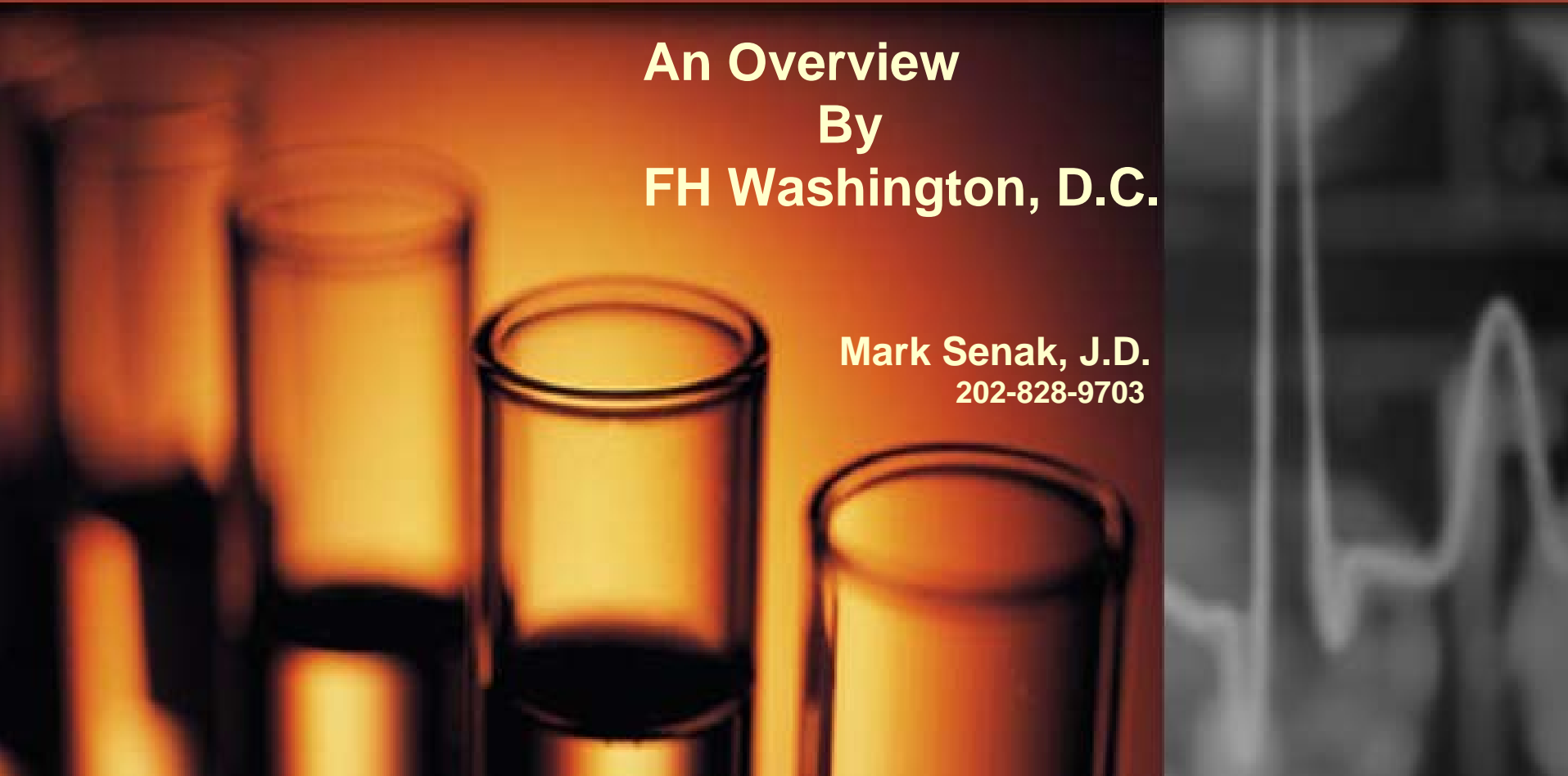


The FDA, the Drug Approval Process and Communications

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**An Overview
By
FH Washington, D.C.**

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Agenda

- About the FDA
- About Research and Development
- Phases of Research and Development
 - Phases I-III
- NDA Review
 - Advisory Committees
 - Outcomes
- PR Issues
- Current Issues/Future Outcomes

