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Innovative Drug Development in a Pharmacovigilant Environment

"Moving from Pharmacovigilance to Pharmacodiligence"

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August 24, 2006

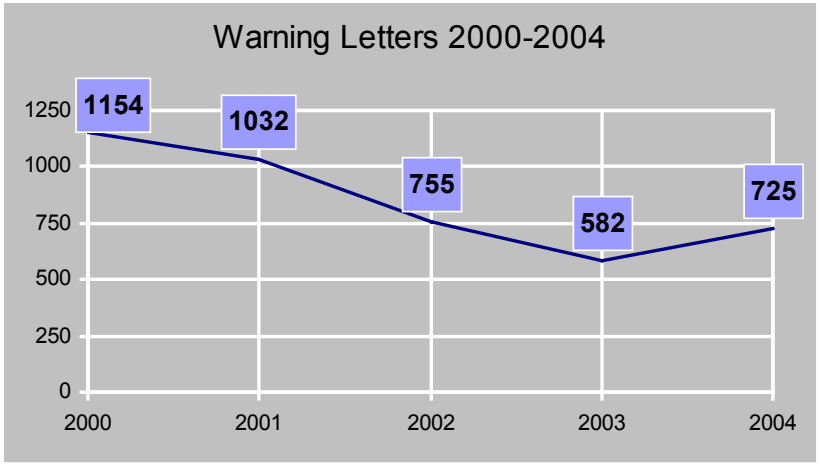
Agenda

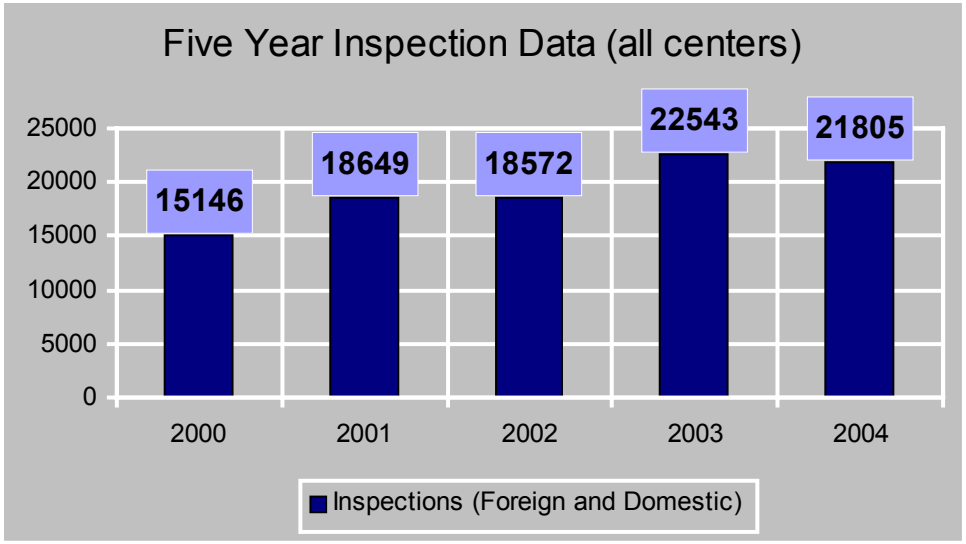
- **FDA history and current efforts**
  - Enforcement
  - Public view
  - What all this means
- **Product development in a changing pharmacovigilant environment**
  - PDUFA and clinical trial drivers
  - Risk based clinical trial management
- **Strategic responses**
  - “Information Integration” vs. “Data Management”
  - What are others doing to address these issues?
- **Questions**

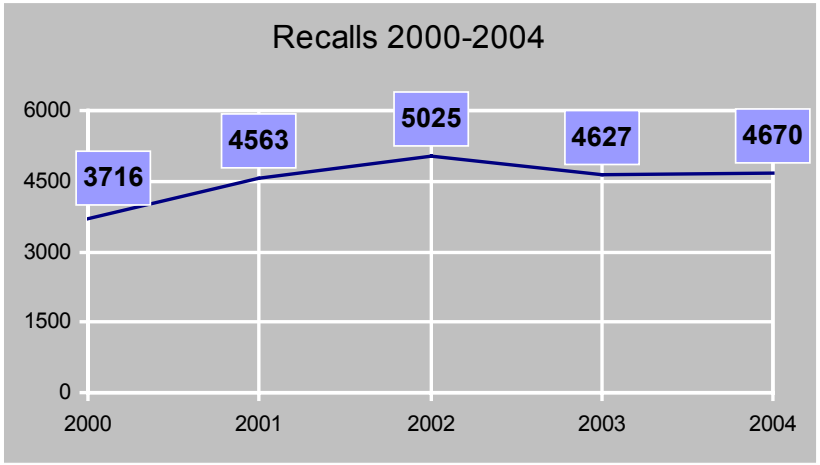
FDA Activity: Recent History

Between 2000 and 2004

- Less warning – More legal action







*Source of 2000 – 2003 Data - http://www.fda.gov/ora/about/enf_story/archive/2003/ch10/stats_charts.htm

