Panel 1

Vicki Seyfert-Margolis

FDA Driving Biomedical Innovation-A Critical Role for Regulatory Science

Johns Hopkins University Carey Business School - Advancing the Theory and Practice of Regulatory Science – Panel

December 2, 2011 |Washington, DC

Vicki Seyfert-Margolis, PhD.
Senior Advisor, Science Innovation and Policy
U.S. Food and Drug Administration


NIH
Small Businesses
Biotech/ Pharma
Physicians
Patients
Public
Payor
Academia
FDA U.S. Food and Drug Administration

FY 2011 Innovative Drug Approvals

Released November 3, 2011

Notable FY11 Approvals

Drug	Target	Review Pathway	Approval Time
Zytiga	Late-stage Prostate Cancer	Priority Review	4.2 months
Zelboraf	Late-stage Melanoma	Fast Track/Priority Review	3.6 months
Xalkori	Late-stage Lung Cancer	Fast Track/Priority Review/ Accelerated Approval	4.9 months
Yervoy	Late-Stage Melanoma	Fast Tack/Priority Review	9.0 months
Adcetris	2 Types of Lymphoma	Fast Track/Priority Review/ Accelerated Approval	5.7 months
Caprelsa	Thyroid Cancer	Fast Track/Priority Review	9.0 months
Halaven	Metastatic Breast Cancer	Fast Track/Priority Review	7.6 months
Victrelis	Chronic Hepatitis C	Fast Track/Priority Review	5.9 months
Incivek	Chronic Hepatitis C	Fast Track/Priority Review	6.0 months
Benlysta	Systemic Lupus	Fast Track/Priority Review	9.0 months
Pradaxa	Reduce Risk of Stroke	Priority Review	6.0 months
Brilinta	Reduce Cardiovascular Death and Heart Attack	Priority Review	20.1 months
Teflaro	MRSA	Fast Track	10.0 months
Nulojix	Prevent Rejection of Transplanted Kidneys	Fast Track	23.5 months

Common Themes from Discussions with Stakeholders:

- Need to do more to help small businesses navigate the regulatory process.
- Need to adapt current FDA policies to address personalized medicine.
- Need to take advantage of cutting-edge IT and scientific computing.
- Need to address regulatory uncertainty.
- Need to streamline FDA policies and procedures.
- Need to develop more efficient regulatory pathways for companion diagnostics.
- The need to build regulatory science capacity within FDA and the broader medical device community.

Despite Massive Investments We are Not Producing Enough New Medicines

Situation	Consequence	Solution
Limited knowledge of clinical disease	Attrition for pioneer targets at clinical POC is greater than 90%	Pool expertise and capabilities with a focus on building better maps of disease
Poorly predictive pre-clinical assays	Largest attrition up to Phase II, is in Phase II	For pioneer targets explore safety and efficacy as quickly as possible in patients
Many organizations work on same narrow set of targets – in parallel, in secret, over several years	Multiple, parallel clinical studies likely to fail i.e. patients are being "unnecessarily doses"	Minimize duplication up to and including Phase II. Investigate more pioneer targets
Continue to secure IP on reagents, assays and molecules, for targets yet to be explored in patients	Makes an already difficult process even more slow and expensive	Secure IP post clinical validation
Clinical safety and efficacy data is not rapidly published	Both industry and academia continue working on targets for which data do exist but not known- wasting further resources	Rapidly publish all data, especially clinical
Fewer than five new drugs are being produced p.a., across all organizations	Pharma/biotech downsizing and reducing and/or externalizing early research	Create a public private partnership focused on early drug discovery and development.

Driving Biomedical Innovation: Initiatives to Improve Products for Patients

Released October 5, 2011

First Steps FDA is Taking to Address Most Immediate Concerns:

- Rebuilding FDA's small business outreach services.
- Building the infrastructure to drive and support personalized medicine.
- Creating a rapid drug development pathway for targeted therapies.
- Harnessing the potential of data mining and information sharing.
- Increasing consistency and transparency in the medical device review process.
- Training the next generation of innovators.
- Streamlining and Reforming FDA regulations.

FDA's Role

- Bringing together stakeholders to identify and overcome the challenges ahead
- Implementing reforms that adapt to the changing scientific and technological landscape
- Assuring modern, streamlined regulatory pathways

Pathway to Global Product Safety and Quality

Imported Products

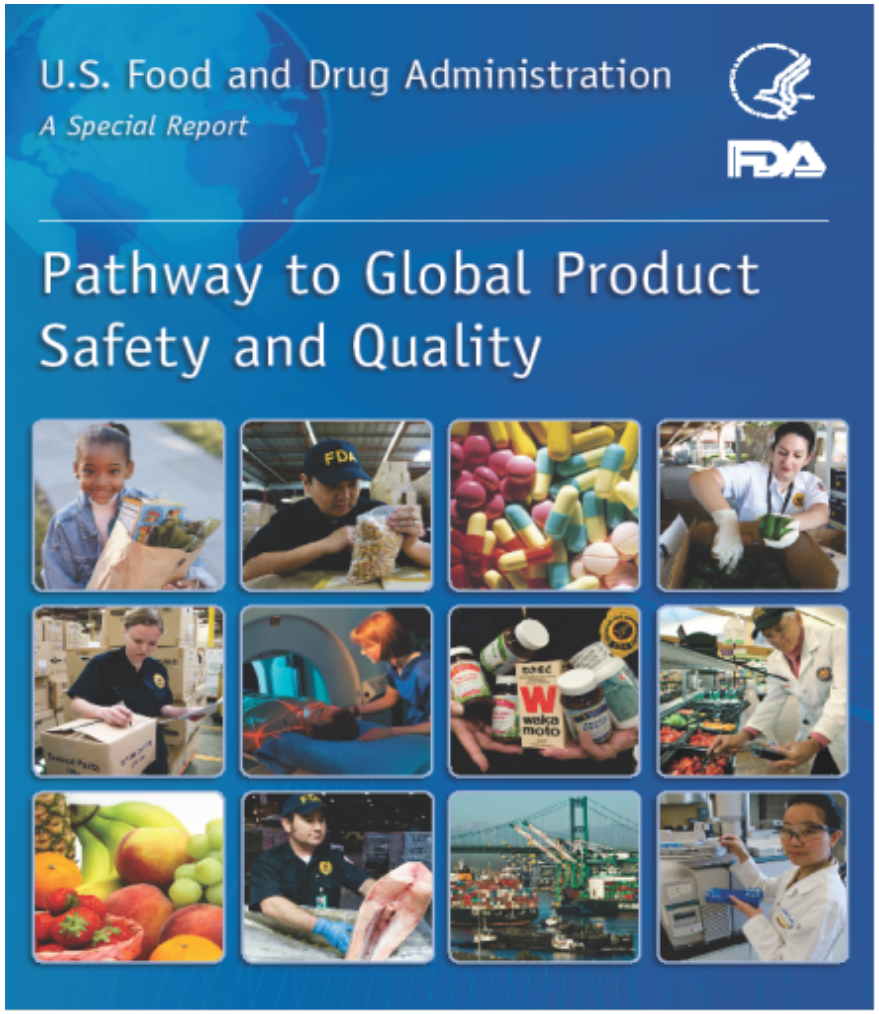
- About 80% of APIs in drugs on U.S. shelves are from foreign sources
- About 40% of finished drug products are imported
- Dramatic increase in the volume of imported pharmaceuticals
  - Drug imports increased 13% per year during the last 7 years
  - Imports account for 30% (by value) of finished pharmaceutical products
- Pharmaceutical imports from >150 countries
- At current FDA inspection rate, it would take ~9 years for FDA to inspect every high-priority pharmaceutical facility just once

Globalization Challenges

- Explosion of production of FDA-regulated goods
- Distinction between domestic and imported products is obsolete
- Supply chain more complex, oversight much more difficult
- FDA-regulated products originate from more than 150 countries
  - 130,000 importers
  - 300,000 foreign facilities
- Increase in variety and complexity of imported medical products
- Growing demand, yet constrained supply

Supply Chain Threats

- Economic incentives vs. public health goals
- Economic adulteration
- Counterfeiting, drug diversion and cargo theft
- Availability of products sold over the Internet