About the FDA

Regulated Areas

- **Biologics**
 - Product and manufacturing licensing
 - Safety of blood supply
 - Research to establish product standards and testing methods
- **Cosmetics**
 - Safety
 - Labeling
- **Foods**
 - Labeling
 - Safety of most food products
 - Bottled Water
- **Drugs**
 - Product Approvals
 - OTC and RX drug labeling
 - Drug manufacturing standards
- **Medical Devices**
 - Premarket approval of devices (510k)
 - Manufacturing and performance standards
 - Tracking reports of device malfunctioning and AEs
- **Radiation Products**
 - Radiation safety performance standards for microwaves, televisions, diagnostics
 - X-Ray equipment

About the FDA

- What the FDA does not regulate
 - Advertising
 - Alcohol
 - Consumer Products (household goods)
 - Drugs of Abuse (DEA)
 - Health Insurance
 - Meat and Poultry – (USDA, except for game meats – ostrich, venison, snake, e.g.)
 - Pesticides
 - Restaurants/Grocery Stores
 - Water (unbottled)

About Research and Development

- It currently takes approximately 10 years to take a drug from investigation to market at a cost of more than \$800 million
- Only 1 drug in 10 that makes it into human testing actually makes it to market – and only 1 drug in 10,000 that is discovered actually makes it to clinical trials.
- The investment in research in 1999 was twice the rate of 1990
- Length of time from conception to market is 10-15 years

Overview of Phases of Research and Development

Pre-Clinical
Research

Phase 1 Clinical Trials

Phase II Clinical Trials

Phase III Clinical Trials

Phase IV Clinical Trials

Accelerated Approval
Fast Track Approval

Phases of Research and Development

- Pre-Clinical Research
 - Target a particular disease
 - Synthesis and purification of molecule seeking chemical compound through various methods
 - Different screening methods have varied timelines, accuracy, costs and success rates attached to them.
 - Analyze drugs physical and chemical properties
 - What does it do in the test tube?

Phases of Research and Development

– Animal Testing

- Rodent and non-rodent
 - Short term (2-3 weeks)
 - » How is drug processed?
 - Long term (3 weeks to several years)
 - » Is it safe?

– Institutional Review Board

- Review and approve trials and ensure rights of all involved
- Connected with hospitals and research institutions

– Submission of IND

- Outlines plans for clinical trials, 30 day FDA review time

Phases of Research and Development

- Phase I
 - First introduction of drug into healthy humans
 - Exceptions – HIV, Oncology
 - 20-80 people
 - Objective of studies
 - Safety
 - Pharmacology, pharmacokinetics
 - Side effects, maximum dosing
 - Several months in length
 - Need FDA approval to move to Phase II

Phases of Research and Development

- Phase II
 - 100-300 volunteers to determine safety/dosage
 - Subjects have the disease
 - Pilot studies to define efficacy
 - Doses studied most likely to be marketed
 - Define short term side effects
 - Well controlled – closely monitored
 - Several months-3 years in length
 - FDA approves to Phase III

Phases of Research and Development

- Phase III
 - At least 2 adequate and well controlled trials
 - Double blinded
 - 1000-5000 patients
 - 1-4 years in length
 - Objective to expand upon established efficacy, long range use issues
 - Basis for extrapolating to general population

Phases of Research and Development

Testing in Humans

| | Number of Patients | Length | Purpose | Percent of Drugs Successfully Tested |
|---------|-------------------------------------|---------------------------|--|--------------------------------------|
| Phase 1 | 20–100 | Several months | Mainly safety | 70 percent |
| Phase 2 | Up to several hundred | Several months to 2 years | Some short-term safety, but mainly effectiveness | 33 percent |
| Phase 3 | Several hundred to several thousand | 1–4 years | Safety, effectiveness, dosage | 25–30 percent |

For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70 percent will successfully complete phase 1 and go on to phase 2; about 33 percent of the original 100 will complete phase 2 and go to phase 3; and 25 to 30 of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

NDA Review

- New Drug Application (NDA) Submission
 - Formal request to propose approval of the drug
 - Contains all the clinical and non-clinical data
 - Descriptions of the manufacturing process
 - Proposed prescribing information (PI or label)
 - FDA has 60 days to determine whether the NDA can be filed.
 - Once NDA is deemed fileable by the FDA, agency will have 10 months to take an action
 - 6 months if drug is deemed a priority review

