Essential Update on Contract Manufacturing and Quality Standards

CPhI, Paris.

Guy Villax

7th of October 2014

Hovione

Agenda

Short Introduction to Hovione

Driving Forces Shaping the Market

CMOs – Innovators and Generics perspectives

FDA tips on vendor qualification programs

New Regulations

Quality Metrics

Hovione's Product and Service Offering

Contract Manufacturing Services

Drug Substance

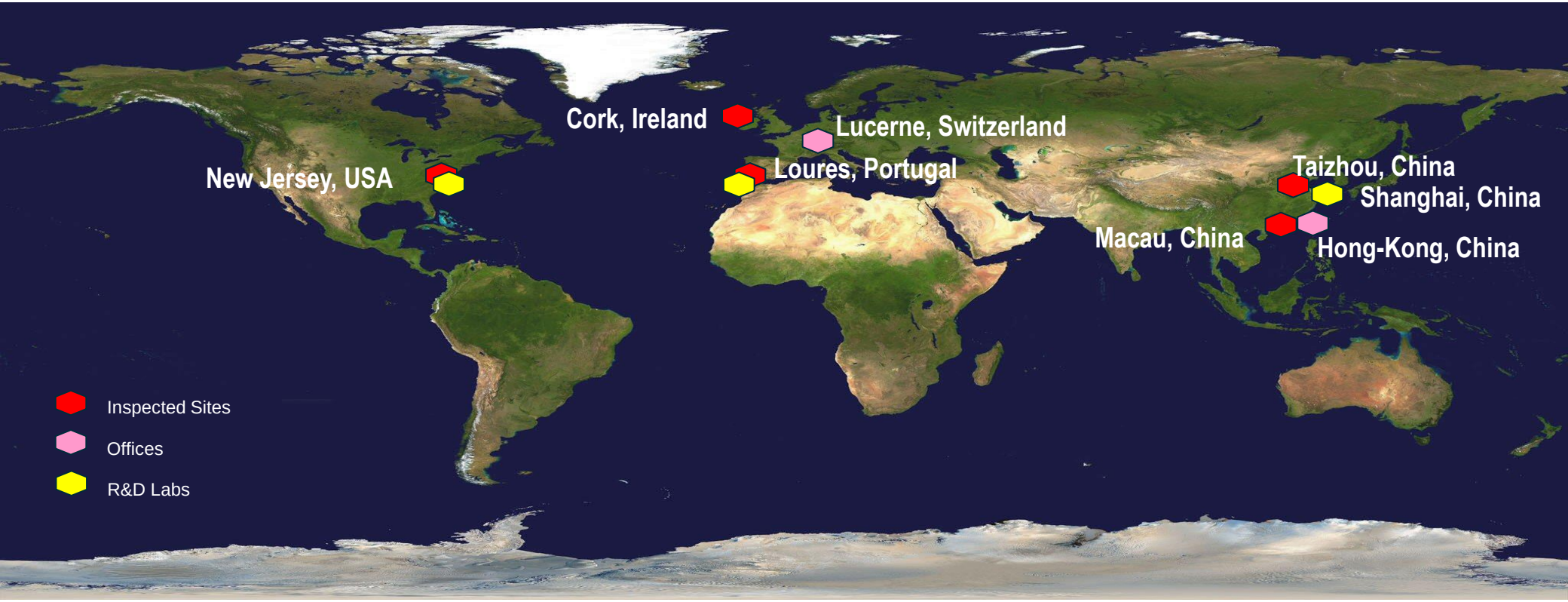
Particle Engineering

Drug Product

Off-Patent APIs

Proprietary Product Licensing

Global Presence

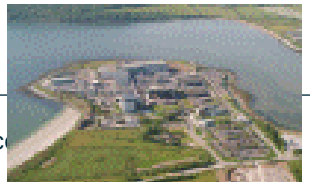


New Jersey, USA
Technology transfer center.
Process chemistry R&D Labs, Kilo plant and pilot plant.
Sales and marketing for North America
35 scientists
20 SG&A

Loures, Portugal
430 m^3 manufacturing facilities.
Process chemistry R&D Labs, kilo and pilot plants
600

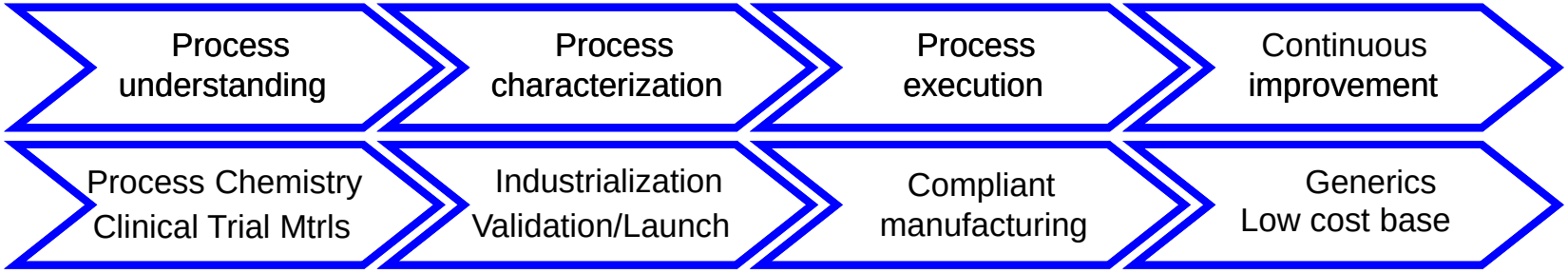
Macau, China
100 m^3 manufacturing Facilities
160

Cork, Ireland
427 m^3 manufacturing Facilities
142



Taizhou, China
350 m^3 manufacturing Facilities
290

Science based, present in all segments



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At Hovione we are making strides into the third evolutionary stage of the industry

1st Stage	2nd Stage	3rd Stage
Vessels		
Vessels	+ Technology	
Vessels	+ Technology	+ Methodology

- Predictive mathematical models
- Model based scale-up approaches
- Scale–down tools
- Knowledge Management

It’s not longer trial and error, we offer guarantied results.