www.fda.gov/AboutFDA/CentersOffices/OC/GlobalProductPathway/

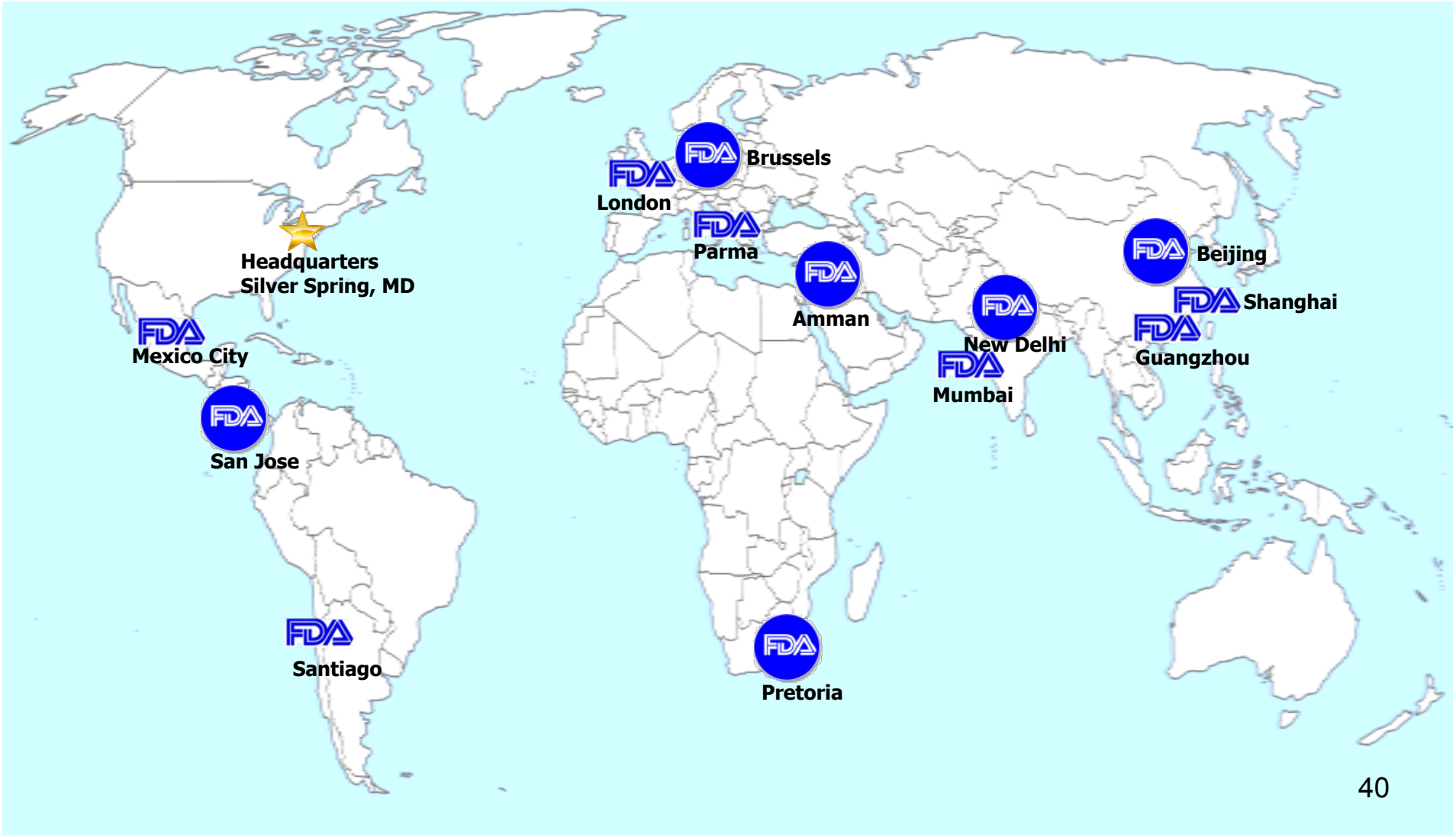
Four Pillars of the Strategy

1. Create global coalitions of regulators
2. Build global data-information systems and networks and proactively share data with peers
3. Expand intelligence-gathering, with an increased focus on risk analytics
4. Effectively allocate agency resources based on risk, and leveraging government, industry and public and private third parties

What FDA is Doing

- Increased Foreign Inspections
- IOM Consensus Study, “Understanding the Global Public Health Implications of Substandard, Falsified and Counterfeit Medical Products”
- PREDICT
- Standard-setting through International Conference on Harmonization
- PIC/S Membership

FDA Foreign Offices



What Still Needs To Be Done

- Level the playing field
- Enhance product safety
- Increase information-sharing to enhance prevention and detection

Advantages and Benefits

- Borders become less relevant to product safety
- International coalitions of regulators have the capability and technology to rapidly share public health information
- Fewer inspections, stream-lined regulation, level playing field between foreign and domestic producers, elimination of the competitive advantage of non-compliance
- Increased safety and security for American consumers

Vicki.Seyfert-Margolis@fda.hhs.gov

Panel 1

Hilde Boone

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Inspections collaboration between FDA and EMA

Johns Hopkins University Health Care symposium
Washington DC - December 2, 2011

Presented by: Hilde Boone
European Medicines Agency Liaison Official at the U.S. FDA

An agency of the European Union

CONTENTS

1. EMA in the regulatory network
2. Collaboration with FDA
    - Product Development
    - Product Evaluation & Surveillance
    - Product Manufacture & Compliance
3. International API inspection pilot

1. EMA in the regulatory network

EMA and the EU Regulatory System

- EMA was created in 1995
- Platform for public health issues at EU level
  Pooling of best scientific expertise from EU
- **EU approval routes for new medicines**:
  - Mutual Recognition & Decentralised Procedure ->Member States
  - **Centralised Procedure** ->**EMA**
    1 application, 1 evaluation, 1EU-wide authorisation
- European medicines system composed of national authorities and EMA together
- EMA = Networking agency
  Interface of cooperation and coordination of Member States' activities with respect to medicines

EMA's long term international vision

Creating synergies through **c**ommunication, **c**ollaboration and **c**ooperation with international regulatory partners

Supporting a global approach to authorisation and supervision of medicines (based on ICH and WHO requirements)

Ability to rely on local regulators

- Focus on where products are being produced and tested
- Assurance of equivalent approach to manufacture and control of medicines and authorisation and supervision of clinical trials, local pharmacovigilance
- Clinical trial subjects to be fully protected

Using existing partnerships and regulatory tools

2. Collaboration with FDA

EMA-FDA Confidentiality Arrangements

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

STATEMENT OF AUTHORITY

AND

CONFIDENTIALITY COMMITMENT FROM

THE EUROPEAN MEDICINES AGENCY

NOT TO PUBLICLY DISCLOSE NON-PUBLIC INFORMATION

SHARED BY

THE UNITED STATES FOOD AND DRUG ADMINISTRATION

The United States Food and Drug Administration (FDA), has affirmed that it has the authority to protect non-public information, including commercial confidential information, provided to its officials or representatives in confidence by the European Medicines Agency (EMA), under the U.S. Freedom of Information Act (5 U.S.C. § 552); the Trade Secrets Act (18 U.S.C. § 1905); section 301(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 331(j)), and other applicable laws, and will protect such information from public disclosure. FDA is authorized under 21 C.F.R. § 20.89 to disclose non-public information to EMA regarding FDA-regulated products as part of cooperative law enforcement or cooperative regulatory activities.

EMA has affirmed that it has the authority, within the scope of its activities to protect non-public information, including commercial confidential information, provided to its officials or representatives in confidence by the United States Food and Drug Administration (FDA), and will protect such information as information not to be disclosed under Article 4.1(a) of Regulation (EC) No 1049/2001.

EMA understands that some of the information it receives from FDA may include non-public information exempt from public disclosure under the laws and regulations of the United States of America, such as confidential commercial information; trade secret information; personal privacy information; law enforcement information; or internal, pre-decisional information. EMA understands that this non-public information is shared in confidence and that FDA considers it critical that EMA maintain the confidentiality of the information. Public disclosure of this information by EMA could seriously jeopardise any further confidential scientific and regulatory interactions between FDA and EMA. FDA will advise EMA of the non-public status of the information at the time that the information is shared.

Therefore, EMA certifies that it:

1. has the authority to protect from public disclosure such non-public information provided to EMA in confidence by FDA;

2. will not publicly disclose such FDA-provided non-public information without prior agreement from the FDA or the written authorisation from the individual who is the subject of the personal privacy information, or a written statement from FDA that the information no longer has non-public status, without prejudice to any different obligations which may originate from judicial requirements imposed by the European Court of Justice;

3. will inform FDA promptly of any effort made by judicial or legislative mandate to obtain FDA-provided non-public information from EMA. If such judicial or legislative mandate orders disclosure of FDA-provided non-public information, EMA will take all appropriate legal measures in an effort to ensure that the information will be disclosed in a manner that protects the information from public disclosure; and

4. will promptly inform FDA of any changes to EMA's laws, or to any relevant policies or procedures that would affect EMA's ability to honour the commitments in this document.

[redacted] 14/9 2010

Thomas Lönngren
Executive Director
European Medicines Agency
London, United Kingdom

Date

Framework for regulatory cooperation between Agencies

Commitments to **protect non-public information** provided in confidence

Signed September 2003
Extended indefinitely 2010

Scope: Human & Vet products under review by EMA and national prod. referred to CHMP

⬇

Exchange of (draft) guidance/guidelines

Staff/expert exchanges

Sharing of non-public, pre-decisional information

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
Office of International Programs
Silver Spring, Maryland 20993

STATEMENT OF AUTHORITY

AND

CONFIDENTIALITY COMMITMENT FROM

THE UNITED STATES FOOD AND DRUG ADMINISTRATION

NOT TO PUBLICLY DISCLOSE NON-PUBLIC INFORMATION

SHARED BY

THE EUROPEAN MEDICINES AGENCY

The European Medicines Agency (EMA) has affirmed that it has the authority, within the scope of its activities to protect non-public information, including commercial confidential information, provided to its officials or representatives in confidence by the United States Food and Drug Administration (FDA), and will protect such information as information not to be disclosed under Article 4.1(a) of Regulation (EC) No 1049/2001.

FDA has affirmed that it has the authority to protect non-public information, including commercial confidential information, provided to its officials or representatives by EMA, under the U.S. Freedom of Information Act (5 U.S.C. § 552); the Trade Secrets Act (18 U.S.C. § 1905); section 301(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 331(j)), and other applicable laws, and will protect such information from public disclosure. FDA, is authorized under 21 C.F.R. § 20.89 to disclose non-public information to the European Medicines Agency (EMA) regarding FDA-regulated products as part of cooperative law enforcement or cooperative regulatory activities.

FDA understands that some of the information it receives from EMA may include non-public information exempt from public disclosure under the laws and regulations of the European Union, such as confidential commercial information; trade secret information; personal privacy information; law enforcement information; or internal, pre-decisional information. FDA understands that this non-public information is shared in confidence and that EMA considers it critical that FDA maintain the confidentiality of the information. Public disclosure of this information by FDA could seriously jeopardize any further confidential scientific and regulatory interactions between FDA and EMA. EMA will advise FDA of the non-public status of the information at the time that the information is shared.

Therefore, FDA certifies that it:

1. has the authority to protect from public disclosure such non-public information provided to FDA in confidence by EMA;

2. will not publicly disclose such EMA-provided non-public information without prior agreement from the EMA, or written authorization from the individual who is the subject of the personal privacy information, or a written statement from EMA that the information no longer has non-public status;

3. will inform EMA promptly of any effort made by judicial or legislative mandate to obtain EMA-provided non-public information from FDA. If such judicial or legislative mandate orders disclosure of EMA-provided non-public information, FDA will take all appropriate legal measures in an effort to ensure that the information will be disclosed in a manner that protects the information from public disclosure; and

4. will promptly inform EMA of any changes to FDA's laws, or to any relevant policies or procedures that would affect FDA's ability to honor the commitments in this document.