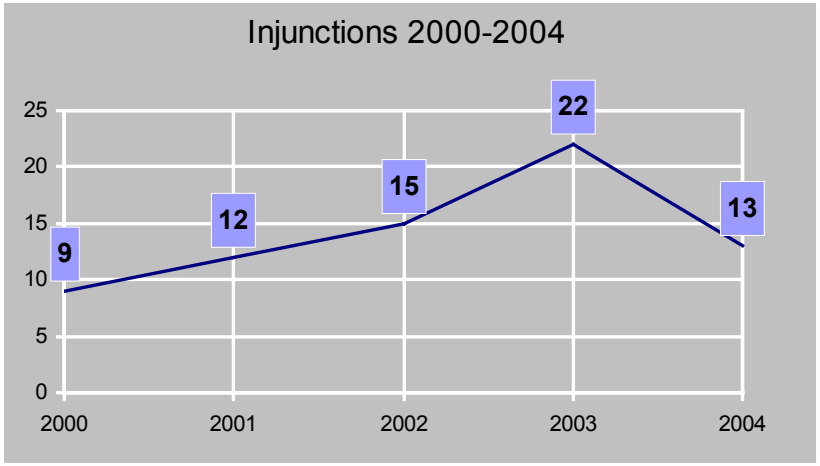
*Source of 2004 Warning Letters & Recalls statistics - http://www.fda.gov/ora/about/enf_story/ch10/

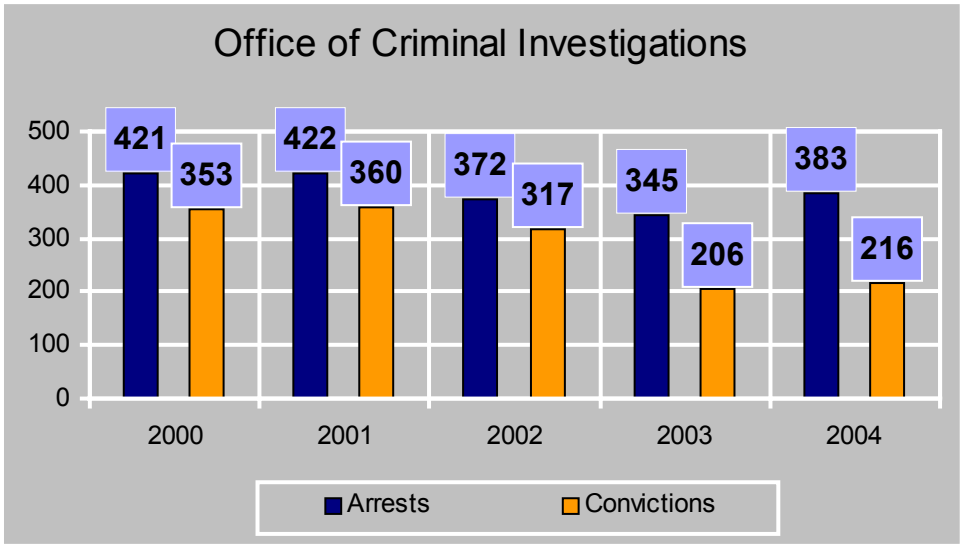
*Source of 2004 Inspections - http://www.asq.org/fdc/conferences/fda-activities-report.pdf