NDA Review

- NDA Review
 - Mandate of the FDA
 - Drug safety and efficacy
 - Risk/benefit ratio
 - Good Manufacturing Practices
 - Exact wording of PI
 - Risk/management program
 - Phase IV requirements

NDA Review

- Advisory Committees (23)
 - Help FDA gain wider expert input on specific product/therapeutic issues and policies
 - Committees have domain over areas of practice
 - Arthritis Drugs Advisory Committee, e.g.
 - Recommendation of panel is advisory only, but generally accepted by the agency

NDA Review

- Advisory Committees
 - Sponsor presents case on efficacy/safety
 - FDA counters with evaluation
 - Opportunity for comment from the public
 - Committee deliberates and answers specific questions posed by FDA
 - Often votes, sometimes does not
 - Makes ***recommendation*** of approval or not

NDA Review

- Accelerated Approval
 - Highly specialized
 - Allows drugs not yet finished with the three phases to get approval
 - Uses surrogate endpoints to establish safety and efficacy
 - Restricts distribution and use
 - Sponsor must continue testing to receive full approval
 - Imposes FDA restrictions on promotional activities
 - Is not Fast Track Review

NDA Review

- Fast Track Review
 - Speedier review of clinical trial data (6 instead of 10 months)
 - Granted by FDA when
 - Drug addresses serious or life-threatening condition
 - There is specific medical need
 - Alternative drugs do not work
 - No promotional restrictions
 - Examples – Sustiva, Pegasys

NDA Review

- Phase IV Clinical Studies
 - Post marketing studies
 - Further examine issues of safety and/or efficacy
 - May look for Adverse Events now that drug is in larger population
 - FDA cannot enforce or mandate a company to conduct Phase IV studies
 - May include head to head studies against other drugs in use

NDA Review

- After Advisory Committee Meeting, FDA will act by PDUFA date to
 - Send APPROVAL letter
 - Can now be said drug is approved
 - Send Approvable letter
 - Drug sponsor must satisfy certain conditions
 - Label modification
 - Risk management
 - New clinical trials for safety and/or efficacy
 - Not Approvable
 - Non Approval Letter

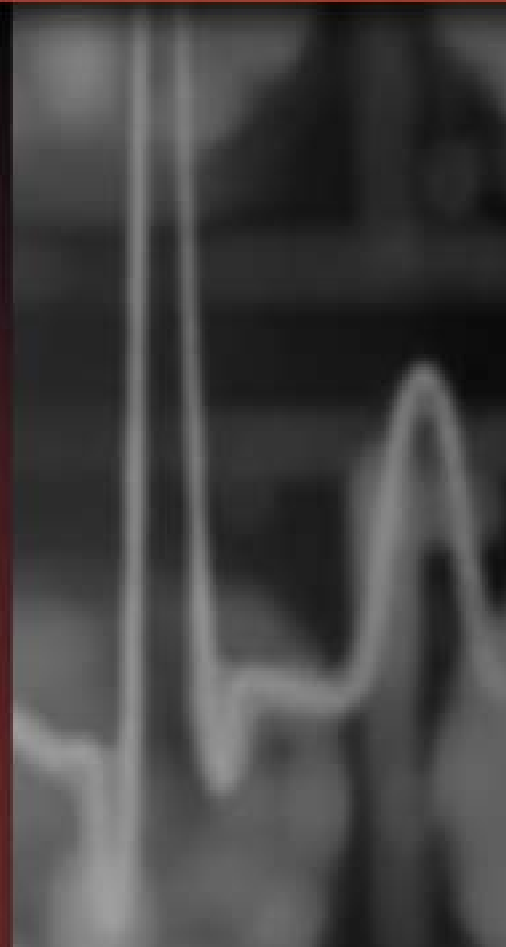
NDA Review Summary

- Media Milestones
 - Clinical Trial Outcomes
 - NDA Filing
 - Advisory Committee Meeting
 - Approval
 - Launch
 - Adverse Events
 - Crisis

Communications and FDA

Pre-Approval Communication of Data Milestones

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Agenda

- Background
- Regulatory Letter Overview
- Pre-Approval Regulatory Actions
- Pre-Approval Promotions
- Pre-Approval Promotion Conclusions
- Recommended Guidelines
- Dos and Don't's
- Conclusions

Background

- Section 312.7(a) 21 CFR

“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 purpose for which it is under investigation or otherwise promote the drug.”