[redacted] 14 Sept 2010

Murray M. Lumpkin, M.D.
Deputy Commissioner for International Programs
US Food and Drug Administration
Silver Spring, Maryland

Date

Product Development

Monthly EMA-FDA teleconferences on paediatric development plans

Monthly EMA-FDA teleconferences on orphan designations

Parallel EMA-FDA Scientific Advice

- Questions on product development sent to both FDA and EMA
- Discussions between EMA-FDA, and jointly with sponsor
- Parallel feedback from both agencies

Joint FDA/EMA qualifications of new biomarkers

→ Facilitate global development plans
Avoid unnecessary repetition of trials

→ Increase dialogue between regulators and with sponsors

→ Share information and expertise in new areas

Product Evaluation and Surveillance

Share information on ongoing EMEA marketing authorisation applications (MAAs) and FDA applications (NDA / BLAs)

‚Clusters' with regular FDA-EMA tele- or videoconferences
e.g. oncology, vaccines, blood products, pharmacovigilance
Biosimilars – kick-off in July 2011 NEW!

EMA, CHMP Rapporteurs/assessors and FDA review division experts

Ad-hoc exchanges on specific review and safety issues

Observers at CHMP meetings / Advisory Committee meetings

→ Awareness of ongoing evaluations
opportunity for discussion / exchange of views

→ Understanding in case of different outcomes

→ Advance notice of important regulatory action

Sept 2009 – Sept 2010

- Average of 55 interactions per month (regular + ad-hoc)

- > 200 ad-hoc product exchanges

  ± 100 teleconferences EMA-FDA
  50% product-specific

- FDA observed 4 CHMP and 4 SAG meetings
  EMA/CHMP observed 8 Advisory Committee meetings

Product Manufacturing & Compliance

Joint FDA-EMA inspections of finished product manufacturing sites in US & EU

2 joint pre-approval inspections in 2009

6 joint routine inspections in 2011

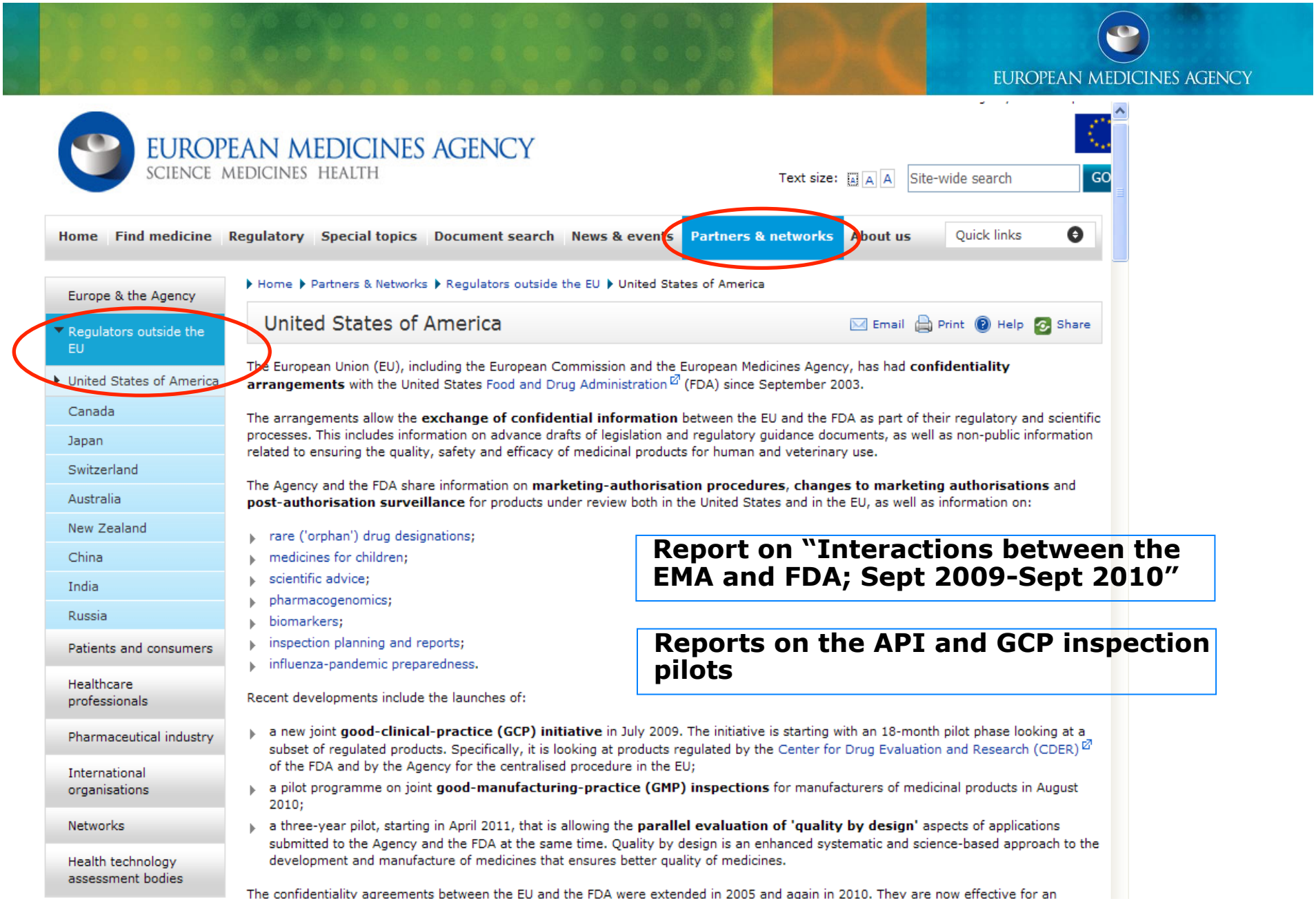
Pilot project to collaborate on inspections of API in third countries
Participants: EU + US + Canada + Australia

Pilot project to collaboration on GCP inspections in EU & US
- set-up joint or observational inspection
- choose other site and exchange inspection reports

→ Save resources, decrease duplicate inspections

→ Increase number of API/CT sites inspected

→ Contribute to risk-based inspection planning approach
Improve inspection efficiency


EUROPEAN MEDICINES AGENCY
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
Text size: A A
Site-wide search
GO
Home
Find medicine
Regulatory
Special topics
Document search
News & events
Partners & networks
About us
Quick links
Europe & the Agency
Regulators outside the EU
United States of America
Canada
Japan
Switzerland
Australia
New Zealand
China
India
Russia
Patients and consumers
Healthcare professionals
Pharmaceutical industry
International organisations
Networks
Health technology assessment bodies
Home ▸ Partners & Networks ▸ Regulators outside the EU ▸ United States of America
United States of America
Email
Print
Help
Share
The European Union (EU), including the European Commission and the European Medicines Agency, has had confidentiality arrangements with the United States Food and Drug Administration (FDA) since September 2003.
The arrangements allow the exchange of confidential information between the EU and the FDA as part of their regulatory and scientific processes. This includes information on advance drafts of legislation and regulatory guidance documents, as well as non-public information related to ensuring the quality, safety and efficacy of medicinal products for human and veterinary use.
The Agency and the FDA share information on marketing-authorisation procedures, changes to marketing authorisations and post-authorisation surveillance for products under review both in the United States and in the EU, as well as information on:
rare ('orphan') drug designations;
medicines for children;
scientific advice;
pharmacogenomics;
biomarkers;
inspection planning and reports;
influenza-pandemic preparedness.
Recent developments include the launches of:
a new joint good-clinical-practice (GCP) initiative in July 2009. The initiative is starting with an 18-month pilot phase looking at a subset of regulated products. Specifically, it is looking at products regulated by the Center for Drug Evaluation and Research (CDER) of the FDA and by the Agency for the centralised procedure in the EU;
a pilot programme on joint good-manufacturing-practice (GMP) inspections for manufacturers of medicinal products in August 2010;
a three-year pilot, starting in April 2011, that is allowing the parallel evaluation of 'quality by design' aspects of applications submitted to the Agency and the FDA at the same time. Quality by design is an enhanced systematic and science-based approach to the development and manufacture of medicines that ensures better quality of medicines.
The confidentiality agreements between the EU and the FDA were extended in 2005 and again in 2010. They are now effective for an
Report on "Interactions between the EMA and FDA; Sept 2009-Sept 2010"
Reports on the API and GCP inspection pilots

3. International API Inspection pilot

API pilot participants & tools

- Europe: EMA, EDQM, Member States: FR + DE + IE + UK + IT
  US: US FDA
  Australia: TGA

- Common reference for API inspections: ICH Q7

- Collaboration on API inspections **outside of own territories**

- 'Master List' to share information on API sites, inspections planned and already performed (2005-2010)

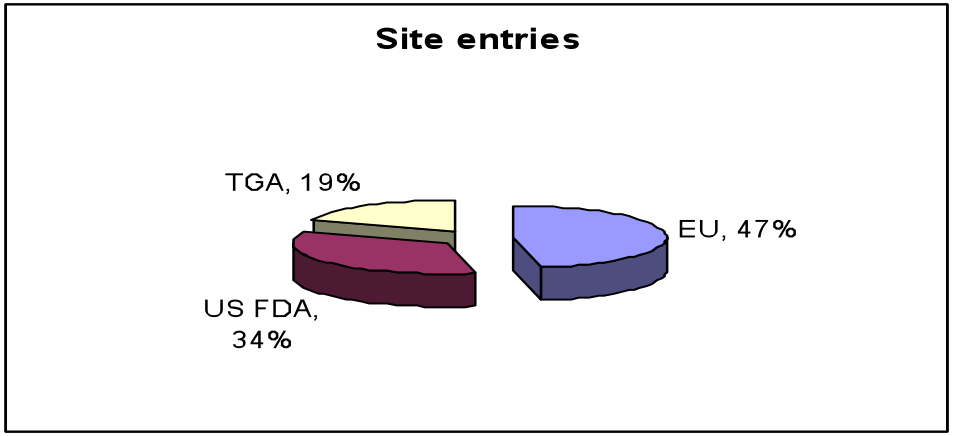
  -> Exchange of results and inspection reports
  -> Request to extend scope of the inspection
  -> Perform joint inspection