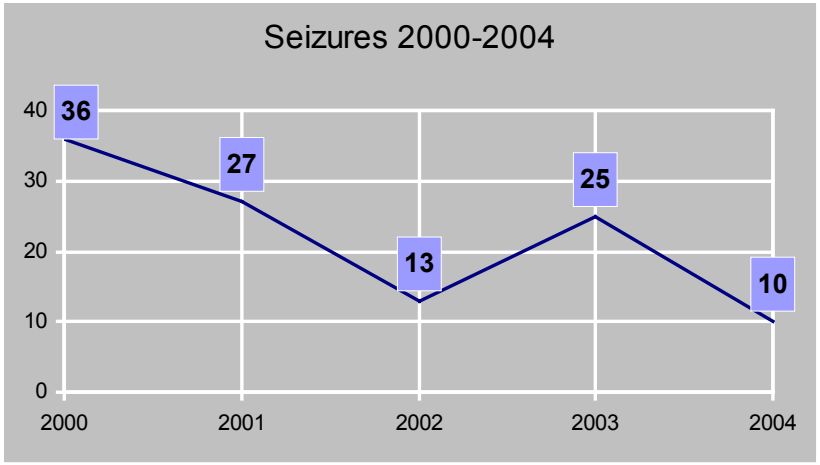
FDA is Still Focused on Post-Marketing Enforcement

Between 2000 and 2004

- FDA still focused on post-marketing enforcement







*Source of 2000 – 2003 Data - http://www.fda.gov/ora/about/enf_story/archive/2003/ch10/stats_charts.htm

*Source of 2004 Injunctions & Seizures - http://www.fda.gov/ora/about/enf_story/ch10/

*Source of 2004 Convictions - http://www.fda.gov/ora/about/enf_story/ch6/oci_charts.pdf

FDA Enforcement Statistics FY 2005

Office of Criminal Investigations: Drug Safety Activities

In FY 2005…

- Initiated over 350 criminal investigations
  - Achieved over 325 arrests,
  - Which led to 225 convictions

Recovered over $55,000,000 in fines and restitution

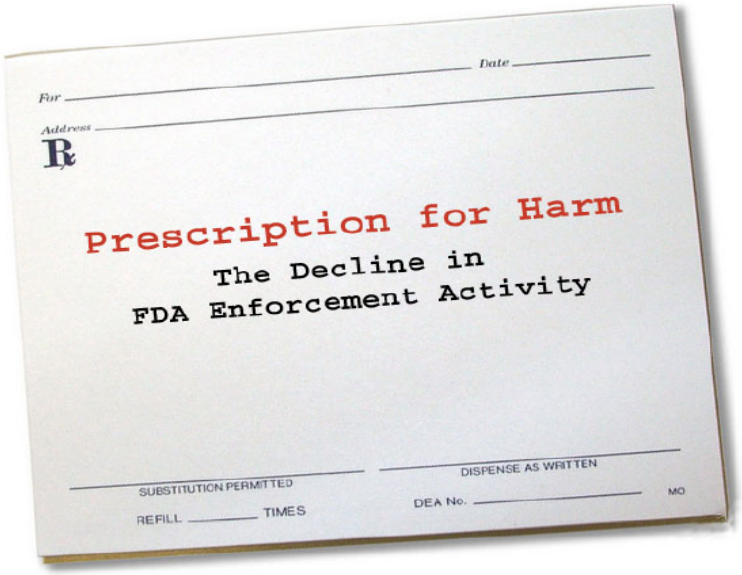
*Source - http://www.fda.gov/oc/oms/ofm/budget/2007/HTML/7FieldActivitiesORA.htm

The Real World…The Medical Device Crisis??

- Rep. Henry Waxman (D-CA..) released the 15-month study, "Prescription for Harm: The Decline in FDA Enforcement Activity,"
  - Despite growing reports of malfunctions in medical devices such as pacemakers and defibrillators," the number of warning letters issued by the Center for Devices and Radiological Health (CDRH) for violations of manufacturing, reporting and quality regulations fell by 66 percent between 2000 and 2005, said Rep. Henry Waxman (D-CA..) in a recent report.
  - "The decline in enforcement does not appear to be the result of increased compliance by manufacturers," as the number of violations observed by FDA field inspectors "has remained fairly constant," the document states.

The Real World …Rx for Harm – the Waxman Report

UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM — MINORITY STAFF
SPECIAL INVESTIGATIONS DIVISION
JUNE 2006



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PREPARED FOR
REP. HENRY A. WAXMAN

The Real World….Wasted Clinical Studies

The Washington Post

- Repeated tests of the same diagnostic study or treatment are a waste -- of time and money, and of volunteers' trust and self-sacrifice. Unnecessary clinical trials may also cost lives
- The number of unnecessary studies that occur is an open question.
- Nobody requires that medical scientists review previous research to make sure the question they are asking has not already been answered. This may change, though.
- The *Lancet*, a British journal, announced last summer that it will require that authors submitting papers show they performed a meta-analysis of previous research or consulted an existing one.