Driving Forces

Quantity

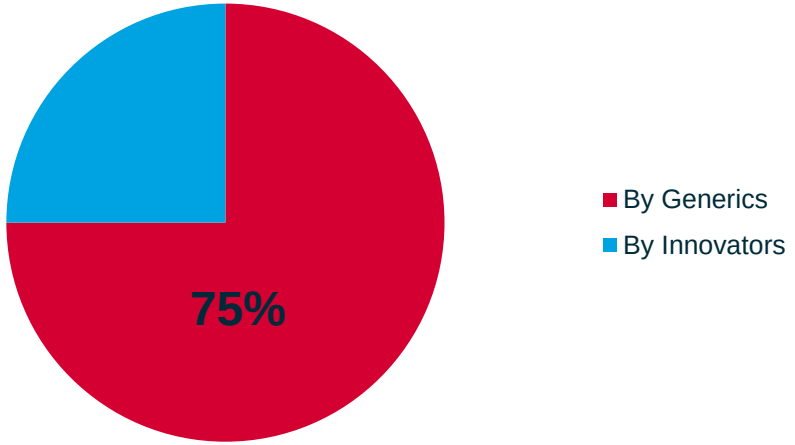
- **Big Pharma: now a Minority Player**
- **Generics: from Pirates to Leaders**

The vast majority of the medicines found in pharmacies today was invented in the 2nd half of the 20th century,

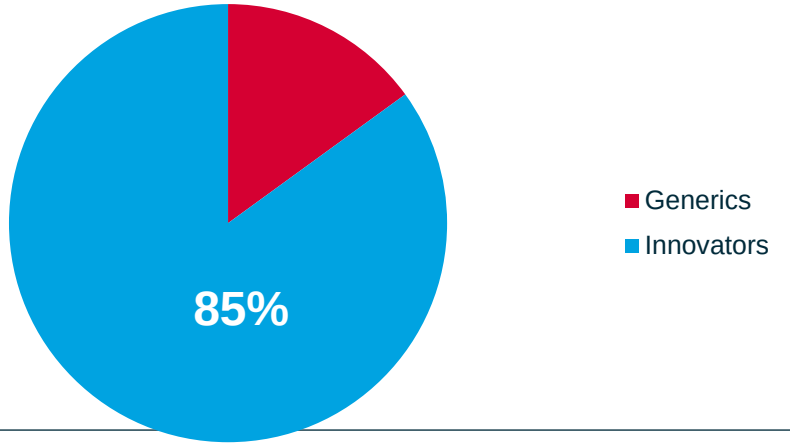
Today 7 billion people can now enjoy the fruits of 50 years of R&D for a few cents per tablet.

No other industry has offered so much to so many for so little.

Prescriptions filled



Sales in Value

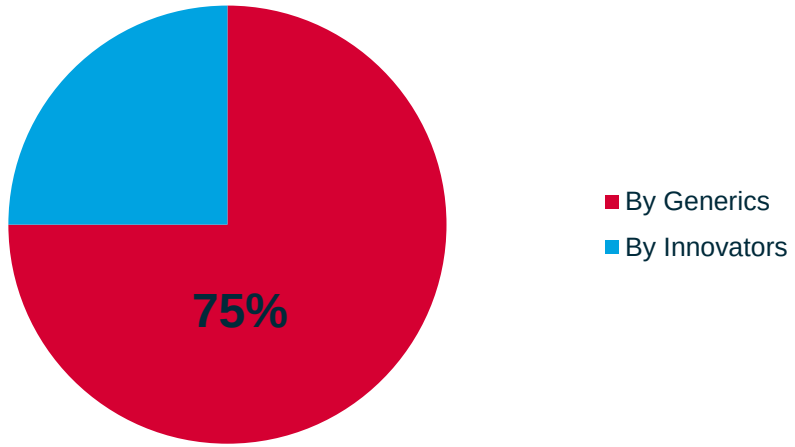


Driving Forces

Quantity

- Big Pharma: now a Minority Player
- Generics: from Pirates to Leaders
- NDAs approved: no longer blockbusters
- An ageing population
- Cost pressures