- Regular teleconferences to review 'Master List', identify sites of common interest, and plan for joint inspections

- Feedback forms for inspection teams

API site entries

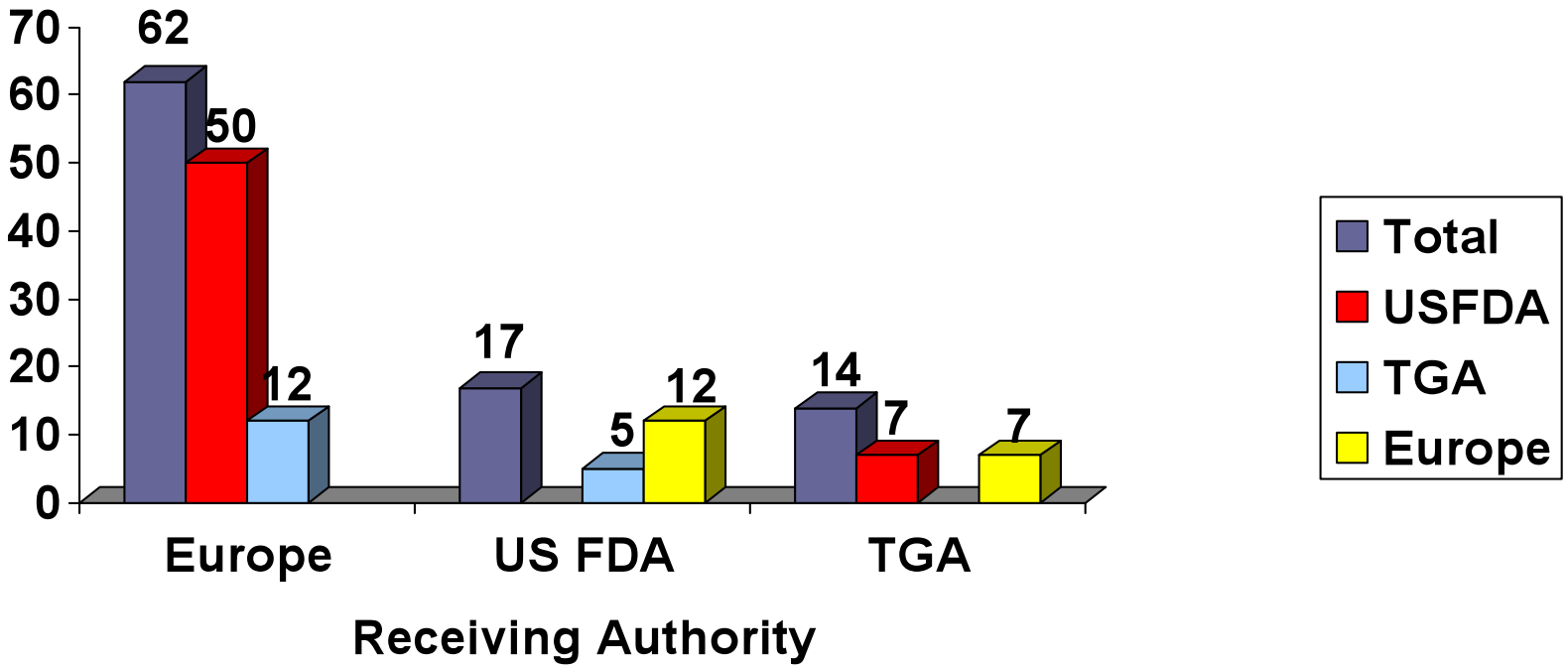
- 1110 API site entries included in the 'master list' by all participants
  642 individual manufacturing sites



- 137 sites common to 2 participants + 97 sites common to 3 particip.

  25% of listed sites in China, and
  44% of listed sites in India
  supply at least 2 different regions

Sharing of inspection reports



9 Joint inspections

Europe (EDQM) / TGA:	India (3 inspections)
Europe (UK) / TGA:	India
Europe (EMA-UK) / FDA:	Croatia
Europe (EMA-SLO) / FDA:	India
Europe (EMA-IT) / TGA:	Japan
FDA / TGA:	Mexico
Europe (EMA-FR) / FDA / TGA :	China

Performance indicators

- ✓ Increased transparency and visibility of participants' inspection plans and inspections performed
- ✓ Decrease in "duplicate inspections" i.e inspections of the same product or sites carried out by more than one authority within a similar time period
- ✓ Increase in number of inspections performed of value to more than one authority
- ✓ Better understanding of other participants' inspection practices
- ✓ Increased mutual confidence

Next steps & developments

- Pilot continues as a 'Programme'
- Extend participation to new partners (eg all EU MSs, HC, WHO)
  Different levels or participation (eg observer, full participant)
- Use of EudraGMP Planning Module
- Move from 'receiving of' to '**relying on'** inspection information
- Develop a common policy related to the re-inspection of shared API sites.
- Increase API inspection coverage; pool resources
- Increase international inspection collaboration in support of global supervision of APIs.

Hilde Boone

European Medicines Agency
Liaison Official at FDA

White Oak, Silver Spring

+ 301 796 8357
hilde.boone@fda.hhs.gov
hilde.boone@ema.europa.eu

Abbreviations

• API	• Active Pharmaceutical Ingredient
• CHMP	• Committee for Human Medicinal Products
• EMA	• European Medicines Agency
• FDA	• Food and Drug Administration
• GCP	• Good Clinical Practice
• GMP	• Good Manufacturing Practice
• HC	• Health Canada
• ICH	• International Conference on Harmonisation
• MA(A)	• Marketing Authorisation (Application)
• MS	• Member State
• SAG	• Scientific Advisory Group
• TGA	• Therapeutic Goods Administration (Australia)
• WHO	• World Health Organisation

Panel 1

Robert Stewart

Watson Pharmaceuticals

Focused on Global Growth

Business Realities in the Global Supply Chain

Robert Stewart, EVP Global Operations

A Global Leader - At-a-Glance

OUR WINNING BEHAVIORS: CHALLENGE CONNECT COMMIT	
Stock Ticker:	NYSE: WPI
Founded:	1984
Revenues (2010):	Approximately $3.6 billion
Employees:	Approximately 6,500
Mission:	To improve the quality of life for patients around the world through the development and distribution of trusted generics and advanced, specialty branded pharmaceuticals.
U.S. Operations:	Copiague, NY; Corona, CA; Davie, FL; Grand Island, NY; Groveport, OH; Gurnee, IL; Mt., Prospect, IL; Salt Lake City, UT; Weston, FL; Sunrise, FL
Int'l Operations:	Australia, Brazil, Canada, China, Denmark, Finland, France, Germany, Greece, India, Ireland, Malta, New Zealand, Poland, Slovenia, Sweden, Turkey, U.K.
Business Divisions:	Global Generics, Global Brands
Distinctions:	Ranked 3rd largest generic manufacturer in the U.S.; 4th largest globally

Watson Pharmaceuticals.

Watson's Integrated Global Operations Function

Integrated Global Supply Chain

- Global R&D
- Quality
- Americas Manufacturing

  International Manufacturing
- Distribution

Information Technology, Engineering, Health, Safety

Watson Pharmaceuticals

Watson's Global Footprint

US Statistics

- 40% of all drugs in US are imported
- 80% of all APIs come from ex-US sources
- FDA able to inspect 11% of 3,765 foreign establishments annually
  - 40% of US facilities annually
  - Would take 9 years to inspect all foreign facilities
  - FDA 2011 Work Plan: 62 foreign PAIs; 47 US PAIs
- ~ 2300 ANDAs pending
  - Median approval time 32 months

Source: Industry Statistics; GAO Report September 2010

Global Supply Chain Realities - External

- "Local" Regulation of Global Supply Chains
  - Need for cooperation, harmonization
- FDA Inspection Constraints
  - International Inspection Resources
  - Challenges with Site Changes, Sourcing, Product Approval Delays
- Other Challenges
  - DEA quota approvals, allocations
  - Global Security, Climate Challenges (Volcanoes, Hurricanes, etc impacting shipments)