Brown, David. “Superfluous Medical Studies Called Into Question”

The Washington Post on the Web 02 Jan. 2006

http://www.washingtonpost.com/wp-dyn/content/article/2006/01/01/AR2006010100749.html

The Real World….Clinical Data Validity ????

Public Citizen

- Public Citizen argues in a recent article in The Lancet that GlaxoSmithKline (GSK) manipulated data in a clinical study of its asthma drugs Serevent (salmeterol xinafoate) and Advair (fluticasone propionate/salmeterol xinafoate) to downplay their risks.
- The bill, known as the Fair Access to Clinical Trials (FACT) Act, would require drugmakers to submit clinical trial results to an electronic database or face stiff monetary fines. The proposal, S. 470, has been stalled in the Senate Health, Education, Labor & Pensions Committee since it was introduced Feb. 28 by Sens. Chuck Grassley (R-Iowa) and Christopher Dodd (D-CT..).

"GlaxoSmithKline Misled FDA, Doctors and Patients with Faulty Asthma Drug Study, Public Citizen Writes in Lancet Medical Journal"

Public Citizen on the Web 07 Oct. 2005

http://www.citizen.org/pressroom/release.cfm?ID=2060

The Real World….Inconsistent Approval Policy

Government Accountability Office

- An unreleased federal report bolsters allegations that the FDA made a political rather than a scientific decision when it delayed Barr Pharmaceuticals' application to sell the Plan B contraceptive without a prescription, congressional sources say.
- The GAO concluded that the FDA's actions on Plan B represented a significant departure from standard agency policy and indicated potential problems in the agency's review of Barr's application. The FDA's later rejection of an independent advisory panel's recommendation that Plan B be sold OTC also was unprecedented, the GAO found. According to the report, of 23 drugs recommended for OTC sale by FDA advisory panels over a 10-year period from 1994 to 2004, Plan B was the only one the agency later rejected.

United States. Government Accountability Office. Food and Drug Administration Decision Process to Deny Initial Application for Over-the-Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual

http://www.gao.gov/new.items/d06109.pdf

The Real World….The Drug Discovery Question

The New York Times

- Even as pharmaceutical companies poured a record amount of money into drug development in 2005, statistics from the Food and Drug Administration, show it approved only 20 new drugs, down from 36 in 2004. Only once in last 10 years has the number of newly approved drugs been lower than last year's figure.
- But the F.D.A. and the companies seem to agree that the process for testing and developing new drugs needs improvement.
- Even as the F.D.A. looks for ways to speed the testing of new treatments, members of Congress and some consumer groups are calling for even more testing before drugs are approved.
- The drought in new drugs has led some industry executives to complain that the F.D.A. is denying approval to good new treatments because of the criticism the agency has faced from lawmakers over Vioxx.
- The number of potential new drugs in Phase I and II testing has nearly doubled in the last decade, to 1,971 in 2004 from 1,010 in 1995. But that has not translated into success in Phase III development; the number of drugs in Phase III has been flat at fewer than 400.

Berenson, Alex. “Drugs in '05: Much Promise, Little Payoff”

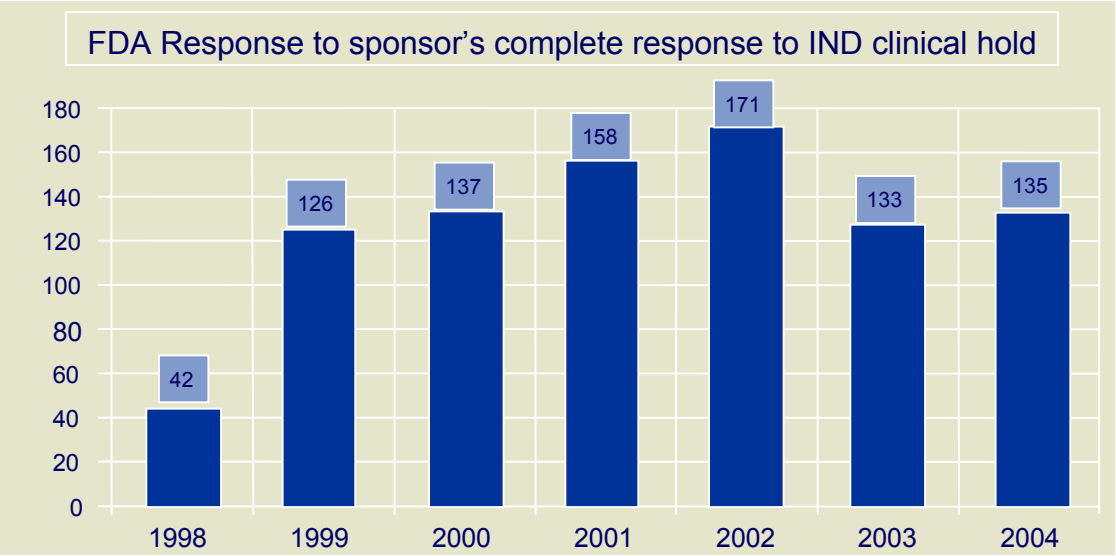
The New York Times on the Web 11 Jan. 2006 Business