Background

- As a product passes through clinical milestones, several stakeholders want to know outcomes.
- The most obvious vehicle for companies to deliver news is a press release
- FDA issues Warning Letters for the promotion of drugs outside regulatory boundaries
- Pre-Approval communications have special considerations
- Increased interest in transparency

Background – Types of Regulatory Letters

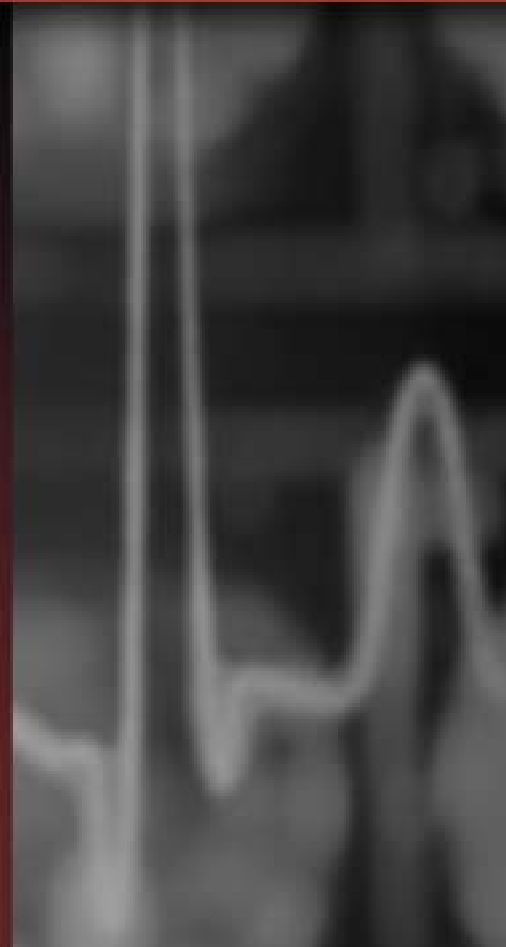
1. Warning Letters – Agency Wide
 - From district offices
 - Focus on cGMP
2. Warning Letters – CDER
 - Multiple divisions
 - Can focus on promotional activities
 - Also focused on site inspection results
 - Demands rectification of activities deemed outside regulatory guidelines
3. Untitled Letters - CDER
 - Same general purpose as Warning Letter, but implies a less serious posture than a WL
 - Sometimes more limited focus
 - Single advertisement, e.g.
4. Cyber Letters
 - Letters focused on activities of Internet marketers

Background

- Division of Drug Marketing, Advertising and Communications
 - Regulate industry and consultants on promotion of drugs prior to approval
 - Monitor post-approval promotions for fair balance and claims
 - Issue Warning Letters or Untitled Letters to industry when violation occurs

Regulatory Letter Overview

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Regulatory Letter Overview

- Examination of Warning Letters and Untitled Letters issued by DDMAC retrospective to 1/1/2004
 - 55 Communications Sent
 - 134 Violations
 - Reviewed
 - Company
 - Product
 - Vehicle for message delivery
 - Overview of violations

Regulatory Letter Overview

- Nature of Violations – top violations included
 - Minimization of risk
 - Overstatement of efficacy
 - Superiority Claims
 - Broadening of indication
- Full range of companies represented
 - Largest number sent to
 - Pfizer
 - Abbott
 - Boehringer Ingelheim

Regulatory Letter Overview

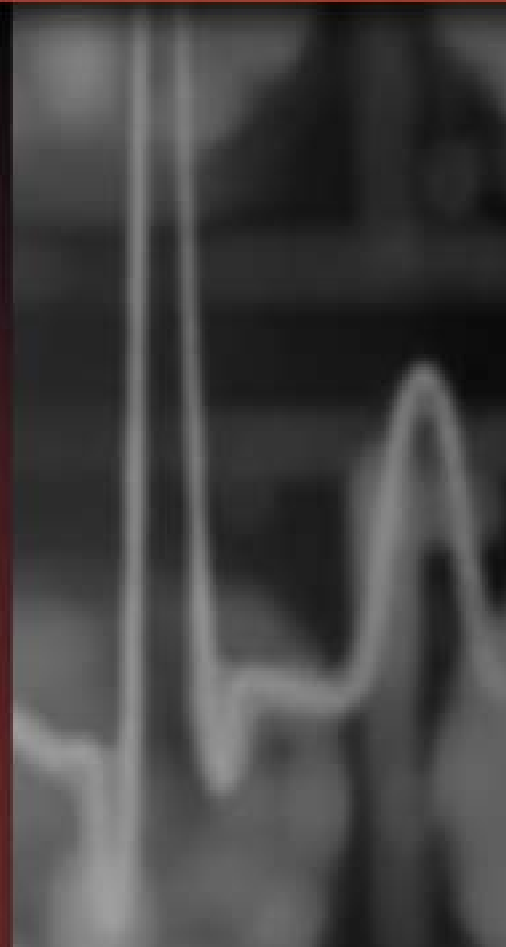
- Vehicles for Violations
 - Web site information
 - Electronic brochures
 - Print ads
 - Sales aids
 - Patient videos
 - Dear Doctor Letter
- No Press Releases have been subject of a Warning Letter during 2004-2006