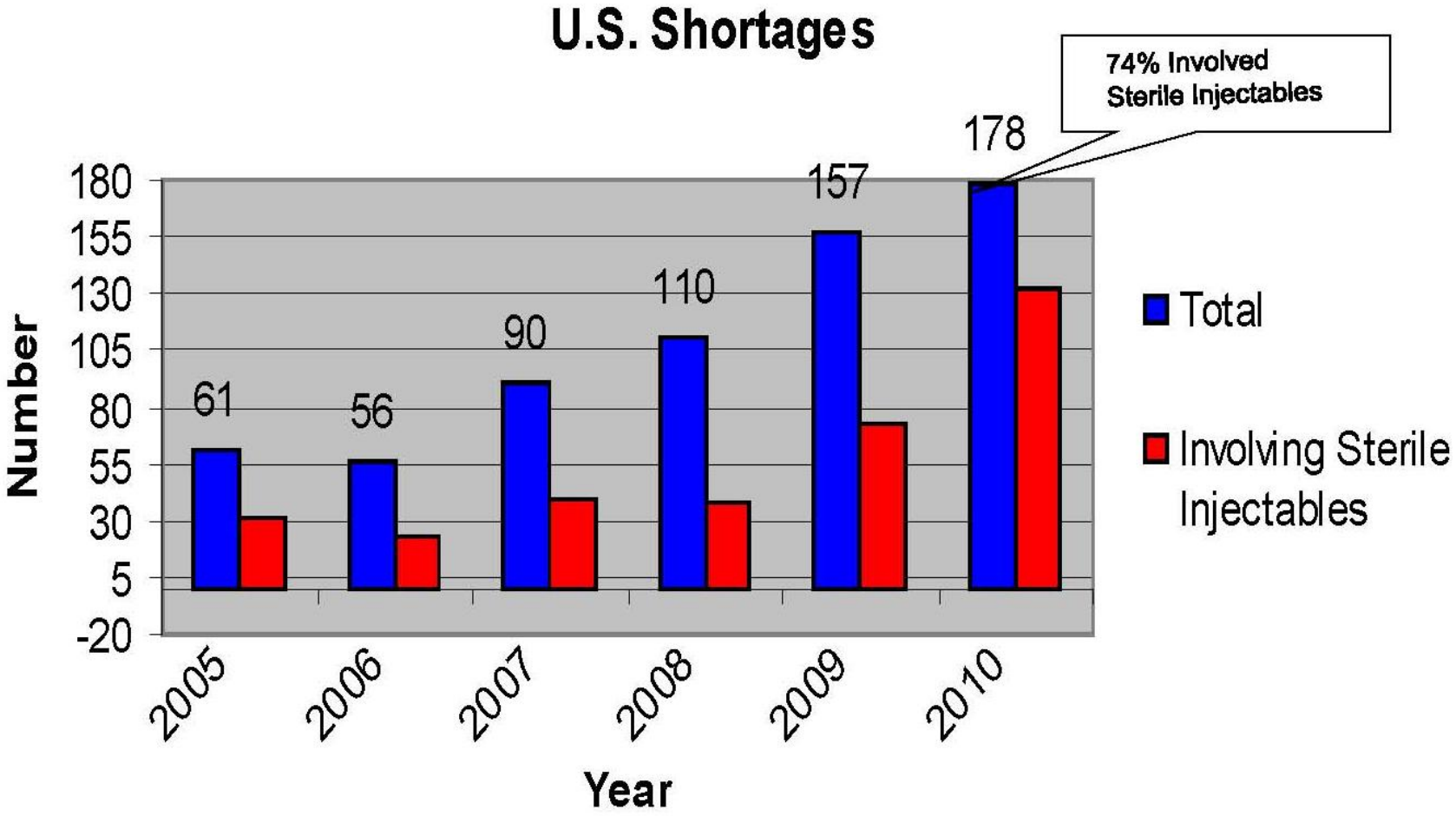
Global Supply Chain Realities - Internal

- COGs is Key
  - Increasing country pressures on price challenging margins
    - Key is efficient manufacturing, balancing production and supply chain
    - Regulatory impact of delays in inspections, site transfers, approvals make difficult to respond
  - Balancing production of simple vs complex products and product transfer challenges
- In Global marketplace, supply chain efficiency is critical

Some Solutions on Horizon

- U.S. Generic Drug User Fees will help
  - Resources to globalize inspections
  - Reduction of backlog in application approvals
  - Improved communication with industry
- Opportunities for greater cooperation between global agencies
  - Mutual recognition of inspections
  - Risk-based approach

Drug Shortages – An Overview

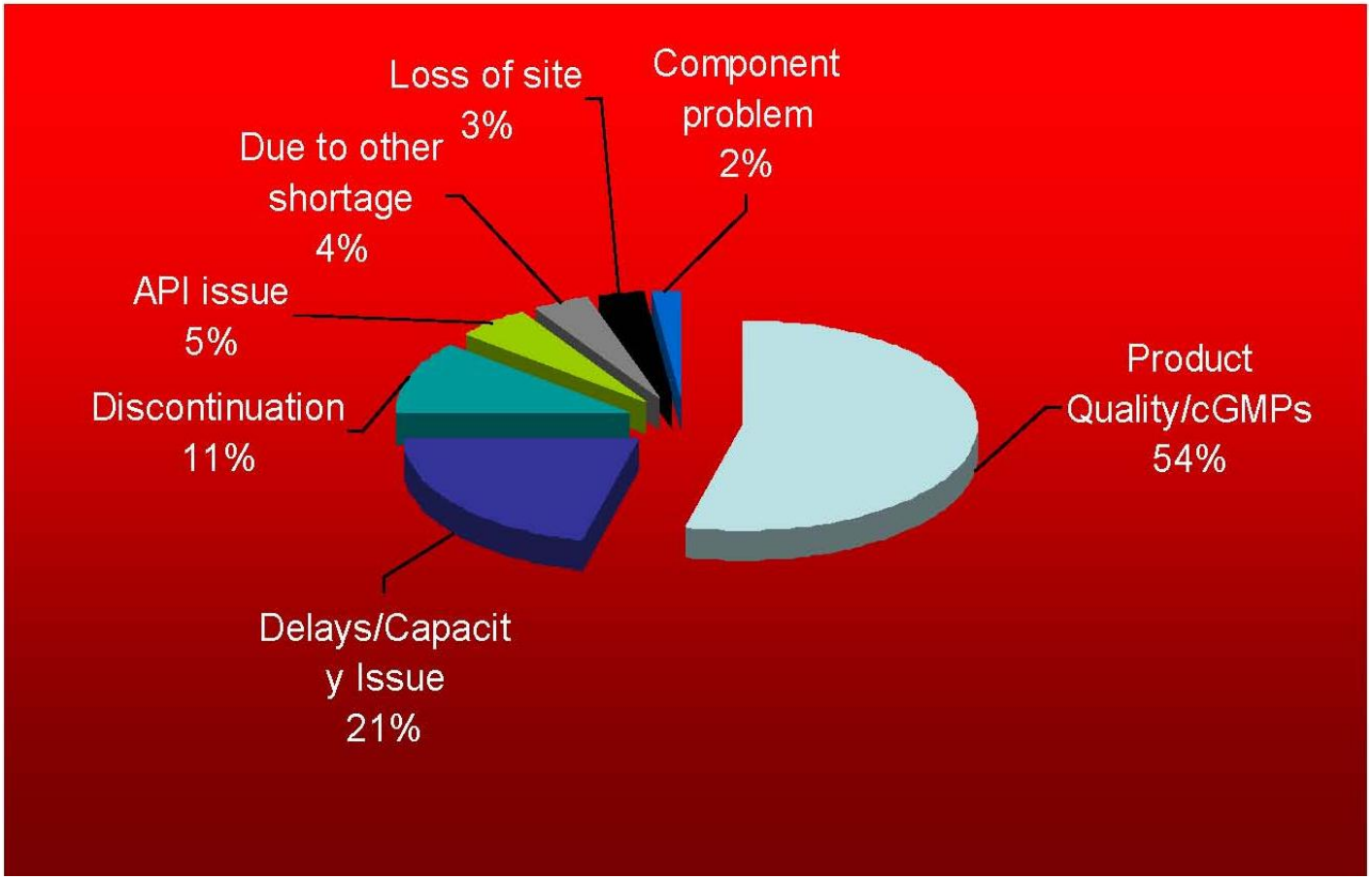


Source: FDA

Watson Pharmaceuticals

Drug Shortages – An Overview

Causes of Shortages in 2010



Source: FDA

Watson Pharmaceuticals

Solutions

- Increased early communication between regulators and regulated
- More streamlined and timely process for approval of new or alternate raw material suppliers and/or alternate manufacturing facilities
- Reciprocation between regulators
- Streamline manufacturing production quotas in response to drug shortages (DEA)
- Implement formal process and communication flow throughout supply chain in which manufacturers communicate real and potential shortages

Supply Chain Is Critical

- The solution to the drug shortage issue transcends the generic industry and involves:
  - Brand and generic manufacturers
  - API suppliers
  - Component Suppliers
  - Wholesalers and Distributors
  - FDA, ex-US Regulators, DEA, and other government agencies

Summary

- Industry and Regulators share commitment to ensure highest quality supply chain
- Must recognize costs (real and intangible) of excessive or duplicative regulation to industry ***AND*** consumers
- Recognize opportunities to strengthen supply chain through enhanced regulatory responsiveness and timeliness
- Need to increase communications and cooperation
  - Improves overall process
  - Enables more timely response to shortage and other challenges
  - Benefits consumers

Panel 2

Dr. Ron Ginor

Regulatory Realities:

