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Compliance in a Complex Environment

Daniel E. Troy

The Situation Before 2004

- Healthy appreciation for risk/benefit
- All drugs have risks
- FDA as a risk management agency
- Lessons of the AIDS experience
- Bayesian statistics discussion
- Focus on post-marketing systems
- Role of PDUFA

2004

- Preemption
- Importation
- Flu Vaccine
- SSRIs
- Vioxx

The last three all involve substantial compliance issues!

Consequences

- Pendulum has swung
- Slow-down in approvals
- Increased requests for pre-market studies
- Routine use of black box warnings
- Routine use of RiskMAPs
- Tysabri “pause”
- Palladone withdrawal

Key Development – Introduction of other "regulators"

- US Attorneys\DOJ
- State Attorneys General
- Plaintiffs' Lawyers\State Juries
- NGO's\Medical Journals

Most of whom are NOT scientific!

Others to worry about

- Congress
- Media
- Public Citizen and other so-called consumer groups
- EU and other countries' authorities
- Physicians
- Patients!

Impact of the Preemption Preamble

- In the Physician Labeling Rule, FDA declared that state law challenges to the label are, in its view, preempted
- In response, plaintiffs lawyers and state AGs are increasingly focusing on company activity outside the label
- Next major focus of lawsuits – failure to comply with GMPs, GCPs, GLPs?
- Almost every 483\WL leads to lawsuits, bad press, and competitive\reputational harms

Global Regulatory Trends

- While FDA Has Moved Toward A Risk-based Approach, Emphasizing Internal Controls And A GMP-type Regime, Congress Is Pushing The Other Way
- EU Authorities Have Ramped Up Enforcement Machine
- Criminal Enforcement Being Utilized To Create Industry "Poster Children"
  - *Companies In U.S.; Individuals In EU; Countries On Other Continents Are Investigating As Well*
- Product Liability "Export" To Europe

U.S. Legal Landscape

- Federal Food, Drug and Cosmetic Act Concerns Transmogrified Into Fraud and Abuse Offenses
  - Drug Safety Failures Implicate Both The Federal Food, Drug and Cosmetic Act (GMPs, GCPs, Adulterated Drugs) and The Health Care False Claims Act and Anti-Kickback Law
- Huge Penalties /Exclusion Even Where Underlying FFDCA Issue Not Clearly a Violation
  - Corporate Healthcare Settlements Up to Almost $1 Billion
  - Debarment From Working in the Pharmaceutical Industry if plea or conviction
  - Criminal Exposure: Jail And Large Fines
    - Felony -- Imprisonment and d penalties for individuals: up to $250,000
    - Misdemeanor - up to 1 year and penalties for individuals: up to $100,000
  - Civil Penalties for Individuals: Up to Tens of Millions
  - Injunctions Naming Companies and Individuals
- State Consumer Fraud, Product Liability, and Securities Class Actions Now Follow
  - Paying Many Times for the Same Allegation

EU Enforcement Trend

- Increased Pharmacovigilance *Enforcement* Focus
  - EU Requiring Member States to Impose "Effective and Dissuasive Penalties"
    - Numerous Criminal Investigations Under Way
    - Product Liability-Type Actions Being Pursued
    - May Serve as Predicates for Private Lawsuits
- Commission Guidelines Leave Companies With Open Compliance Issues and Difficult Legal Counseling Decisions

*Maurits Lugard, Sidley Austin Brussels

FDA AND THE EU: Recent Developments

- FDA BIMO Initiative
- FDA Enforcement Focus
- EU Pharmacovigilence
- Promotional Issues

BIMO - Objectives and Conclusions

- Protect human subjects in trials of FDA-regulated products
- Ensure high-quality and integrity of data used to:
  - Support marketing applications
  - Support regulatory decision making
  - Provide evidence base for clinical use of regulated products
- Regulatory program that provides assurance of integrity must not inhibit innovation — ideally will facilitate
- Regulatory program must modernize as practices change

Evolution of Clinical Trial Practices

- New trial methods and designs
- New methods of data collection and processing (e.g., electronic data capture)
- New arrangements between sponsors and various contractors, among investigators, among institutions, among IRBs, and rise of free-standing for-profit study centers
- Greater number of studies in children and other vulnerable populations
- Approaches to studies using existing human specimens