http://select.nytimes.com/gst/abstract.html?res=F70D14FA3D5B0C728DDDA80894DE404482

The Real World….

FDA's clinical response times are still getting longer

- Under PDUFA, FDA's goal is to reply to a sponsor's complete response to a clinical hold within 30 days of the Agency's receipt of that response (90 percent of the time)
- Rapid resolution of safety issues that led to clinical hold helps confirm patient safety while enabling access to the experimental treatment.
- The figure below shows the total number of Clinical Holds increased by more than 200 percent (from 42 to 135 per fiscal year) between 1998 and 2004



*Source - http://www.fda.gov/oc/pdufa/PDUFAWhitePaper.pdf

The Real World …..FDA Drug Approval Rates - Impacted by Safety Concerns?

Fears that the FDA's focus on safety concerns (arising from product safety problems with Vioxx and Baychol) would trigger more conservative FDA decision-making in drug reviews, appear to be unfounded

- CDER cleared 48% of the original NDAs in the FY2004 (up from 37% in 2003) in the first review cycle, the highest percentage in at least the last nine years*
- An "early-indicator" analysis of the FY2005 NDA filings shows that CDER has approved 54% of the FY2005 NDAs in the first review cycle (thru Feb 2006, when CDER had taken first actions on 54 of 101 NDAs).

These results indicate that safety concerns are not paralyzing the agency's ability to review and approve NDAs in a timely fashion

*Statistical data taken from PAREXEL's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007

What All This Means …

- Clinical data evaluation is difficult and controversial but remains absolutely critical to the drug approval process
- R&D investments remain central to Pharma growth despite recent record of low productivity
- Higher visibility and increased public scrutiny of clinical studies is probably inevitable

- The public's perceptions of risk and risk management are "uninformed" at best
- The industry's (and agency's) communication of the risks and benefits associated with the introduction of new drugs ranges from poor to nonexistent
- Politics plays a real role in the functioning of FDA

PDUFA III and Risk Management

In 2002, Congress reauthorized the Prescription Drug User Fee Act (PDUFA III) under which the FDA agreed to meet certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products

- Guidance for premarketing risk assessment
  - *Final guidance issued March 2005*
- Development and use of risk minimization action plans
  - *Final guidance issued March 2005*
- Good pharmacovigilance practices and pharmacoepidemiologic assessment
  - *Final guidance issued March 2005*
- Guidance for clinical trial sponsors (data monitoring committees)
  - *Draft guidance issued Dec 2005*
- Guidance for exploratory IND studies (streamlined studies)
  - *Final guidance issued Jan 2006*

The Changing Guidance Environment – May 2006

- FDA is announcing the withdrawal of five and the revision of two guidances for industry because of inconsistencies with the agency's 21st Century CGMP Initiative (August 2002). FDA introduced the Initiative for a number of reasons:

1. **Enhance the CGMP**
2. **Focus our resources and regulatory attention on those aspects of manufacturing that pose the greatest risk to the quality of the product,**
3. **Ensure that FDA's work does not impede innovation in manufacturing**
4. **Promote consistency in FDA's regulatory approach.**

The Changing Guidance Environment – May 2006

FDA withdrew

- *Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application*, (February 1987)
- *Submitting Documentation for the Stability of Human Drugs and Biologics*, (February 1987)
- *Stability Testing of Drug Substances and Drug Products* (Draft), (June 1998)
- *Drug Product: Chemistry, Manufacturing, and Controls Information* (Draft), (January 2003)
- *Submission of Chemistry, Manufacturing and Controls Information for Synthetic Peptides (Nov 1994)*

FDA revised

- *BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post approval Changes: CMC Documentation, February 2001.*
- *Drug Substance: Chemistry, Manufacturing, and Controls Information (draft), January 2004*

The Changing Guidance Environment – May 2006

FDA recommended use of the following ICH documents

- *M4: Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use* (CTD), October 2001.
- *M4: The CTD—Quality*, August 2001.
- *Q1A(R2) Stability Testing of New Drug Substances and Products*, November 2003.
- *Q1B Photostability Testing of New Drug Substances and Products*, November 1996.
- *Q1C Stability Testing for New Dosage Forms*, May 1997.
- *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*, Jan 2003.
- *Q1E Evaluation of Stability Data*, June 2004.
- *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV*, Revision 1, July 2004.
- *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, December 2000.
- *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*, Aug1999.
- *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, August 2001.
- *Q8 Pharmaceutical Development* (Draft), February 2005.