Prescriptions filled



Sales in Value

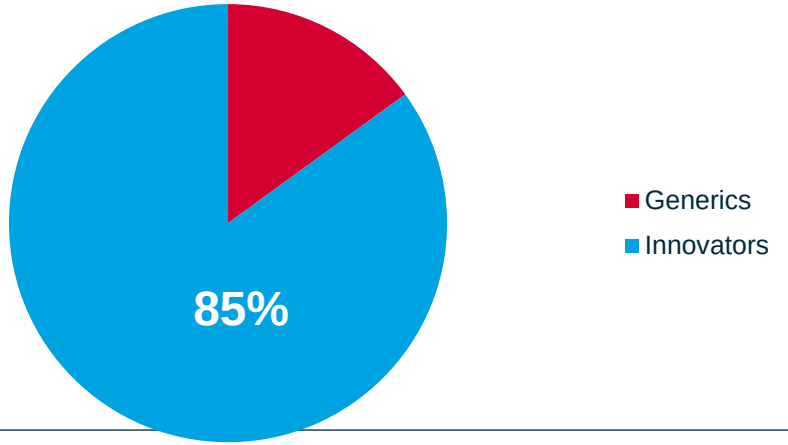
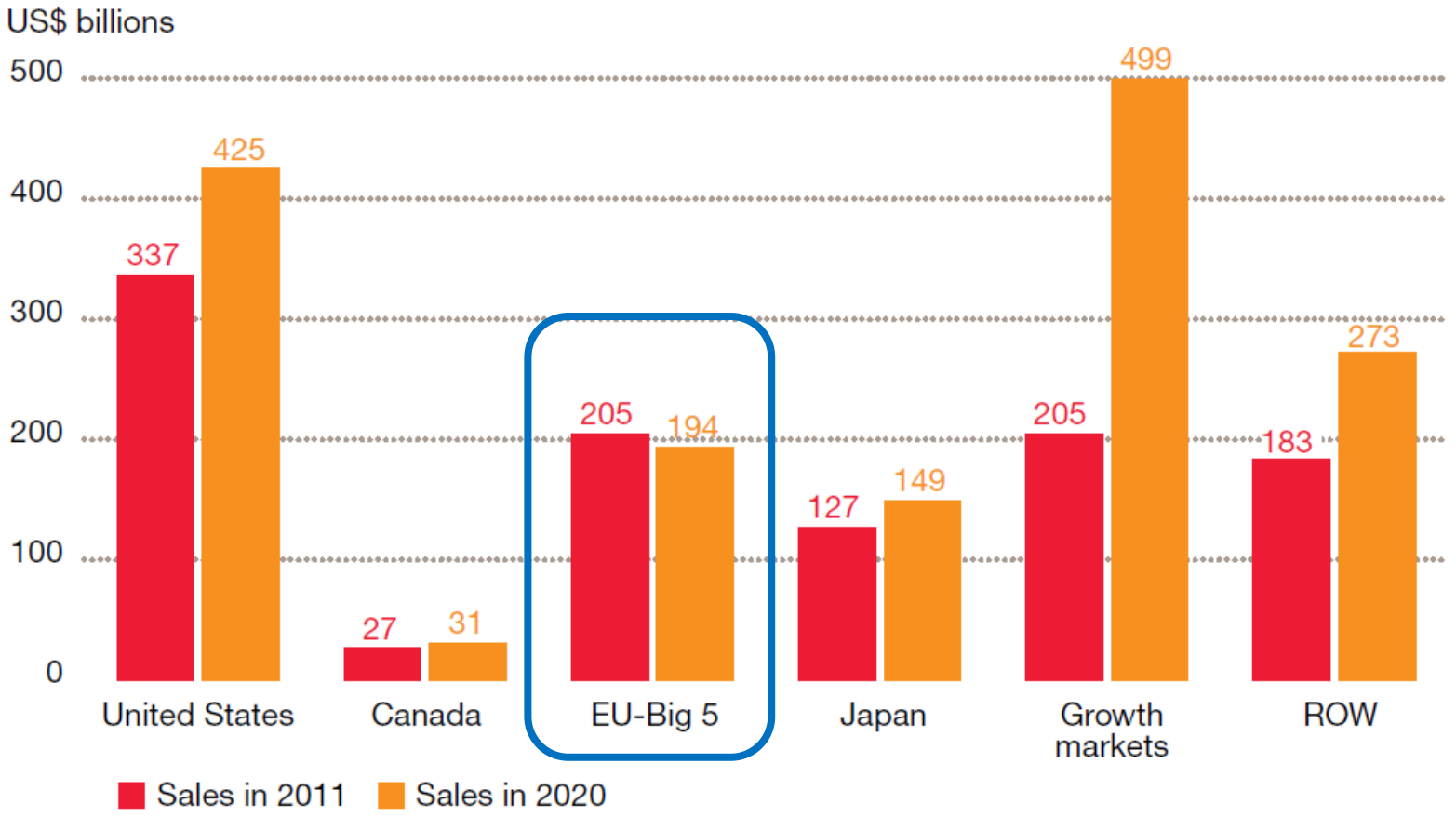


Figure 2 The global pharmaceutical market could be worth nearly $1.6 trillion by 2020

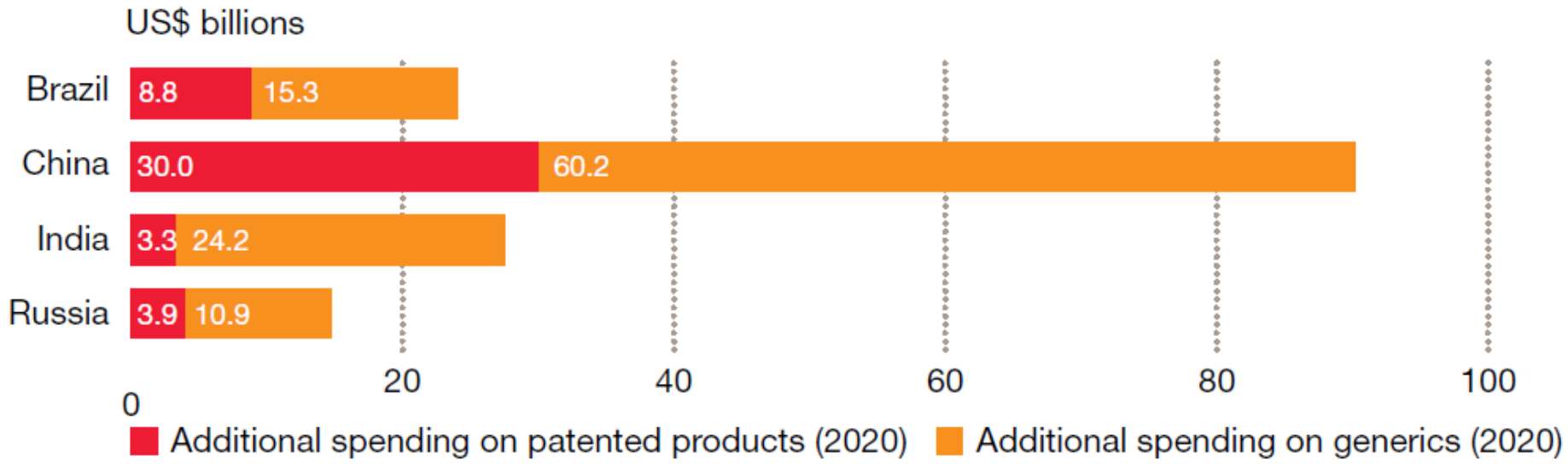


Source: Business Monitor International

Notes: (1). All sales are expressed in US dollars at constant exchange rates; (2). The growth markets include, in descending order of size, China, Brazil, Russia, India, Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam. (3) EU-Big 5 is France, Germany, Italy, Spain and United Kingdom.

