



*Second Annual Pharmaceutical Industry
Regulatory and Compliance Summit
June 11, 2001*

FDA Enforcement: Advertising and Labeling

June 1, 2000 to June 1, 2001

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BUCHAREST

FDA Enforcement: Advertising and Labeling

- FDA tools for monitoring potential violations
- FDA tools for enforcement of violations
- Remedies available to FDA to enforce law and regulations
- Types of violations – What does FDA look for?
- What has FDA done in the last year?
 - What has been cited?
 - What remedies/tools used?
- Unresolved/potential future enforcement issues

FDA Tools for Monitoring Potential Violations Relating to Advertising and Labeling

- Pre-launch review of promotional materials
- Ongoing pre-clearance
- Submission for review prior to dissemination
[21 C.F.R. §202.1(j)(4)]
 - Mostly DTC Advertisements
- Submission for review after dissemination
[21 C.F.R. §314.81(b)(3)]
 - Form 2253

FDA Tools for Monitoring Potential Violations Relating to Advertising and Labeling (cont'd)

- Competitive and other Third Party Complaints
- Media Surveillance
- Attending Meetings of Professional Societies

FDA Tools for Enforcement of Violations Relating to Advertising and Labeling

- Untitled Letters (Notice of Violation Letters)
- Warning Letters
- Consent Decrees
- Civil Actions (Seizures)
- Criminal Fines and Penalties

Remedies Used by and Available to the FDA in Enforcing Laws and Regulations Relating to Advertising and Labeling

- Discontinuation
 - Piece/Advertisement in Question
 - Other pieces
 - 2 week response
- Dear Healthcare Professional Letters
- Corrective Advertising
- Pre-clearance
- Formal Legal Action

Types of Violations: What Does FDA Look For?

- Lack of Fair Balance
- Unsubstantiated Comparative Claims
- Unapproved Uses/"Broadened Indication"
- Unapproved Dosage Regimens
- Claims for Investigational Products; Pre-approval Promotion
- Overstated Efficacy
- Misleading/Unsubstantiated Claims

Types of Violations: What Does FDA Look For? (cont'd)

- Minimizing Risk Information or Safety Concerns
- Mechanism of Action Claims
- “New” Claims
- Reminder Advertisements
- Misleading Economic Claims

Types of Violations: What Does FDA Look For? (cont'd)

- Technical Violations –
 - Failure to Submit
 - Graphics/Text
 - Use of Outdated Labeling
 - Indications for Use
 - Failure to provide disclosure

What Actions Has FDA Undertaken in the Past 12 Months

- NOV Letters: 70
- Warning Letters: 2
 - Pharmacia – CELEBREX® – February 1, 2001
 - AstraZeneca – DIPRIVAN XL® – September 1, 2001
- Consent Decrees: 0
- Civil Actions: 0
- Criminal Fines and Penalties
 - NEURONTIN Grand Jury Investigation

What Has Been Cited – Lack of Fair Balance

Times Cited: 28

Illustrative Examples:

- April 2, 2001 – Letter to Merck – MIACALCIN and EXELON – Convention Panels With Claim but No Risk Information
- March 26, 2001 – Letter to Baxter – BREVIBLOC – Calendar lacked fair balance. Efficacy claims bulleted/large headings, risk information too small/no headers. Also failure to disclose warning.

What Has Been Cited – Lack of Fair Balance (cont'd)

- November 16, 2000 – Letter to Lilly – SARAFEM – Graphics accompanying presentation of risk information in DTC Broadcast Advertisement alleged to be distracting, minimizing risk information.
- October 23, 2000 – Letter to Watson – NORCO – Flashcards without risk information lack fair balance.
- September 7, 2000 – Letter to King – ALTACE – Announcement letter that does not include black box warning lacks fair balance.

What Has Been Cited – Unsubstantiated/ Misleading Comparative Claims

Times Cited: 21

Illustrative Examples:

- March 26, 2001 – Letter to Allergan – LUMIGAN – Comparison of LUMIGAN, second line therapy to TIMOLOL, first line therapy.
- December 8, 2000 – Letter to Schering – NASONEX – Comparisons to Fluticasone not supported since based on selective secondary endpoints from one study.

What Has Been Cited – Unsubstantiated/ Misleading Comparative Claims (cont'd)

- November 16, 2000 – Letter to ALZA – DITROPAN XL – Claims of “Let Your Patients Try DITROPAN XL and be Convinced”, “Compare and Be Convinced” and “Delivers a Difference” misleading as they imply superiority to DETROL based on an “across label” comparison of the products.
- July 18, 2000 – Letter to AstraZeneca – PRILOSEC – Use of non-clinical data to suggest clinical effect better than other product misleading.
- June 27, 2000 – Letter to Bausch & Lomb – ALREX – Table comparing product to products with other indications a misleading claim of superiority.