FDA's Oversight Must Evolve

- Must provide regulatory guidance and perhaps new regulatory scheme that encompasses modern trial arrangements
  - Responsibilities of investigators
  - Data integrity
- Must facilitate effective IRB oversight of evolving clinical trials arena to facilitate
  - IRB oversight of human subject protection
  - FDA oversight of IRB function
- Need common standards and regulatory requirements for electronic data handling
- Must be able to accommodate globalization of clinical trials
- Must ensure comprehensive approach to protection of vulnerable populations

BiMo Initiative Work Plan

- Continue to gather information from internal and external stakeholder groups
- Continue and complete work on short-term deliverables (e.g. guidances and rules)
- Conduct workshops and create other opportunities for public input
- Define *desired states* and develop longer term plan for achievement

FDA 2003 Strategic Plan – FDA's Enforcement Policy

Identified key principles in agency's science-based enforcement policy:

- Clarity – clear and consistent guidance
- Science – allow for latest innovations, and be no more burdensome than necessary
- Leveraging – work with federal and state partners
- Deterrence – punish using most effective tools

What FDA Is Talking About

- Drug “Re”-Importation
- GMP Reform
  - Dispute Resolution
  - Pharmaceutical Inspectorate
  - What we have left to do
- Compounding
- Counterfeits
- Imports
- Individual Responsibility
- Restitution/Disgorgement

Key Threats

- Counterfeiting
- Potentially unsafe foods and medications
- New infectious disease threats
- Imported pharmaceuticals
- Terrorism
- Intentional Contamination

Source: John Taylor

Enforcement Policy

- Cooperative and educational efforts
- Fair, risk-based, scientifically sound principles to assure efficient enforcement
- Risk-based approaches to inspection, compliance, and enforcement activities
  - using available enforcement tools commensurate with violations, or
  - relying on voluntary action
- Punish violations of fraud, gross negligence, or intentional violations and deter others through action

Source: David Elder

Enforcement Policy (cont)

- Collaborate and cooperate with federal, state, local, foreign governments, international organizations
- Evaluate and improve programs
- Assure quality in all work products while meeting productivity expectations

Source: David Elder

Numbers

(Source: David Elder)

	FY 05	FY 04	FY 03	FY 02	FY 01
Conviction	259	196	206	271	360
Injunction	15	13	22	15	12
Recall	5,338	4,670	4,627	5,025	4,563
Seizure	15	10	25	13	27
Warning Letter	535	737	545	755	1,032

Beyond Numbers

- Examples of FY05 Seizure Cases
  - Drug products
  - Enclosed hospital beds
  - Test kits for HIV, syphilis
  - Dietary supplements with EA
  - Adulterated food

Source: David Elder

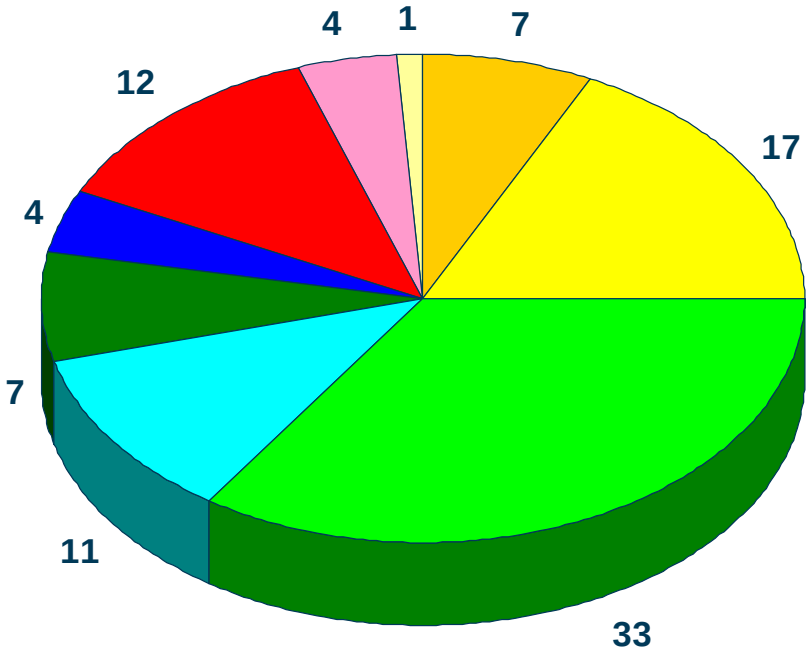
Beyond Numbers

- Examples of FY05 Injunction Cases
  - Device GMP/MDR
  - Drug GMP
  - Seafood HACCP
  - Illegal Drug Residues

Source: David Elder

FY'04 CDER Warning Letters
Total 62

(Source: David Elder)