Growth yes, but somewhere else, and again in Generics

Figure 3 Patented medicines will play a small role in driving up pharmaceutical sales in the growth markets



Source: Business Monitor International

Note: All sales are expressed in US dollars at constant exchange rates.

Driving Forces

Quantity

- Generics: from Pirates to Leaders
- Big Pharma: now a minority player
- Fewer NDAs approved
- An ageing population
- Cost pressures
- Explosion in technologies and methodologies

Shape

- Value chain
  - Fragmentation,
  - Specialization,
  - Consolidation.
  - New R&D model emerges, but funding is a challenge
- Globalization
  - Delocalization of manufacture (de-industrialization of the West, loss of R&D base for the CMC section)
  - Governments everywhere want to reduce health costs through Generics
  - National regulators not equipped or coordinated to control a global industry
  - Pharma crime is growing and out of control

First, accept that the World has changed

My first job at Hovione was selling Portuguese made APIs to India

in 1985:

A industry that was very profitable is now under pressure to perform, and has to re-invent itself – many options available

Italy used to be the foreign country with most FDA inspected sites; now India, soon China

From all-inhouse, or all within borders, then all Western - medicines globally are now mostly made with Chindia API; and along an increasingly fragmented and complex supply-chain: won't change

Regulators not organized to control a global industry

Absent a change in driving forces the quality of medicines will decline globally

Trends in the Supply Chain - Innovators

Big pharma will evolve :

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Some will become more like Unilever

Trends in the Supply Chain - Innovators

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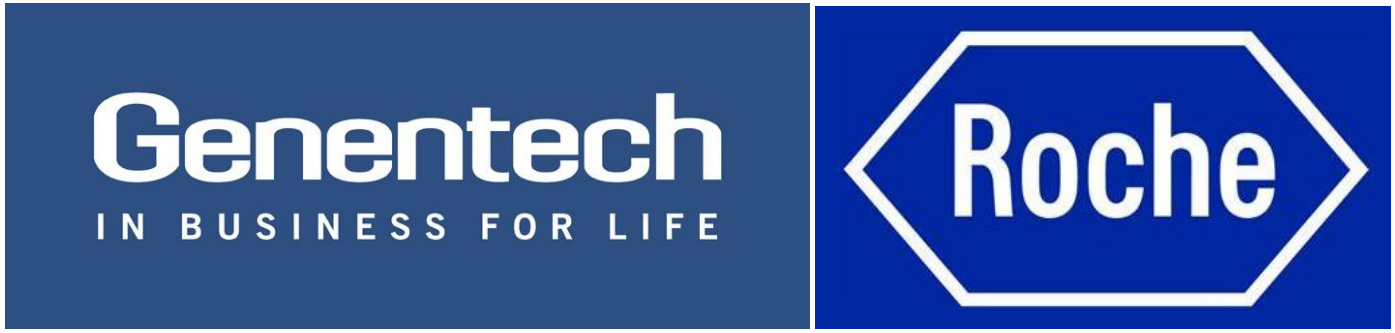
Some will focus on innovating only



Trends in the Supply Chain - Innovators

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Some will stop being of two minds

Trends in the Supply Chain - Innovators

Big pharma will evolve :

Some will become more like Unilever

Some will focus on innovating only

Some will stop being of two minds

Some will get focused

Nestlé completes acquisition of Pfizer Nutrition

zoetis

FOR ANIMALS. FOR HEALTH. FOR YOU.

Trends in the Supply Chain - Innovators

...and new companies will emerge

Trends in the Supply Chain - Innovators

Rapidly escalating diversity and depth of technology and methodologies, with specific purposefulness to address:

Increasingly complex molecules, decreasingly bioavailable

Increasingly compounds are patient group specific (smaller volumes)

Deliberately specificed delivery mechanism and place

QbD, PAT, DOE, mathematical models

so... Outsourcing becomes a necessary strategic option.
A new skill set is required:

- Nurturing relationships
- Governance mechanisms
- Project Management (external)

e it all i

...this assumes technology rich CMOs of sufficient size exist to meet the needs of Innovators in science, technology, and across all necessary scales – meeting the necessary hygene factors