Comprehensive Solutions to Developments in Compliance

December 2, 2011

Ron Ginor, MD

CEO

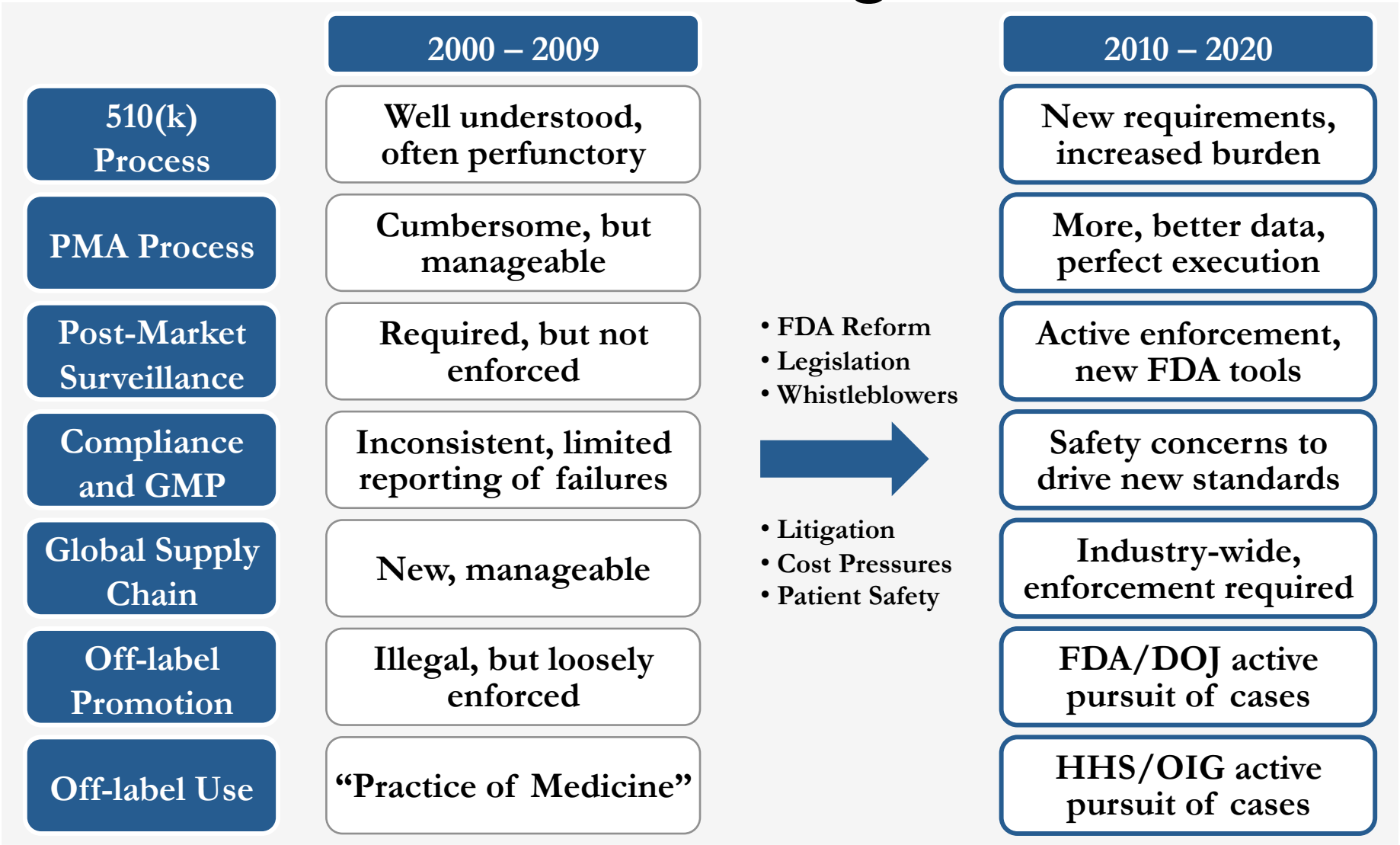
Current Environment

Life Sciences Industry is Experiencing a Fundamental Shift

- Unprecedented change in regulation of drugs, medical devices, and enforcement of cGMP and other practices
- Tremendous impact, billions of dollars in flux
- Services market is highly fragmented
- Industry focus on total product lifecycle solutions

Fragmented approach is sub-optimal: Need for a Comprehensive, Integrated Solution

Critical Industry Drivers: New World, New Challenges



Focus on Enforcement: Legislation as the "Lab"

- Food Safety and Modernization Act (2011)
  - FDA authority to order mandatory food recalls
- Dodd-Frank Wall Street Reform and Consumer Protection Act (2010)
  - Whistleblower protection
- False Claims Act & Anti-Kickback Act Amendments (2010)
  - Allows easier, indirect whistleblowing; expands definition of false claims
- Amendment to Corporate Culpability Provisions of US Sentencing Guidelines (2010)
  - Compliance officers should have "direct reporting obligations" to Board or other senior executives
- Enforcement of Park Doctrine (2010)
  - Executives can be liable for violating FDCA even without knowledge or intent

How Serious is FDA About Compliance?

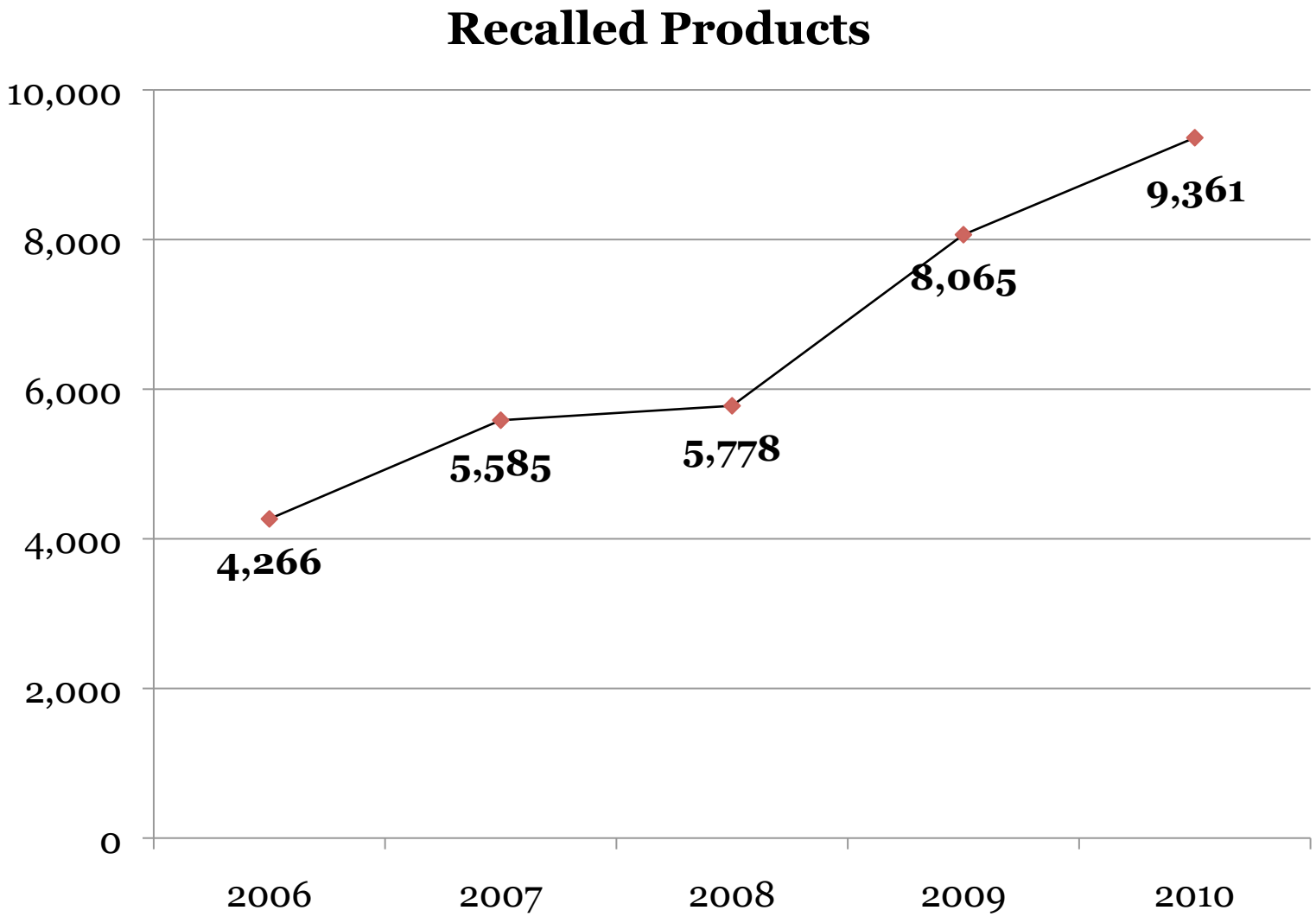
- FDA Commissioner Hamburg's new policies:
  - Enforcement action can proceed without a Warning Letter
  - 400 new investigators
  - 10 offices OUS
  - Aggressive Criminal Prosecution Guidelines
  - Expand healthcare fraud-related investigations
  - Reorganized FDA, August 2011

"Companies must have a realistic expectation that if they are crossing the line, they will be caught; if they fail to act, we will."

"….FDA will be prepared to act swiftly and aggressively to protect the public… If we find that we must move quickly to address significant health concerns or egregious violations, we will consider ***immediate*** *action…"*

FDA Commissioner Margaret A. Hamburg, MD

How Serious is FDA About Compliance?



The Significance of Compliance

- Compliance issues are the most significant and potentially devastating risks to any pharmaceutical or medical device company.
  - Client X had three hundred employees until a single consent decree. Now they have four.
- FDA and the US Department of Justice are increasing their compliance scrutiny.
  - Ready to penalize companies with fines of nearly a billion dollars for promoting unapproved use (Company M paying $950 million).
- FDA is increasingly looking OUS for compliance issues.
- By instituting strong compliance systems as a priority at every stage of development, companies invest in security and peace of mind.

New Target: OUS Activities

- FDA is seeking to expand its compliance scrutiny internationally
- Dedicated offices focused on China, India, Africa and Asia, Latin America, Middle East
  - FDA has doubled its regulatory agreements with foreign counterparts in the past five years to over 100 formal agreements
  - These agreements allow for the sharing of inspection reports and joint inspections
- Release of the "Pathway to Global Product Safety and Quality" in 2011
  - Stated Goal: "FDA will transform itself from a domestic agency operating in a globalized world to a truly global agency fully prepared for a regulatory environment in which product safety and quality know no borders."

FDA International Actions

- Inspections of overseas drug manufacturing plants increased from 333 in 2007 to 424 in 2009
- Currently working over the next 12 months to create "global coalitions of regulators" in order to expand the reach of FDA
- Company R in India
  - FDA cited manufacturing defects at two of the company's plants in India
  - Barred from selling 31 different drugs in the US
  - Shares fell 8.7% after reports that the company may have to pay over $1 billion to settle the dispute with FDA

FDA International Harmonization

- FDA is an active participant in the Global Harmonization Task Force (GHTF) and the International Conference on Harmonization (ICH)
- The GHTF not only works to converge regulatory rules, but it also "serves as an information exchange forum" for medical device regulatory practices
- Companies need to prepare their international activities for this type of harmonized overhaul of regulation

Negotiation vs. Escalation

- Company leadership must respond to compliance issues by actively initiating discussion directed towards a solution.
  - They increasingly lose control of the situation by anticipating FDA's suggestions.
- FDA wants immediate and demonstrated action.
  - If FDA does not see the action they expect, they quickly escalate to a warning letter.
  - Waiting for FDA's next move only works to your disadvantage; this puts the ball in their court in a game where you must play by their rules.

Do not expect a chance to negotiate. You need to respond with immediate and aggressive action.