What is Clinical Safety Risk Assessment?

- The pre-marketing risk assessment guidance document focuses on clinical development risk assessment
  - Risk assessment is the process of
    - *Identifying*
    - *Estimating*
    - *Evaluating the nature and severity of risks associated with a product*
- Risk management is an iterative process designed to enhance the benefit-risk balance for regulated products
  - Requires ongoing review and evaluation

A CHANGE IN FDA DRUG SAFETY STRATEGY?

- Senior FDA official recommends that risk management plans not be required in NDAs
  - Deputy commissioner for medical and scientific affairs, Scott Gottlieb announced at an AMA meeting that risk management plans (RMPs), while important in some instances, may be too prevalent.
  - He recommends that the agency look to a more collaborative approach involving the medical community and physician organizations.
  - Traditionally, the agency has used RMPs in response to a known or reported drug safety issue but in recent years the agency has proposed that RMPs should become part of almost all NDAs

It is possible that this announcement signals a change in the agency's focus on risk avoidance and a shift to a more balanced view of risk/benefit evaluation and management

How Do Compliance and Risk Work Together?

FDA's position

- FDA has begun changing it's compliance approach, giving additional value to upfront investment in problem avoidance rather than back-end remediation
- FDA will focuses more agency resources on identified risk companies

Approach

- Develop upfront investments in quality systems to avoid appearing to FDA as "high risk" company - stay off the radar!
- Replace traditional "validation task" focus with a quality systems management (QSM) approach

Our POV

These points highlight the large gaps many companies have to in the areas of QSM and clinical compliance requirements

Risks exist but can be effectively managed through an appropriate investment and these risk avoidance investment can help minimize the experience review cycle time and agency scrutiny

When is Risk Assessment Finished?

FDA's position

- FDA believes that risk assessment occurs throughout a product lifecycle
- Beginning with the early identification of a product as a candidate, through the premarketing development process, all the way thru to post-marketing studies

Approach

- Develop a risk management plan
- Perform post-approval pharmacovigilance
- Define (as much as possible) the product's underlying risks and benefits prior to approval
- Ensure that the clinical data plan defines the product's safety profile as well as its efficacy

Our POV

A critical component of FDAs approval process will include an evaluation of the pre-marketing/phase 3 studies that attempt to define the product's safety profile within a risk/benefit framework

Agency's focus will be on risk side of equation Industry must define risk/benefit and effectively communicate that definition to both the agency and public

How is Risk Information Managed During Clinical Trials?

FDA's position

- FDA recommends that sponsors pay careful attention to safety issues from the outset of the product development cycle
- Decisions on approvability will be based upon both existing risk information and safety questions as part of a product's risk assessment

Approach

- Investigate potential problems from preclinical data
- As experience accrues, refine/modify product safety evaluations
- If the product offers no new benefits, the safety risk must be low (must be almost nonexistent in the near term)

Our POV

FDA's focus on risk/benefit data requires continual review, evaluation and documentation of pre-market safety data

Industry innovators will develop risk evaluation into a formalized, controlled and managed process – They will set the standards for FDA and the rest of the industry

How is the Scope of a Clinical Safety Database Determined?

FDA's position

- Expand studies to help define unknown and unstudied interactions
- The larger and more comprehensive the database, the more likely it is that serious adverse events will be detected.
- More comprehensive clinical studies
- Studies to detect unanticipated interactions will be required