Trends in the Supply Chain - Innovators

... Implications of QbD to the CMC section and Regulatory Approval

CMC cant be “thrown over the wall”, the regulatory review will need dialogues

Sponsor is not just the ONE company; but a team of specialists in-house & CMOs

Reviewers and Inspectors need to work together – before and after the filing

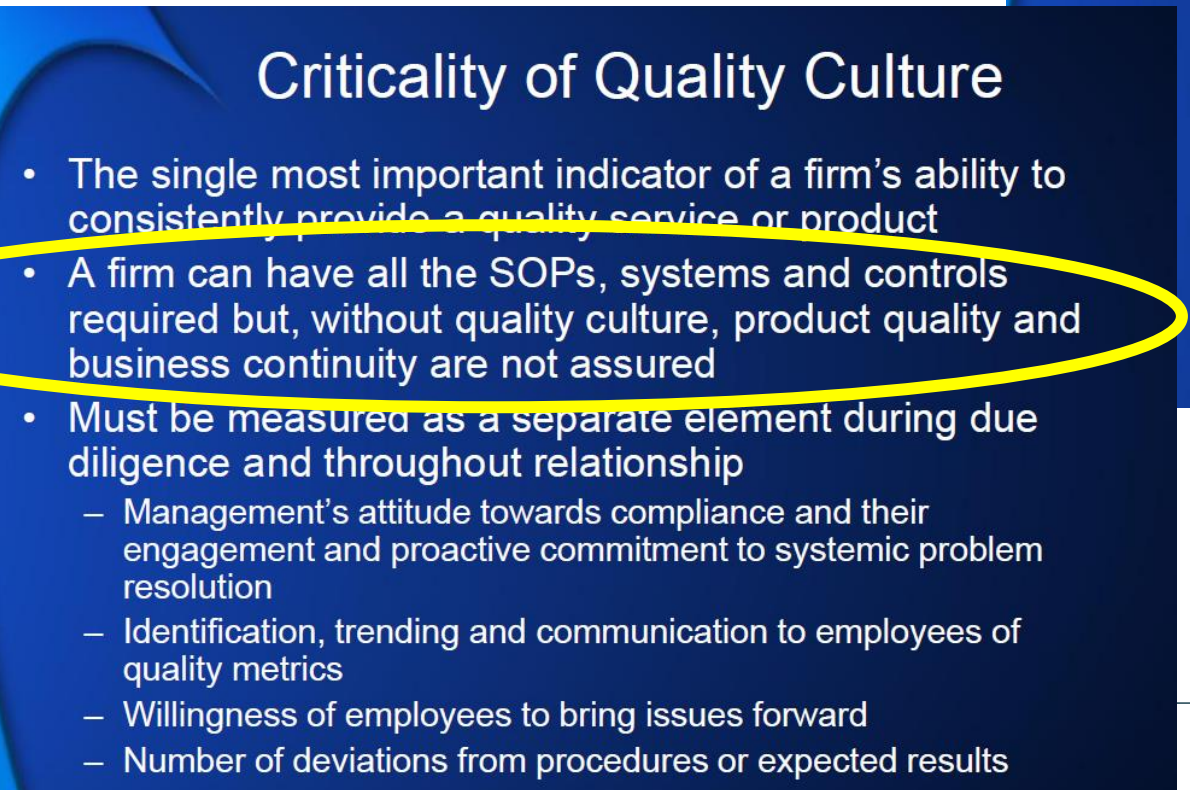
- Adversarial confrontation must make way for a science based debate, the review and the inspection -as far as CMC is concerned- needs to be an honest challenge and an education – both ways.

Changes to the supply chain – Innovators outsource

Big Pharma has been looking for cost reductions in Asia...

Bad news: CEP suspensions, warning letters, import alerts...

Big Pharma QA is Red-faced:



Trends in the Supply Chain – Generics

Supply chain structure under intense price pressure – hence:

Fragmentation, Specialization, Consolidation

Geographical de-localization to lower cost / lower regulation / patent friendly locations :

- API is 10-25% of ex-works cost of a generic medicine
- API is from 0 to 2% of ex-works cost of a patented medicine

Western Regulators no longer in denial, they accept they are not in control, action has been taken:

- EU's FMD – now demands a "written confirmation"
- USA's FDASIA and GDUFA – doubling of foreign inspections

Audits to API producers are now mandatory every 3 years

Expect shared audits to become the norm

Trends in the Supply Chai

Generics must change :

New generics (small molecules and bio-similars) are far more complex

See GDUFA's regulatory science goals

FDA is demanding that Generics start doing QbD filings and evidence process understanding

FY 2013 Regulatory Science Plan

Topic 1: Bioequivalence of local acting orally inhaled drug products
Impact: Continue to develop new and improved PD endpoints and study designs or establi
of alternative approaches to ensure equivalent local delivery of orally inhaled drug produc
lung would lead to more efficient development of generic products in a sector that lacks a
generic competition

Topic 2: Bioequivalence of local acting topical dermatological drug products
Impact: Continue developing new bioequivalence methods in order to reduce the need for
relatively insensitive clinical endpoint bioequivalence studies. Development of in vitro rel
tests or other product characterization to ensure consistent drug release or product perform

Topic 3: Bioequivalence of local acting gastro-intestinal drug products
Impact: Developing new bioequivalence methods for direct measurement of drug concentr
in the GI tract and establishing better correlations between pharmacokinetic measurements
concentration would allow more efficient demonstration of bioequivalence than by clinica
endpoint studies.

Topic 4: Quality by design of generic drug products
Impact: Continue developing science-based recommendations for product development, ra
material, APIs and process controls, and life-cycle management of complex dosage forms
orally inhaled drug products and modified-release dosage forms)

Topic 5: Modeling and simulation
Impact: Modeling and simulation (including in-vitro and in-vivo correlations) is essential
efficient implementation of quality by design and can help to identify and eliminate unnec
in-vitro and/or in-vivo studies. Models (PK/PD, exposure-response, clinical use simulation
support generic drug evaluation policies especially for NTI drugs and complex products.

Topic 6: Pharmacokinetic studies and evaluation of anti-epileptic drugs
Impact: Improving public confidence in bioequivalent generic epilepsy drugs.

Topic 7: Excipient effects on permeability and absorption of BCS Class 3 Drugs
Impact: Extension of biowaivers to BCS Class 3 Drugs and eliminating the need for unnec
in vivo bioequivalence studies

Topic 8: Product- and patient-related factors affecting switchability of drug-device combination products (e.g., orally inhaled and nasal drug products and injection dru

Trends in the Supply Chain – Generics

Low R&D productivity of the past decade will result in few generics to launch this decade:

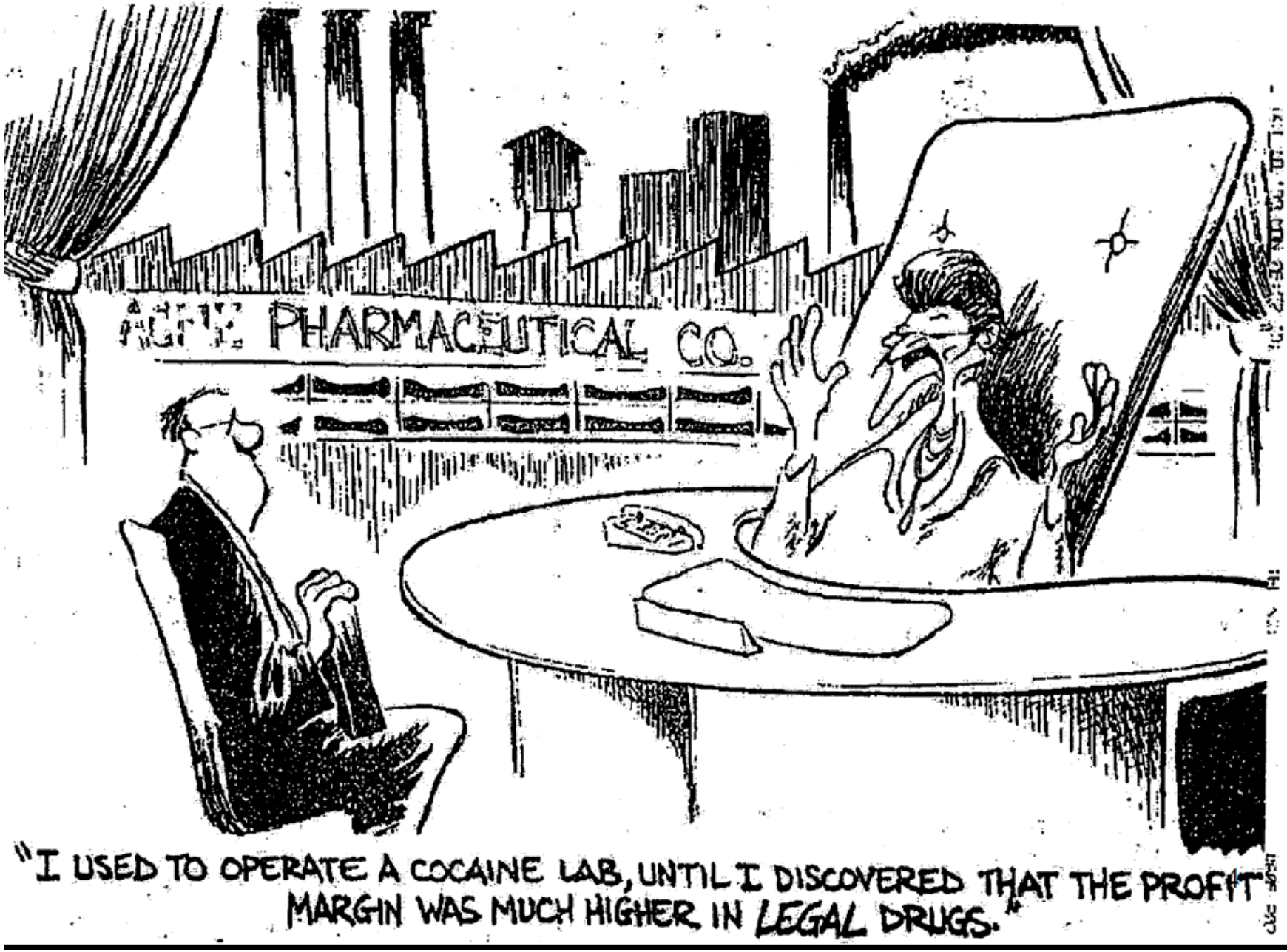
- Generics' business model will be questioned ?
- Consolidation ?

Opportunities in fast growing emerging markets ?

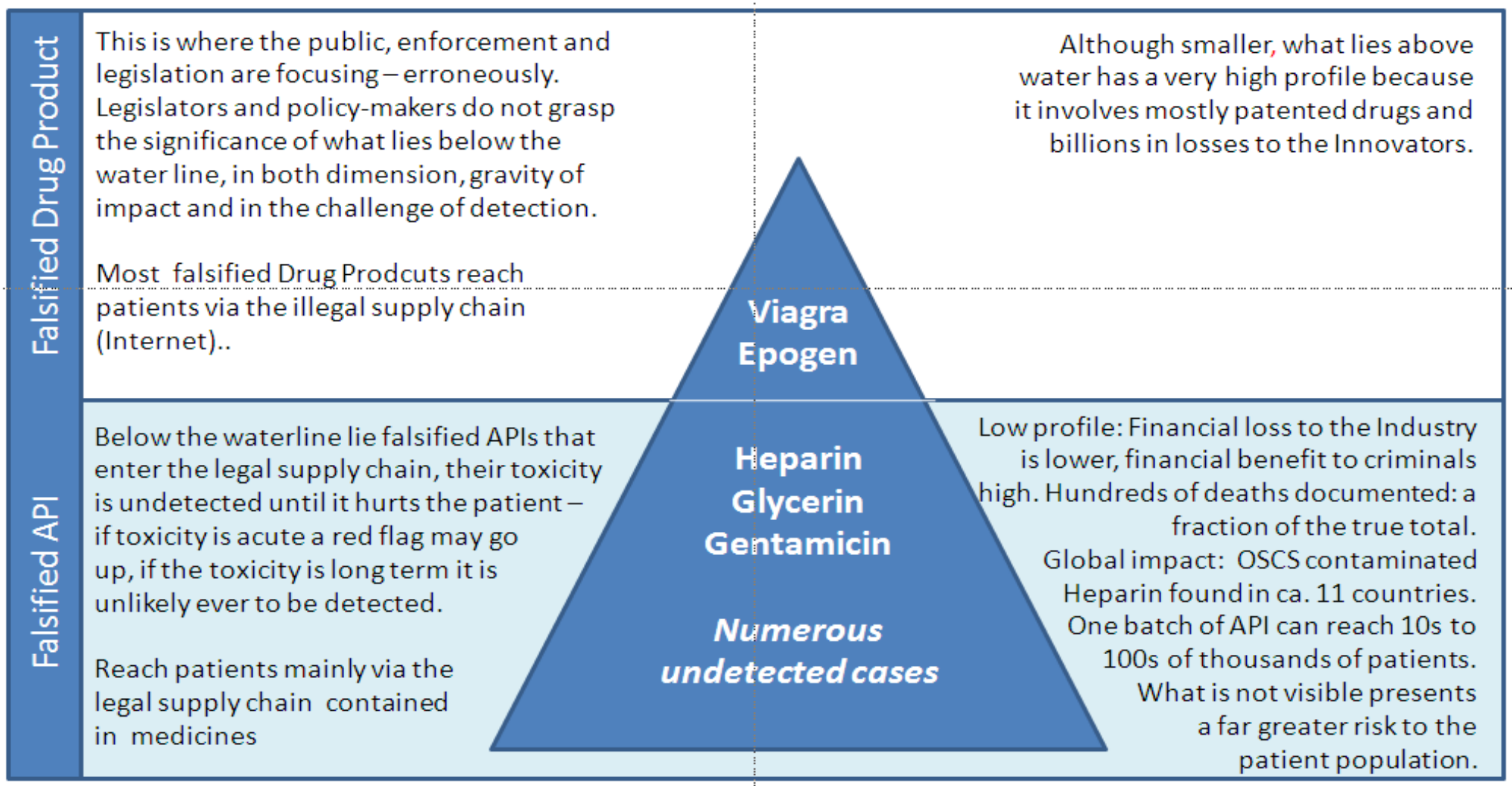
- Patients in emerging markets dont trust their Regulators
- = Opportunities for branded generics