What Has Been Cited – Unapproved Uses/ “Broadened Indication”

Times Cited: 16

Illustrative Examples:

- May 1, 2001 – Letter to Novo Nordisk – PRANDIN – Reference to cardiovascular risks, diabetes type 2 and post-prandial glucose suggest PRANDIN reduces cardiovascular morbidity and mortality, when not so approved.
- March 16, 2001 – Letter to LifeCycle – CEFTIN – Implied efficacy for treatment of drug resistant infections, when not so approved.

What Has Been Cited – Unapproved Uses/ “Broadened Indication” (cont’d)

- February 2, 2001 – Letter to Novartis – FEMARA – Reference to study for preoperative treatment to reduce tumor size broadens indication.
- November 9, 2000 – Letter to Shire Richwood – ADDERALL – Home Made Sales Sheet by sales representative using 1999 prescribing data involving depression promotes unapproved use; approved only for ADHD and narcolepsy.
- August 7, 2000 – Letter to Shire – FARESTON – “First Line Therapy For Advanced Breast Cancer” claim broadens indication, since limited to “postmenopausal women with estrogen-receptor positive or unknown tumors”.

What Has Been Cited – Unapproved Dosage Regimens

Times Cited: 4

Illustrative Examples:

- July 18, 2000 – Letter to AstraZeneca – PRILOSEC – Suggested dosing of 40 mg a day for up to 12 years when indicated at 20 mg for 4 to 8 weeks.

What Has Been Cited – Pre-Approval Promotion

Times Cited: 9

Illustrative Examples:

- May 10, 2001 – Letter to Supergen – RUBITECAN – Promotion of product on website for cancers for which IND's in effect.
- February 13, 2001 – Letter to OraPharma – MINOCYCLINE – Claims of safety and efficacy and comparisons to approved products at a promotional exhibit for product subject to IND.

What Has Been Cited – Pre-Approval Promotion (cont'd)

- June 22, 2000 – Letter to Sanofi-Synthelabo Inc. – ELOXATIN – Booth at ASCO meeting promoting product for treatment of solid tumors unacceptable pre-approval promotion. [“A novel compound under investigation for the treatment of solid tumors”].

What Has Been Cited – Overstated Efficacy

Times Cited: 19

Illustrative Examples:

- May 19, 2001 – Letter to Sanofi-Synthelabo Inc. – PLAVIX – Selectively presented risk reduction of PLAVIX vs. aspirin on 2 of 3 outcome clusters.
- October 11, 2000 – Letter to Wyeth-Ayerst – EFFEXOR – Claims that EFFEXOR gets patients “beyond well to better” or “to true wellness” imply remission of depression.

What Has Been Cited – Overstated Efficacy (cont'd)

- September 14, 2001 – Letter to Lilly – EVISTA – Claims that overstate problems of osteoporosis imply greater efficacy and outcomes than demonstrated.

What Has Been Cited – Misleading Claims

Times Cited: 23

Illustrative Examples:

- April 16, 2001 – Letter to Pfizer – ESTROSTEP – Histogram showing 2 lb. difference, implied benefit but no statistical significance; use of 6 month study to show no weight gain, when not a prospectively defined endpoint.
- January 18, 2001 – Letter to Abbott – MIVACRON – “Only short acting non-depolarizing neuromuscular blocker” claim misleading since RAPLON also is.

What Has Been Cited – Misleading Claims (cont'd)

- December 27, 2000 – Letter to Forest – LEVOTHROID – Comparison of AWP's between levothyroxines misleading because does not disclose lack of bioequivalence.
- June 14, 2000 – Letter to Aventis – ALLEGRA – Claim that FAA authorizes use of ALLEGRA misleading without context that each pilot/controller has to be on medication long enough to demonstrate no adverse effect.

What Has Been Cited – Minimizing Risk or Safety Concerns

Times Cited: 15

Illustrative Examples:

- March 26, 2001 – Letter to Allergan – LUMIGAN – Bolded warning – not prominent compared to effectiveness claims.
- February 1, 2001 – Warning Letter to Pharmacia – CELEBREX – Minimize risk of interaction with coumadin – statement that VIOXX has interactions with coumadin and CELEBREX does not minimize risk of use of product in patients on coumadin.

What Has Been Cited – Minimizing Risk or Safety Concerns (cont'd)

- October 20, 2000 – Letter to SmithKline – AVANDIA – Claims for use of product in hepatically impaired patients minimizes risk information; not one mentioned.
- June 1, 2000 – Letter to ALZA – DITROPAN XL – Presentation of discontinuation rates without contextual information minimized risks with product use.