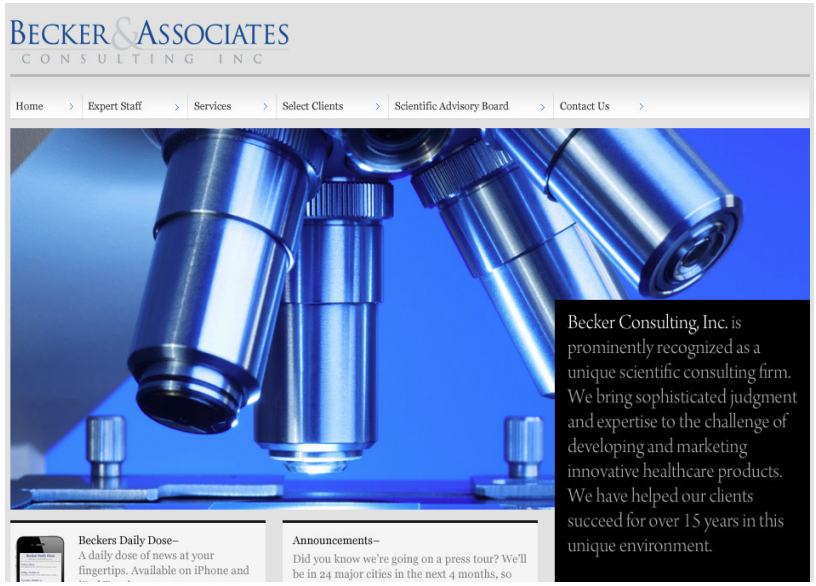
The Necessity of a Total Compliance Strategy

- Companies can protect themselves from ruinous compliance-related issues by making compliance a first priority
  - A small investment in compliance protection can be the difference between a blockbuster product and a billion dollar fine and criminal charges.
- Total Product Lifecycle Approach
  - Institute comprehensive and interconnected systems at every stage of product development
  - Facilitate communication within the stages such that each informs the other
  - Begin with strong and trustworthy data, manufacture with well-designed and robust systems, conclude with well-formulated and honest labels.
  - Innovate with integrity → market with integrity.

Q&A

BECKER & ASSOCIATES
CONSULTING INC

BECKER
COMPLIANCE
A BECKER & ASSOCIATES COMPANY



BECKER
COMPLIANCE ASIA
A BECKER & ASSOCIATES COMPANY

A BECKER & ASSOCIATES COMPANY

Panel 2

Lillian Gill

Cosmetic Ingredient Review

Trends in Compliance and Enforcement in the Global Setting

Lillian Gill, MS, DPA
Cosmetic Ingredient Review
December 2, 2011

Assessing the safety of cosmetic ingredients in an open, unbiased, and expert manner, and publishing the results in the peer-reviewed scientific literature.

Trends: What is changing and Why

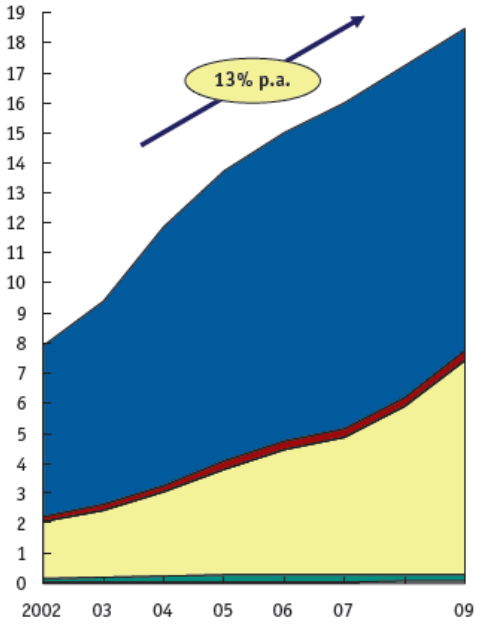
- Explosive growth in global production of medical supply chain
- Greater risk of unknown product quality and integrity
- Wide variability in global regulatory oversight
- Increased responsibility with decreased resources

Growing import volume

Import shipments of FDA-regulated products have been growing at 13 percent per year.

Imported lines[1] (millions)

Total = 7.9 MM in 2002; total = 18.5 MM in 2009

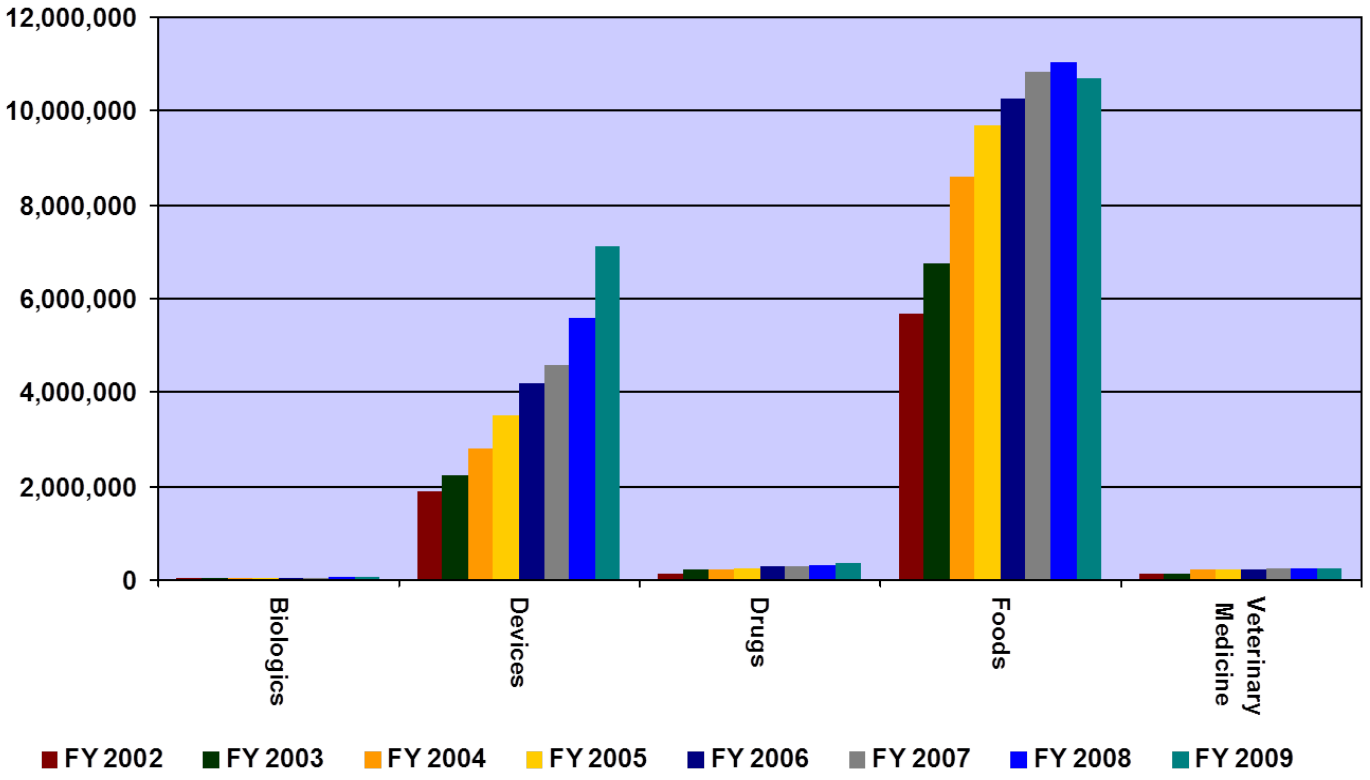


	CAGR 2002-09	Explanation of center's products
Foods	9.5%	• Food products for human, animal, pet use, except meat and poultry • Articles for cleansing, beautifying, promoting attractiveness of body
Drugs	12.9%	• Prescription and OTC drugs for human
Devices	20.8%	• Medical devices for human use • Products that emit radiation (e.g., microwaves, lasers, x-ray machines)
Veterinary products	6.7%	• Drugs, devices, and food additives for animals and pets
Biologics	15.8%	• Blood products, vaccines, and tissues for transplantation

1 An import line represents the portion of a shipment listed as a separate item on an entry document. The number of units can vary.

Source: FDA

Increase imports of FDA-regulated product



Cosmetic Ingredient Review

Assessing the safety of cosmetic ingredients in an open, unbiased, and expert manner, and publishing the results in the peer-reviewed scientific literature.

Challenges of Globalization

- More foreign facilities and clinical trials sites supplying the U.S.;
- Increasing volume of imported products and data;
- More outsourcing of manufacturing and clinical trials;
- Greater complexity in supply chains and clinical trials;
- Imports of products and data coming from countries with less well developed regulatory systems;
- Greater opportunities for economic fraud.
- Complex medical devices - once primarily manufactured in U.S. – increasingly manufactured overseas.