What if developed countries dont stop fake medicines effectively and soon ?

- Trust in pharmacies is lost.
- Logic of non-brand generics / substitution disappears. Big pharma can leverage its brand and quality guaranties


PHARMACEUTICAL CO.
"I USED TO OPERATE A COCAINE LAB, UNTIL I DISCOVERED THAT THE PROFIT MARGIN WAS MUCH HIGHER IN LEGAL DRUGS."

Falsified Pharmaceuticals
An Iceberg



Falsified Pharmaceuticals

Pharma crime pays: the victim swallows the murder weapon, nobody is caught, nobody goes to jail and the sanctions are light

“the competitive advantage of non-compliance”

Stakehodlers are taking action:

- Laws: EU’s Falsified Medicines Directive, USA’s GDUFA & FDASIA
- Better Resourced Regulators
  - **FDA doubled the number of foreign inspectors and inspections**
  - **Regulators collaborate Globally**
- Industry collaborates
  - **Rx-360 is now in its 5th year**

What FDA expects as a Vendor Qualification Program

- **Increasing Control in the Supply Chain of Incoming Components**
- Improving Analysis and Testing Strategies and Technologies
- Monitoring and Responding to Signals in the Market Place
- Enhancing Drug Product Distribution Supply Chain Controls and
- Use of Serilization Track and Trade and ePedigree

What FDA expects as a Vendor Qualification Program

Increasing Control in the Supply Chain of Incoming Components

#	Topic	Examples of Recommendations
1	Apply a risk based approach to supplier management	- Senior management support - Keep refining the model - Keep it simple - Take action
2	Conduct Suppler Meetings	- Assign a Leader, does Quality have the final word ?
3	Share intelligence with other companies	- Supplier Quality bulletin - Embrace Rx-360
4	Provide a scorecard to your suppliers	- Keep it simple - Don't' catch suppliers by surprise - Be cross-functional - Have two-way feedback
5	Document supplier disqualification decisions	- Use to enable others to understand the reasons - Use change control to document and manage change - Integrated into you quality management system - Define what makes a supplier disqualified - Share internally (R&D)
6	Quality agreements	- Make it simple and clean - Leverage standard templates - Use it
7	Conduct effective audits	

What FDA expects as a Vendor Qualification Program

Improving Analysis and Testing Strategies and Technologies

#	Topic	Recommendations	Examples
1	Supply route security and verification	Know your material supply chain	
		Proactive risk management based on knowledge of material supply chain	- Pedigree tool - Record GPS coordinates to ensure you audit the right facility in other countries
		Apply risk management strategies	- Include security organization - in risk assessments
		Identify and implement systems to minimize and detect incoming counterfeits, contamination and substitution	- Photo Library - Tracer chemicals - Importation tools
2	Authentication of Supporting documentation	Authenticate CoAs using new methods	- Water stamp - Obtain directly from manufacturer before receipt of material
		Strategies to implement agreed upon solutions	
		Map supply chain and apply risk management	
		FDA and appropriate industry groups work together on a consistent approach to importation certification	

What FDA expects as a Vendor Qualification Program

Monitoring and Responding to Signals in the Market Place

#	Topic	Examples of Recommendations
1	Supply communication and transparency	– Build relations with suppliers; beyond audit interactions – Single point of contact – Understand suppliers concerns with confidentiality and transparency
2	The Weakest Link – Identification, Support, Strengthening and Discontinue	– Develop financial model to calculate total cost used in selection process – Set expectations for continued compliance in business agreements including class for discontinuation – Well-defined exit strategy
3	Common auditing approach	– Holistic approach – Supplier should be included in discussion – Existing training certification/accreditation – Mora than GMP involved
4	Think tank for signal detection	– Create library of info sources – Staffing – Evaluate similar functions - such as Rx-360 and IMPACT

What FDA expects as a Vendor Qualification Program

Enhancing Drug Product Distribution Supply Chain Controls and Use of Serilization Track and Trade and ePedigree

#	Topic	Examples of Recommendations	Best Practices
1	Transportation and logistics service provider selection	–Incorporate security considerations intro Request for Proposal process and define evaluation criteria –Meet with providers –Non-disclosure agreements –Response to theft – impact to patient safety	- Organization model for effective transportation and logistics management - Continuous process
2	Leveraging regulatory efforts and collaboration with trading partners	–Stronger uniform licensing requirements and penalties –Build database/registry of partners –Improve audit tools and resources –Due diligence	
3	Serialization and Track & Trace	–Partner with regulatory and legislative bodies to clearly define scope and rule of engagement –Accelerate adoption of existing and emerging standards for identification and data sharing –Define stepwise deployment roadmap	- Leverage trade and industry organizations to develop serialization knowledge - Educate your organization on standards and impact to functional efforts