- Lack Adequate Directions for Use (7)
- Misbranded (17)
- GMP (33)
- Unapproved New Drug - OTC (11)
- Unapproved New Drug (7)
- Adverse Drug Reporting (4)
- Drug Advertising (12)
- Drug Listing (4)
- Drug Compounding (1)

Current Areas of Concern – Recalls

- Top 5 Reasons for Recalls in FY04
  - Labeling
  - Stability
  - Sterility
  - Product Approval
  - Counterfeit
- Correlation to GMP compliance

Source: David Elder

Top 10 Drug Observations in Turbo EIR (as of 9/1/05)

1) 21 CFR 211.100(b) -- Written production and process control procedures not followed

2) 21 CFR 211.22(d) -- QC procedure not written or followed

3) 21 CFR 211.110(a) -- Control procedures are not established to monitor the output/validate the performance of the manufacturing process causing variability

4) 21 CFR 211.100(a) --No written procedure for production and process controls designed to ensure . . . identity . . . strength .

5) 21 CFR 211.188 -- Batch production and control record deficiencies

Top 10 Drug Observations cont'd

6) 21 CFR 211.165(a) -- Testing and Release or a drug product for distribution do not include appropriate laboratory determination

7) 21 CFR 211.160(b) -- Laboratory controls do not include appropriate establishment of scientifically sound and appropriate specifications, sampling plans . . .

8) 21 CFR 211.25(a) -- Inadequate employee training

9) 21 CFR 211.68(a) --Routine calibration inspection . . . is not according to a written program and inadequate

10) 21 CFR 211.192 -- Failure to review unexplained discrepancy or batch failure to meet specifications

Source: Joe Famulare

GMP -- Regulatory Actions Processed for FY 2005

Warning Letter	(Domestic)	11
	(Foreign)	3
Seizure		1
(resulting in Consent Decree)		

*Pending actions are not included

Source: Joe Famulare

Issues Raised in Regulatory Actions

- Validation
- Lack of Sterility Assurance
- Failure to Sterility Test
- Inadequate investigation of failure to meet specifications or unexplained discrepancies
- Cross Contamination
- Adequacy of Mix – Blending
- Packaging and Labeling Issues including product mix-ups

Source: Joe Famulare

Some Current FDA Pharmacovigilance Concerns

- Failure to Trend Obvious Data Points
  - Leads to Failure to Report Safety Issues
- Failure to Report Signals Where Appropriate – Including From Foreign Sites
- Inadequate Safety Data Collation In Clinical Trial Stage
- Software Validation
- Bottom Line: FDA Dislikes Surprise -- Wants to be Advised in a Timely Fashion

Importance of a good PV system

- Can be helpful in getting drugs approved
- Not just about compliance – an important tool in ensuring safe use
- Recent shift towards stricter enforcement of stricter EU rules
- New draft of “Volume 9” (EU Guideline on Pharmacovigilance)

Recent shift towards stricter enforcement of stricter EU rules

- Stricter rules to ensure
  - a higher degree of market surveillance
  - more effective sanctions
- Inspections are becoming routine
  - But: need for clear and consistent inspection standards
- « Market surveillance should be **stepped up** »

  (Recital 20 to Directive 2004/27)
- « Member States shall take the necessary measures to ensure …

  effective, proportionate and dissuasive penalties »

  (Directive 2001/83, art. 104(9))
- **Penalties** could well include fines or imprisonment

Source: Maurits Lugard

New draft of "Volume 9" (EU Guideline on Pharmacovigilance)

- Increased importance of the EU QP (qualified person responsible for pharmacovigilance in the EU)
- Contractual agreements: clock start for expedited reports
- Notification of safety concerns

Source: Maurits Lugard

Increased importance of EU QP

- Draft Volume 9A:
  - maintenance of a company's PhV System
  - **full management of the system**
  - **complete oversight** of structure and performance
  - assure system
    - **directly**
    - through **supervision**
  - **contact point** for PhV inspections
  - **only one EU QP per Company**
- **Consequence:** increased risk of liability of/for EU QP
- Draft Volume 9A:
  - MAH should **adequately support** EU QP
  - Consequence: increased risk of liability for MAH

Source: Maurits Lugard

Pharmacovigilance obligations related to "arrangements"

« **Detailed and clear** contractual arrangements for meeting PhV obligations should be **documented** in the case **where there are arrangements** between the MAH and persons or organizations involved in the fulfilment of PhV obligations.