Regulatory Letter Overview

- Products/Indications
 - While a large span of products were represented, some characteristics stood out
 - Highly competitive categories
 - Companies tending to stretch to make claims
 - » Erectile Dysfunction
 - » Blood Pressure Control
 - Sensitive categories
 - Psychopharmacologics
 - » Depression, ADHD

Pre-Approval Communications

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Pre-Approval Communications

- 21 CFR Section 312.7(a)

“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 under which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.”

Pre-Approval Communications

- Example of Press Release Violation
 - May 1998 – Roche issues press release after positive Advisory Committee vote
 - Made statements in the release about the product efficacy *before* FDA approval
- Note, by saying that it was “first-in-class” and MOA this was deemed promotional prior to approval.

“Xenical is the **first of a new class** of non-systemically acting anti-obesity drugs called lipase inhibitors **which act in the gastrointestinal tract to block the absorption of fat by about 30 percent...**” and “Xenical in comparison to other agents – does not achieve its effect through brain chemistry.”

Pre-Approval Communications

- Example of Press Release Violation
 - September 2000 – Synsorb Biotech issues 2 press releases reporting study results
 - Made statements interpreted by FDA to be saying product was safe and effective.
- **Note** - by saying that there is statistical significance implies that the methodology for so determining has been passed off by the FDA when it has not.
- “Approximately 1/3 of the patients... demonstrated a statistically significant lower rate...”
- “We are very excited to see statistically significant clinical data....”
- “The drug appears to offer substantial benefit...”
- “...Synsorb Pk can reduce progression...”
- **Note** - They also left out the fact that the trial missed designed protocol objectives.

Pre-Approval Communications

- Example of Press Release Violation

April 2000 – TAP issues press releases reporting FDA AC recommendation

– Made statements interpreted by FDA to be saying product was safe and effective.

- **Note** - quoted investigator speculating on safety and efficacy – implied strong conclusions.

“New class of Erectile Dysfunction therapy may benefit millions...”

“Uprima could offer several benefits ... data suggest that Uprima is safe and effective....”

“We feel that Uprima would greatly enhance the therapeutic options...”

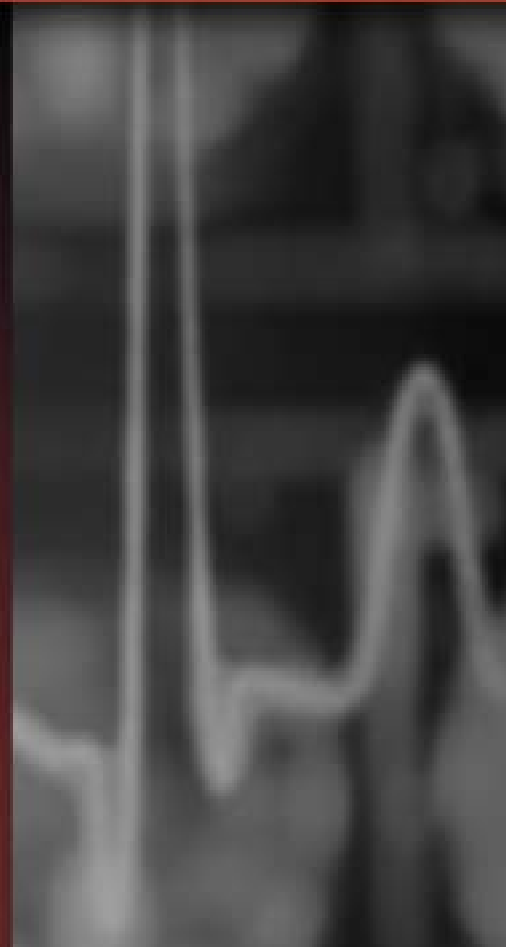
- **Note** - They also left out the boxed warning and specific label cautions.