Approach

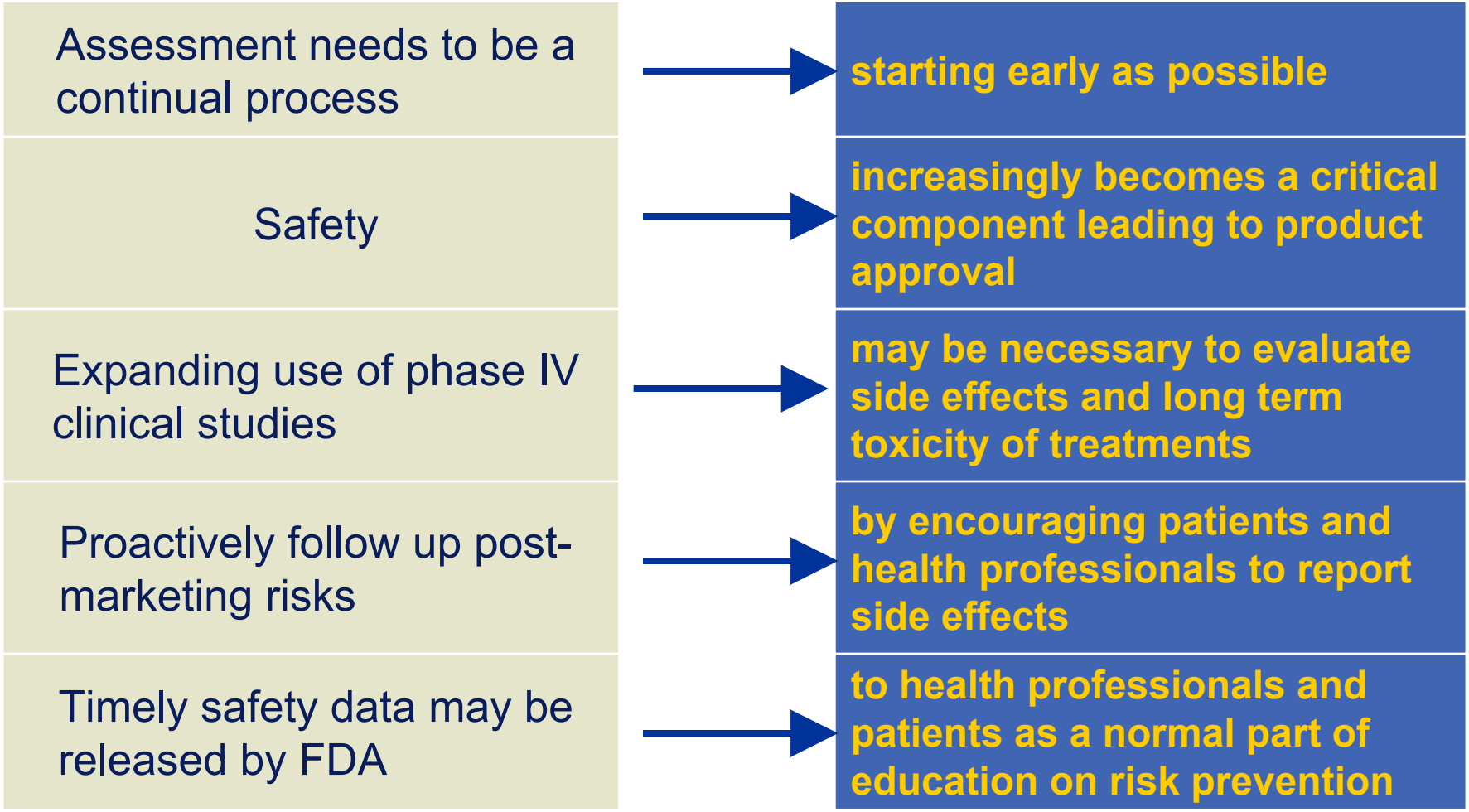
- Drug-drug interactions
- Increase product-demographic relationships study diversity (gender, age, and race.)
- Investigate product-disease interactions (ensure sufficient variability in disease state and concomitant diseases if appropriate)
- Study product-dietary supplement interactions (for commonly used supplements that are likely to be co-administered)

Our POV

Expanded clinical studies - bigger, longer, more comprehensive & diverse - will become the norm and present serious challenges to the industry

Added clinical time & costs do not enter into the FDA's thinking If product isn't a blockbuster – must have almost flawless safety data (good safety data doesn't hurt with blockbusters either)