What FDA expects as a Vendor Qualification Program

Enhancing Drug Product Distribution Supply Chain Controls and Use of Serilization Track and Trade and ePedigree

#	Topic		
1	Transportati logistics ser provider sel		
2	Leveraging efforts and collaboratio trading part		
3	Serialization Track & Trac	Standards for identification and data sharing –Define stepwise deployment roadmap	Standards and impact to functional efforts

- **If you are a Pharma manufacturer - does your vendor qualification address all these points ?**
- **If you are an API supplier does your - vendor qualification program address all these points ?**
- **Are these demands cascaded down ?**

Take home messages

- Give QA & Purchasing a travel budget
- Know your suppliers
- Audit your API suppliers
  - this is now a legal requirement in EU and USA
  - opportunity to buy audit reports via Rx-360
- Buy directly, avoid brokers and traders

Cost is not equal to Price

Membership:

- Over 100 organizations, including FDA.
- All actors participating in the pharma supply chain are welcome

Share information:

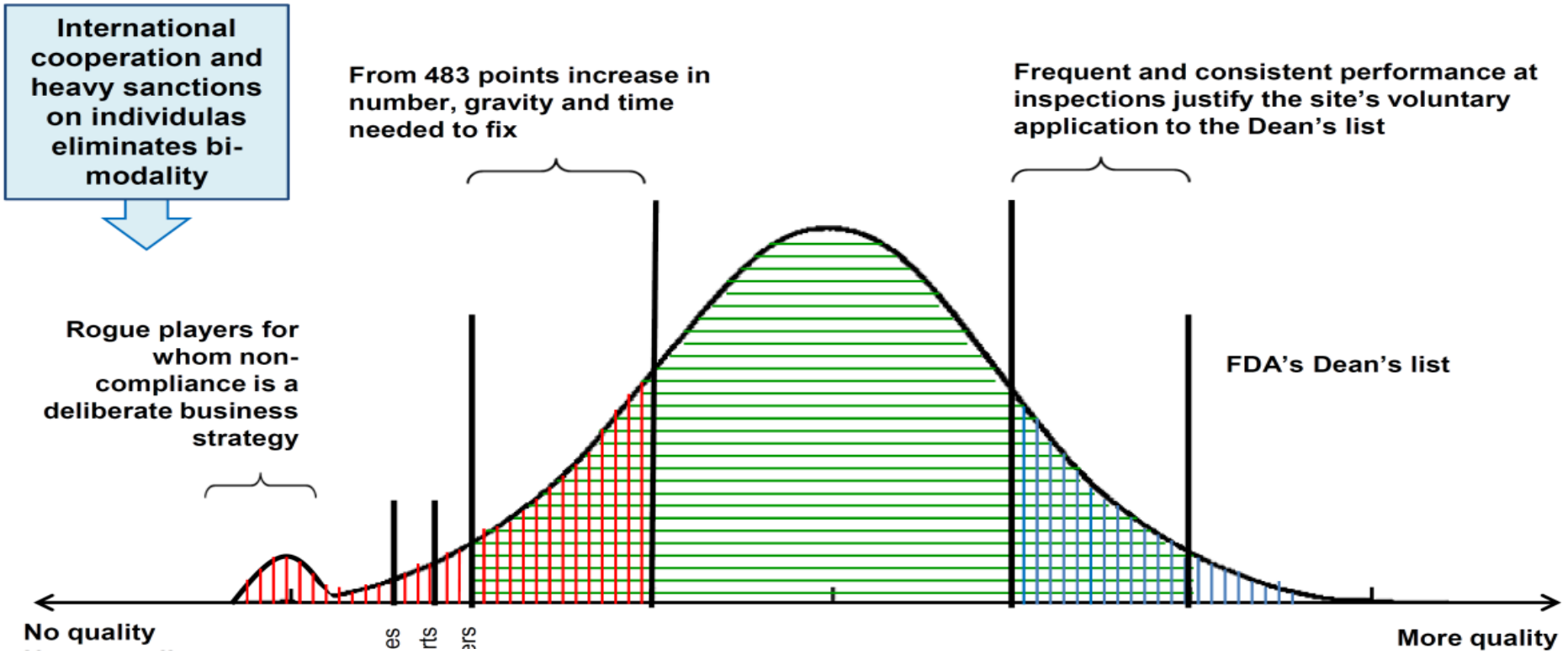
- On falsified pharmaceuticals
- Audit report library: Jointly sponsored audits
- Best practices on Supply Chain Security

…at low cost

Open Day in Cologne on 29th October 2014

www.rx360.org

Pharma Manufacturing Sites
Stratification by level of Compliance



Costly sanctions region	Red flag region	Bulk of sites are compliant	Motivation to-do-better region	Valuable reward region

FDA and EMA: Quality Metrics Initiative
Stratification of Quality in Drug Product and Drug Substance makers
Why Dr. Hamburg needs her Dean's List

If FDA wants to promote a Quality Culture, it needs to reward good behaviors, not just sanction non-compliance

It needs to reward those that perform beyond compliance, that innovate in the right direction:

Walk the Talk

- Have a stellar record of compliance
- Have a history of transparency with the Regulators
- Contribute to the standard setting process
- Early adopters of PAT and QbD
- Allow FDA access to their sites for training of inspectors
- Provide FDA with IT access to perform at any time and in real-time remote inspection to quality data of commercial batch manufacturing and release

FDA has to go out of its comfort zone and publicly name and congratulate the role models

Thank you for your attention
Q&A

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