It is the responsibility of the MAH to ensure that these are in place and to **notify** the competent authorities of such arrangements [...] »

Source: Maurits Lugard

Pharmacovigilance obligations related to "arrangements" (Cont.)

- Unclear provision
  - **When** exactly should 'PhV arrangements' be in place?
  - What should be the **content**?
    - no guidance whatsoever
    - negotiations partner companies
    - increased risks/liabilities
    - minimum requirements?

Source: Maurits Lugard

Pharmacovigilance obligations related to "arrangements" (Cont.)

- The clock for expedited ADR reports « starts as soon as any personnel of the MAH or **the organisation** [having a contractual arrangement with the MAH] receives the minimum information. »
  - No legal basis
  - Unrealistic and impossible to enforce when the organisation is not acting directly on behalf of the MAH

Source: Maurits Lugard

Notification of new safety concerns: EU law

« The MAH shall **forthwith** inform the authorities of **any other new information** which **might influence** the evaluation of **benefits and risks** of the medicinal product concerned. »

Regulation 726/2004, Article 16.2

Directive 2001/83/EC, Article 23

Source: Maurits Lugard

Notification of new safety concerns (Cont.)

- Problem: much stand alone data
  - Do not necessarily give rise to a signal
  - But … can always potentially do so
    - in the future
    - if related to other adverse events
  - « **Might** » influence the benefit risk balance
  - **Any** new information could be a new safety concern
  - If not reported **forthwith**: risk breach of EU Law

Source: Maurits Lugard

Notification of new safety concerns (Cont.)

- Conclusion
  - Urgent guidance needed
  - Data dump
  - Need preliminary evaluation
- System must be practical
  - Industry suggestion: decision tree based on public health impact
- Other problems
  - Meaning of « forthwith »
  - Clock start

Source: Maurits Lugard

Promotional Issues

- Watch out for cumulative effect
- MSLs
  - Avoid suggestions of ROI
- Consider regular audits to ensure compliance with plan
- CME\Meeting Sponsorships
  - minimize influence; independence is key
- WLF leave-behinds
- Direct mail to physicians\unsolicited requests
- Medical writing support
- P & T committees\PE data
- Advisory boards

Current DDMAC Issues

- “Adequate and well-controlled”
- Omission of material information
- Corrective messaging
- Adequacy of disclaimers
- Role of First Amendment

Competitor Complaints

- To complain or not to complain?
  - (At least) 2 views
- GC-to-GC resolution
- Be strategic
  - intended use example
- How-to
  - emphasize level playing field
  - agree steps with business

HHS Guidance to Pharma Companies (Healthcare)

- **"**At a minimum, a comprehensive compliance program should include ...(5) The use of audits and/or other risk evaluation techniques to monitor compliance, identify problem areas, and assist in the reduction of identified problems**"**
- **"F. <u>Auditing and Monitoring</u>**
- …The extent and frequency of the compliance audits may vary depending on variables such as the pharmaceutical manufacturer's available resources, prior history of noncompliance, and the risk factors particular to the company**.** The nature of the reviews may... include a prospective systemic review of the manufacturer's processes, protocols, and practices...
- The reviews should also evaluate the company's policies and procedures regarding **other areas of concern identified by … federal and state law enforcement agencies.**

Audit To Ensure That the Reports Are Accurate

- A Key Factor In Investigations
- Puts Accepted Conclusions to the Test
  - Need to Drill Deeply in Selected Areas
- Keep Privileged to The Extent Possible
  - Try to Ensure A Valid Use of the Privilege
  - Confer with Legal Department

Source: Scott Bass

Emails Become Permanent Evidence

- Write What You Mean To Say
- Avoid Mass Emails--Check Your Cc's
- Use Privilege Where Appropriate
- Use Proper Company Compliance Reporting Procedures
- Do Not Over Characterize
  - "Worst I Have Seen"
  - 'Rumor Has it'"
  - "Can't Believe I Told Her Once Before"
  - "I Hope Management Never Sees This"
- Let The Legal Department Determine The Law

Source: Scott Bass

Organizational Changes May Be Critical in Avoiding Governmental Pain

- As in GMP Compliance, Systems Approach by Authorities
- Critical To Avoid:
  - Decision- Making Voids (Common)
  - Conflicting Jurisdiction
  - Marketing or Sales Top Decision Authority
  - Failure to Fix Acknowledged Weakness

FDA: What Can Industry Do?

- Continue to innovate and develop products that advance public health
- Demonstrate a corporate philosophy of compliance
- Pay attention to signals
- Be forthright and proactive

Source: David Elder

Thank you!

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