such as “breakthrough” or “revolutionary"
- Don’t provide descriptions about your product’s MOA that imply its safety or effectiveness
- Don’t make statements based on a clinical trial unless that trial was designed to evaluate the relevant outcome
- Don’t use quotes from investigators or others that will be problematic when attributed to your company
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Regulatory Affairs Professionals Society

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I am not an attorney!

BUT…everyone has to have a disclaimer!

The views expressed are those of the author (that’s me) alone and do not necessarily represent those of RAPS.
What Can We Do?

Phase II

(while staying within the law)

Phase III

Approval?

OBJECTIVE: To provide you with a baseline understanding of the rules, regulations, and guidelines to do your job!

- Press Releases
- Website
- Market Research
- Round Tables
- Scientific Presentations
- Investigator Meetings
- Conventions
- Investigator Recruitment
- Patient Recruitment
  - Radio/TV
  - Website
  - Print (Newspaper; Brochures)
  - Booth Activity

Reminder Ads (Coming Soon Ads)
- Call attention to drug name not indication
- Can include
  - Ingredients
  - Dosage form
  - Package Content
  - Price
- Cannot include
  - Patient Population
  - Indication
  - Efficacy Claims

[21CFR 202.1(e)(2)(i)]
Key Issues

- Is there a draft PI?
  Physician’s Labeling Rule (PLR) for Human Prescription Drug and Biological Products – new content and format (effective 6/30/06)

- Is the product approved?
- Disease State vs. Product

ALWAYS STICK TO THE FACTS!
EU Clinical Trial Applications and IMP release - recent experiences

Paul O’Connor
Global Vice President Quality
Qualified Person

Agenda

- Quick Reflection and Almac role
- Recent experience – Regulators
- Recent experience – Sponsors
- “New stuff”
- Case Studies
Quick Reflection and Almac role

CTA + PSF + GMP = QP release
Recent experience – Regulators

- Expiry date absence on packs
  - Germany inconsistently says **NO** (JIT approach?)

- Kit Number removal and reliance on another code
  - The Netherlands, Ireland, Italy, Germany often **NO**

- Expiry date selection – Ireland and Czech Republic are very conservative in what they allow

- QP “approval” of testing labs – Hungary **YES**, Germany inconsistently **YES**

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Recent experience – Regulators

- Master Cell Bank Storage Site “approval” by QP
  - Germany **YES**

- Expiry Date extension
  - UK substantial amendment – 35 days,
  - use improved wording in CTA for other countries to permit planned date changes

- Inspection of Drug Substance site for biologics
  - Germany, Czech Rep and Poland **YES**
Recent experience – Sponsors

- Completion of IMPD in CTA inconsistent
  - Not all manufacturing, labelling and import sites described
  - Data gaps e.g. stability timepoints
  - Excess testing recorded e.g. import testing specified
  - Poor internal discussion between departments

- CTA updated repeatedly or separate versions in each country

……..so that at the time of QP release….

Recent experience – Sponsors

- Delay!
  - Missing product locations
  - Specifications have changed in the meantime
  - Unnecessary testing needs to occur
  - Label expiry is not consistent with submission

……..paper chase (versions of IPMDs), CTA update via substantial amendments or QP audit of non-EU facilities

QP release should not be on the critical path!
“New stuff”

- Standalone contract labs on MAs
- DEA and re-export of controlled drugs
- Investigator Initiated Trials and industry challenges
- Site pharmacists asking for C of As and QP release certs for GCP compliance – unblinding risk
- Room Temp shipments starting to be questioned
  - Austria

Case Studies

- Sterile product
  - FDA inspected facility
  - QP audited
  - Trial in US and EU

- Tablets
  - Permitted expiry 12mths
  - Extend to 24 mths. Material newly labelled
  - Subsequent CTAs had new data. First CTA did not
  - Release issues