Pre-Approval Communications Conclusions

- No instance of an FDA Warning Letter or Untitled Letter issued over a single press release during pre-approval could be found in **recent** searches
- Very few regulatory letters have been issued solely regarding press release
- Warning Letters tend to focus on marketed drugs in order to better protect the general public
- It would likely take an egregious press release to prompt agency action
- Always consider the most conservative approach in formulating communications on pre-approved products

Recommended Guidelines

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Recommended Guidelines

- How DDMAC affects PR
 - Cannot say a drug is approved until the FDA (not an advisory committee) sends letter to the drug company
 - Until approval
 - Cannot say drug is efficacious
 - Cannot say drug is safe
 - Cannot imply either
 - Cannot make a claim that the drug is superior to another treatment
 - Reporting medical meeting clinical trial results must be factual

Recommended Guidelines

- Rules of Thumb
 - Do NOT
 - Draw conclusions from data
 - Do not include language that states directly or implies indirectly that the data demonstrate that there is safety, efficacy or superiority.
 - Use adjectives to describe outcomes
 - Do not include additional information besides the study facts
 - Make any statement that would encourage use of the drug (if it is out on the market while being studied for a new indication) off label
 - Dress up a “me too” drug with blockbuster language
 - Do not skip or reduce risk information

Recommended Guidelines

- Rules of Thumb

- DO

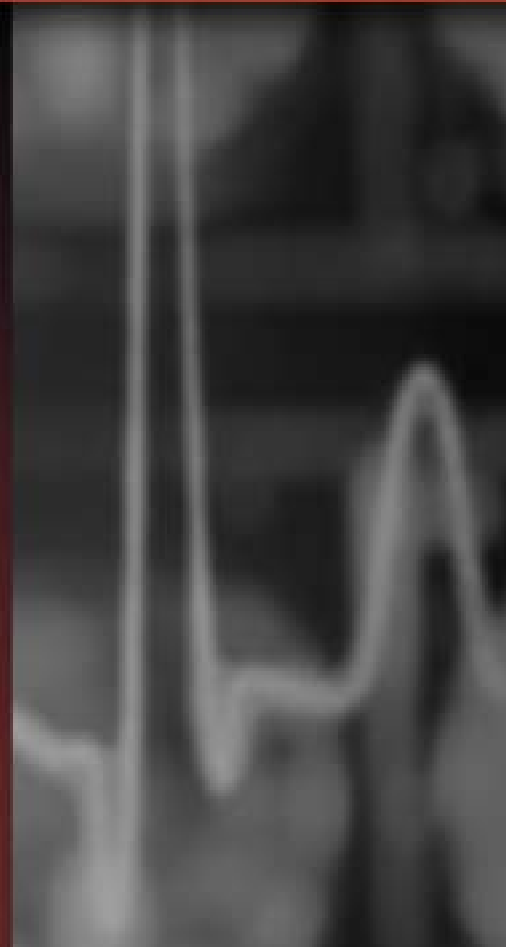
- Stick to the facts and the facts only
 - Be objective
 - Relay the data, not interpret it
 - Inspect thoroughly for any inferences made by language
 - Have a system for review
 - Remember approval is the letter from the FDA, not the advisory committee meeting
 - Include “forward looking statement” language in releases
 - Include a statement of side effects
 - State that the drug being studied is investigational

Recommended Guidelines

- Rationale
 - For Phase I and II – usually only trades will be interested in data milestones, not mainstream media
 - Considerations may vary between public/private companies
 - Phase III, while of greater interest, should not be dressed up for mainstream media
 - No need to create market among patients for drug not yet available
 - Still, a need exists to educate professionals on progress

Examples of Do's and Don't's

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Examples of Do's/Don't's

Actual Press Release

- Brief statement on most common side effects omitted
- specific AC concerns
- New class of therapy *may benefit* millions
- Uprima *could offer several benefits...* data suggest safe and effective...
- Uprima *would greatly enhance* therapeutic options
- Always include all risk information – boxed warning and other AEs were not mentioned
- No speculation on benefit
- Stick only to facts...”Advisory committee recommended approval...”
- Discuss pivotal clinical trial with facts.