Globalization challenge

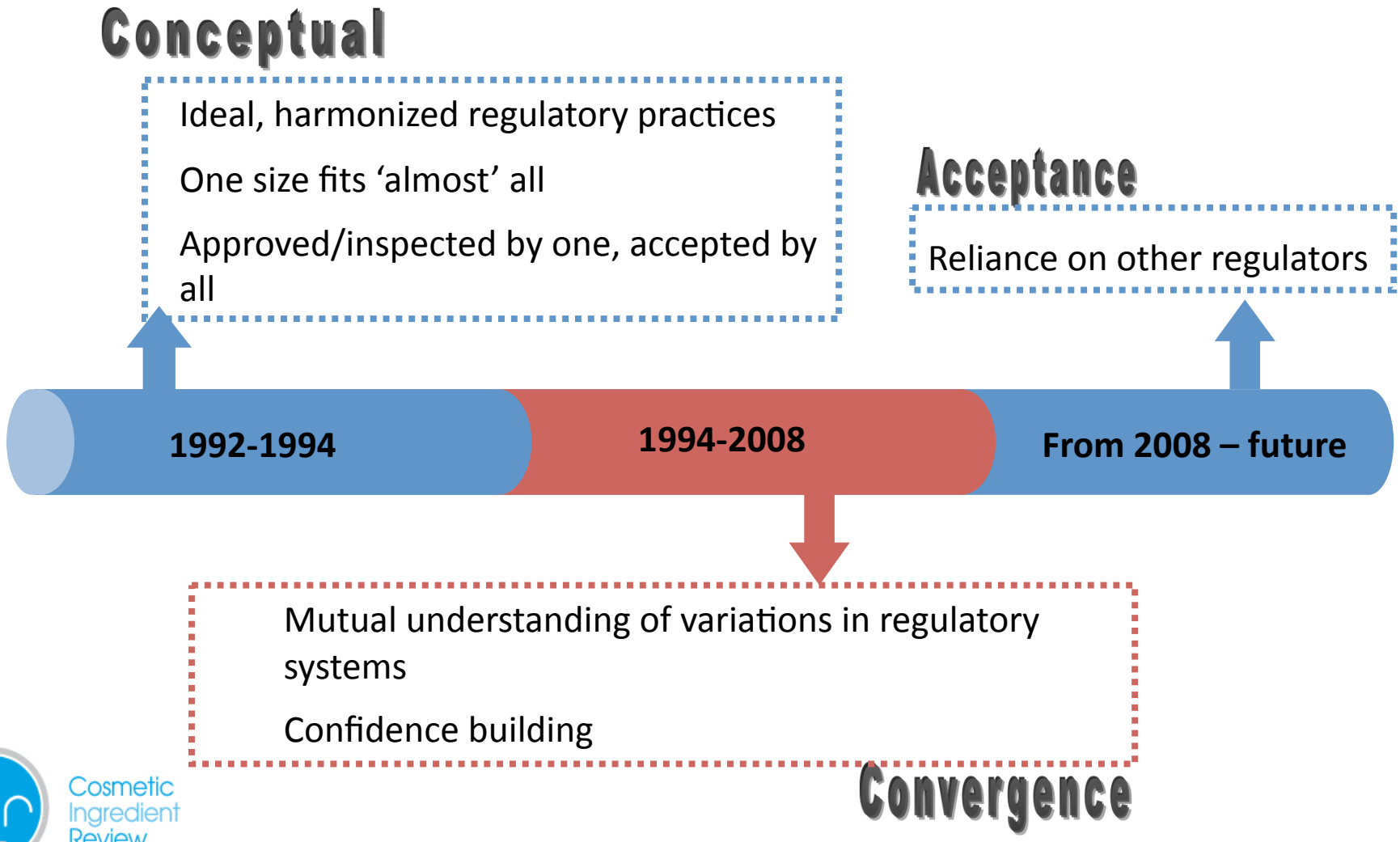
- Results?
  - Increasingly difficult to distinguish risk/complexity based upon where product produced
  - New set of trading partners
  - Multiple regulatory players engaged worldwide

Globalization has fundamentally changed the environment for regulating food and medical products

Global perspective in meeting the challenge

- Utilizing other approaches to compliance and enforcement
- Must consider partnering/leveraging for greater use of resources
- Regulate products as a global commodity
- Must make a significant change in our perspective of global oversight

Global Harmonization (GHTF): Step 1

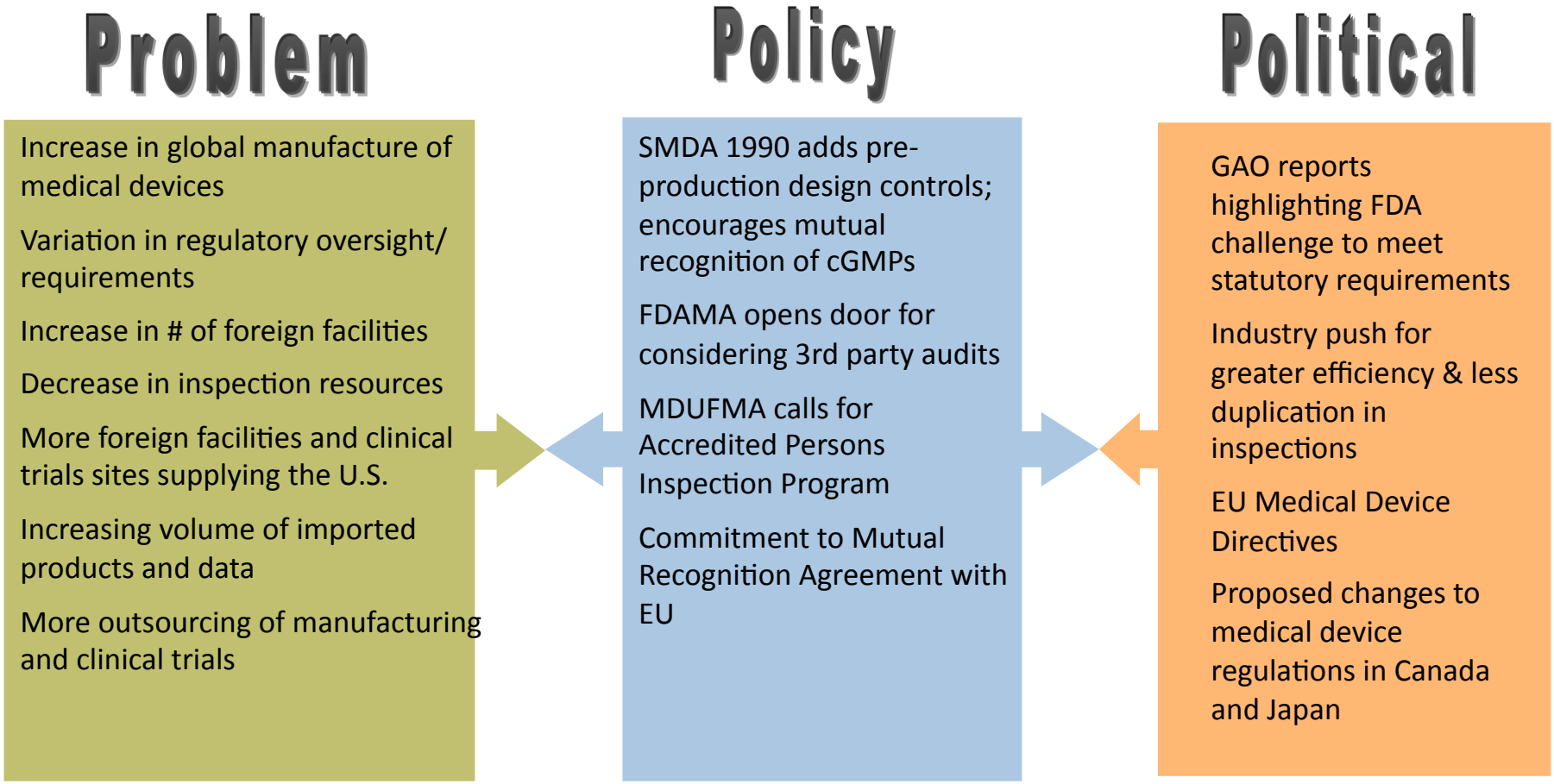


Cosmetic Ingredient Review

Critical Factors for Change

Problem	Policy	Political
Significant and compelling public health issues that require a collaborative or harmonized solution	Incremental additions to regulations or authorities which independently cannot resolve problem but move the agenda forward	External forces that provide the legal support or backing Changes in leadership and philosophy that move the agenda forward

Some Factors that drove GHTF



Step 2: More inclusive, more flexible

- Late 1970s to early 2000s collaboration between advance or mature regulatory systems

- Increase in new regulatory systems since mid-2000s
  - Wide ranging capacity and capability
  - Regulatory environment varies across countries

- Difference in the purpose or goal of regulation
  - Enhance competition benefits economic performance
  - Overly burdensome regulatory process increases bottlenecks to economic growth

Range of global Medical Device regulatory capability

- Advanced/Comprehensive = harmonized and not harmonized
- Less advanced, less comprehensive, not harmonized
- Not comprehensive, harmonized
- Not comprehensive, controls for select devices
- Basic controls, not harmonized
- No regulatory controls

Problems of Global Regulatory Differences

- Products come from countries with little ability to provide the regulatory oversight needed to assure the safety of products exported from their country.
- Lax oversight in many foreign locales presents opportunities for contamination, counterfeiting, or economic "gain" by cutting corners
- Some of products come from countries with governments that do not have good intentions

Step 3: Components of the New Trends

- Partnerships to create global coalitions of regulators focused on global product safety.
- Build and share global data-information system and networks.
- Expand capabilities in intelligence gathering and use.
- Work with government, industry and public and private third parties to for more effective use of resources.
- Promote the market advantages:
  - fewer inspections, stream-lined regulation
  - level playing field between foreign and domestic producers
  - elimination of the competitive advantage of non-compliance.

Conclusion

- None of us has the financial, human, or scientific resources to do all that is expected of us
- Cannot meet 'their' mission by only looking within one's own borders
- No national or regional regulatory authority has a monopoly on good science or good regulatory practices.
- Regulatory cooperation is no longer discretionary.
- Regulatory cooperation must become a standard operating procedure of 21st century medicinal products regulatory authorities
- Borders are boundaries to our jurisdiction ***but not barriers to our activities***

Panel 2

Dr. Thomas Colonna

Johns Hopkins University
Zanvyl Krieger School of Arts and Sciences

Center for Biotechnology Education

Thomas Colonna, PhD, JD

Associate Director Bioscience Regulatory Affairs

Regulatory Realities: Challenges

- **International Global Supply Chain**
- **Multinational Collaboration by Government Regulators**
- **Harmonizing Multiple Legal Systems and Regulatory Schemas based upon a variety of languages and cultural ideals**

Regulatory Science

Challenge is to create a set of science based tools that can facilitate international harmonization of multiple regulatory schemas

Contact Information

Thomas Colonna, PhD, JD

Associate Director Bioscience Regulatory Affairs

302-292-8342

tcolonn1@johnshopkins.edu