What Has Been Cited – Mechanism of Action

Times Cited: 3

Illustrative Examples:

- March 8, 2001 – Letter to Aventis – AMARYL – Implication that product lowers blood glucose by targeting insulin resistance and improving insulin sensitivity, when pi indicates dependent on stimulating release of insulin.
- March 29, 2001 – Letter to Braintree – MIRALAX – “WORKS IN 4 WAYS” claim misleading since product just acts osmotically.

What Has Been Cited – “New” Claims

Times Cited: 2

Illustrative Examples:

- November 20, 2000 – Letter to SmithKline – ARGATROBAN – “New” and “Introducing” makes claims for a product.
- November 6, 2000 – Letter to American Regent – VENOFER – Claims “New” and “Foundation for the Future” representations about a product.

What Has Been Cited – Reminder Advertisements

Times Cited: 10

Illustrative Examples:

- March 30, 2001 – Letter to Hoffmann-LaRoche – XENICAL – Reference to XENICARE support program in advertisement makes it product specific since XENICAL only weight loss product with XENICARE program.

What Has Been Cited – Reminder Advertisements (cont'd)

- February 16, 2001 – Letter to Fujisawa – PROTOPIC – Advertisement stating “Breakthrough research has uncovered a new kind of medicine for eczema. Made of a natural substance, this new treatment is steroid free” are claims for product since only refers to PROTOPIC.
- January 3, 2001 – Letter to AstraZeneca – PRILOSEC – Reference to acid reflux disease and “the purple pill” makes advertisement a branded advertisement.
- November 14, 2000 – Letter to Searle – CELEBREX – “Celebrate, Celebrate. Do What You Like to Do” makes claim for CELEBREX.

What Has Been Cited – Reminder Advertisements (cont'd)

- November 9, 2000 – Letter to Pfizer – ZITHROMAX – “Pfizer brings parents the letter Z” and reference to www.pfizerkids.com makes claim for Zithromax in a patient population and is therefore branded advertisement.

What Has Been Cited – Economic Claims

Times Cited: 3

Illustrative Examples:

- March 26, 2001 – Letter to LifeCycle – CEFTIN – “cost-effective”, “Ceftin + Savings” and related claims misleading because not supported; imply comparison of more than just drug acquisition costs.
- March 29, 2001 – Letter to Braintree – MIRALAX – Cost savings claims misleading because imply comparison beyond just acquisition costs.

What Has Been Cited – Technical Violations

Times Cited:

- Failure to Submit – 8
- Use of Outdated Labeling – 2
- Graphics/Text – 5
- Indications For Use – 4
- Failure to Provide Disclosure – 2

Illustrative Examples:

- Outdated Labeling – April 10, 2001 – Letter to Aventis – NILANDRON – Link on website to outdated p.i. without new serious risk information.

What Has Been Cited – Technical Violations (cont'd)

- Failure to Submit – March 13, 2001 – Letter to Bristol-Myers Squibb – IFEX – Failure to submit website copy.
- Graphics/Text – March 6, 2001 – Letter to Alcon – PATANOL – Use of difficult to read font for established name.
- Indications for Use – February 2, 2001 – Letter to Novartis – FEMARA – Failure to include indications for use in advertisement.

What Has Been Cited – Technical Violations (cont'd)

- Failure to Provide Disclosure – September 8, 2000 – Letter to CibaVision – RESCULA – Press release on website contained no link to p.i. or other risk information.

What Remedies/Tools Have Been Used in the Past 12 Months

- Discontinuation
- Dear Healthcare Professional Letters
 - September 1, 2000 – Warning Letter to AstraZeneca – DIPRIVAN XL
 - February 1, 2000 – Warning Letter to Pharmacia – CELEBREX

What Remedies/Tools Have Been Used in the Past 12 Months (cont'd)

- Corrective Advertising
 - Merck – VIOXX® – Voluntary Action to Correct Overstatement of Benefits/Minimization of Risk by Dorothy Hamill/Bruce Jenner on “Larry King Live”.
 - Pharmacia – CELEBREX® – Action in Response to NOV letter alleging overstatement of efficacy.
 - Novartis Corp. v. FTC, 233 F.3d 783 (D.C. Cir. 2000). (DOAN’S PILLS)

What Remedies/Tools Have Been Used in the Past 12 Months (cont'd)

- Other

Instruct Sales Force

November 9, 2000 – Letter to Shire Richwood –
ADDERALL.

Unresolved/Potential Future Enforcement Issues

- Off-Label Promotion
 - WLF
 - Neurontin Investigation
- Use of Experts
 - February 2, 2001 – Letter to James McMillen, M.D. – CELEBREX
- Internet

Unresolved/Potential Future Enforcement Issues (cont'd)

- DTC Advertisements
- Brief Summaries/Risk Disclosure
- 120 Day Post Launch Dissemination
- Electronic DDMAC Submissions