Examples of Do's/Don't's

Actual Press Release

- Data published in two peer-reviewed articles show that La Jolla Pharmaceutical Company's (Nasdaq: LJPC) novel, orally-active small molecule inhibitors of SSAO/VAP 1 **may provide clinical benefit** for the treatment of stroke, ulcerative colitis, and other autoimmune diseases and inflammatory disorders. (ital. added)
- **Note** the use of the term “may provide clinical benefit”
- While inferring that benefit is being investigated, such tactics are best avoided

Recommended Approach

- Data was recently published in two peer-reviewed articles on results from clinical trials of La Jolla Pharmaceutical Company's (Nasdaq: LJPC) novel orally-active small molecule inhibitors of SSAO/VAP 1 being investigated for use against stroke, ulcerative colitis, and other autoimmune diseases and inflammatory disorders.
- **Note** the language has changed to omit any reference to a potential conclusion being drawn, sticking to the fact of the data publication, not expressing a potential opinion about outcome

Examples of Do's/Don't's

Actual Press Release

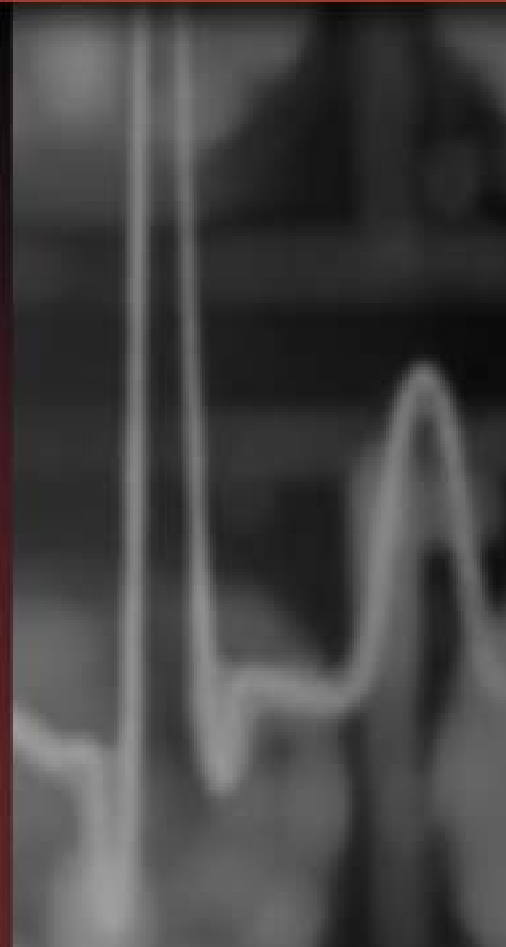
- The first paper, by Xu et al., indicates that a potent and selective SSAO inhibitor, LJP 1207, **may provide clinical benefit** in the treatment of stroke. Data published in this paper **demonstrates** that treatment with LJP 1207 in an animal model resulted in **marked reduction** in the adhesion and infiltration of white blood cells into the blood vessels of the brain after the occurrence of stroke and **significantly** less neurological damage.
- **Note** – Until the FDA has reviewed clinical trials, no one should imply statistical relevance or characterize the outcome.

Recommended Approach

- The first paper, by Xu et al., reported that a treatment group of (an animal model) receiving a potent and selective SSAO inhibitor, LJP 1207, **had a rate of ___ % of adhesion and infiltration of white blood cells into the brain after stroke compared ___ % in an untreated group.** The treatment group also suffered ___% of neurological damage while the untreated (animal model) experienced ___% of neurological damage.
- **Note** – No conclusions are drawn, only the facts are stated.

Conclusions

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Conclusions

- There is increasing pressure for greater transparency by pharmaceutical companies
 - Failure to send press releases could be perceived negatively
- The FDA monitors approved products to protect patients from being misled, not investors

Conclusions

- Communications support analyst interest and on-going
- Warning Letters are highly unlikely without egregious language or without being in tandem with other violations
- Guidelines can reinforce the relative safety of pre-approval communications

What FH DC Can Do

- Profile Advisory Committee Panel Members
- Issues and Third Party Analysis
- Presentation Development
- Mock Panel Rehearsals
- Message Development
- Crisis Preparation
- Meeting Support/Coordination with Marketing Team
- Review communications for compliance

Where to Get More Information

www.eyeonfda.com

My blog