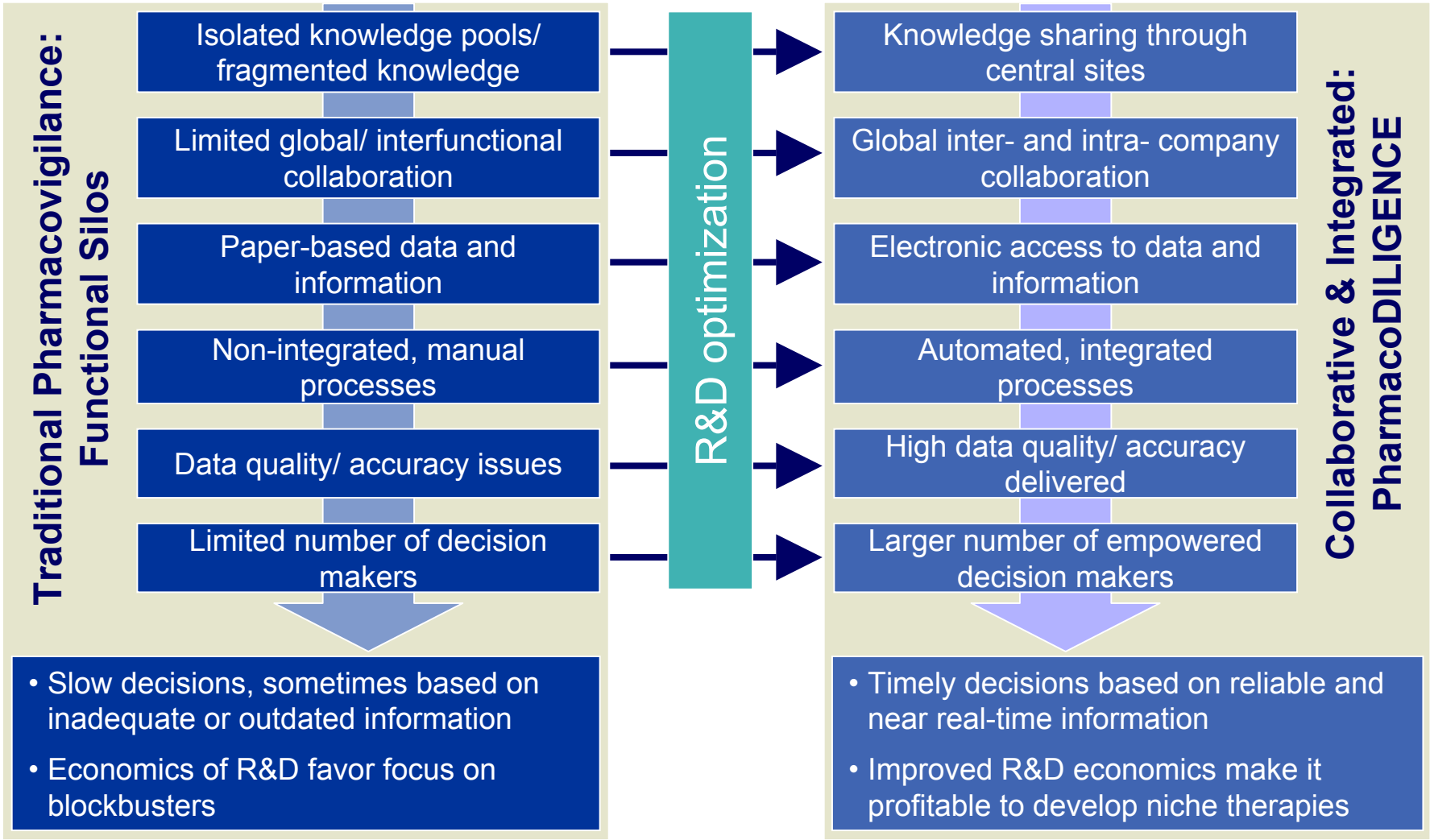
Issues for Clinical Pharmacovigilance



Strategic Responses to the Changing Pharmacovigilant Landscape

Ramping up staffing	→	Create multidisciplinary pharmacovigilance “SWAT Teams”
Movement from risk management	→	towards risk aversion
Monitoring of safety issues and safety data	→	Thru the entire product development cycle
Active pursuit of “forensic” or “investigational”	→	Develop controlled, long-term data and analyze retrospective databases
Improve pre-marketing clinical studies	→	Identify safety signals and scientific rationale behind risk assessment
Effectively link databases	→	to enable continuous risk assessment and real time reporting of trigger events

The End Game - A Connected/Collaborative Organization



Closing Thoughts …

The world is changing and the future is uncertain. Preparations need to be made to :

- evolve from pharmacovigilance to pharmacodiligence
- create the culture and structure to act on those decisions
- modify the risk profile to enable the appropriate changes
- make the decisions required to become best of the best

What can Pharma do now to enhance its culture of innovation without being encumbered by the regulatory requirements?

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Innovative Drug Development in a Pharmacovigilant Environment

"Moving from Pharmacovigilance to *Pharmacodiligence*"

Q & A

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