



Pathway to Global Product Safety and Quality

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Pathway to Global Product Safety and Quality

- I. Ten years from now, the world will be very different than it is today
- II. The coming changes will make FDA's product safety and quality responsibilities formidable and more global in the years ahead
- III. FDA must substantially change its operating model to address the challenges of the future
- IV. FDA is pursuing a strategy with four primary components to address the coming challenges
- V. Implementing the *Pathway to Global Product Safety and Quality*

TEN YEARS FROM NOW, THE WORLD WILL BE VERY DIFFERENT THAN IT IS TODAY

- A. *The great rebalancing*
- B. *The productivity imperative*
- C. *The global grid*
- D. *Pricing the planet*
- E. *Government and the marketplace*



The great rebalancing

- Vibrancy of emerging-market growth – will contribute to reshaping the global economy in the next decade
- This decade – marks the tipping point in a fundamental long-term economic rebalancing that will likely leave traditional Western economies with a lower share of GDP in 2050 than they had in 1700.

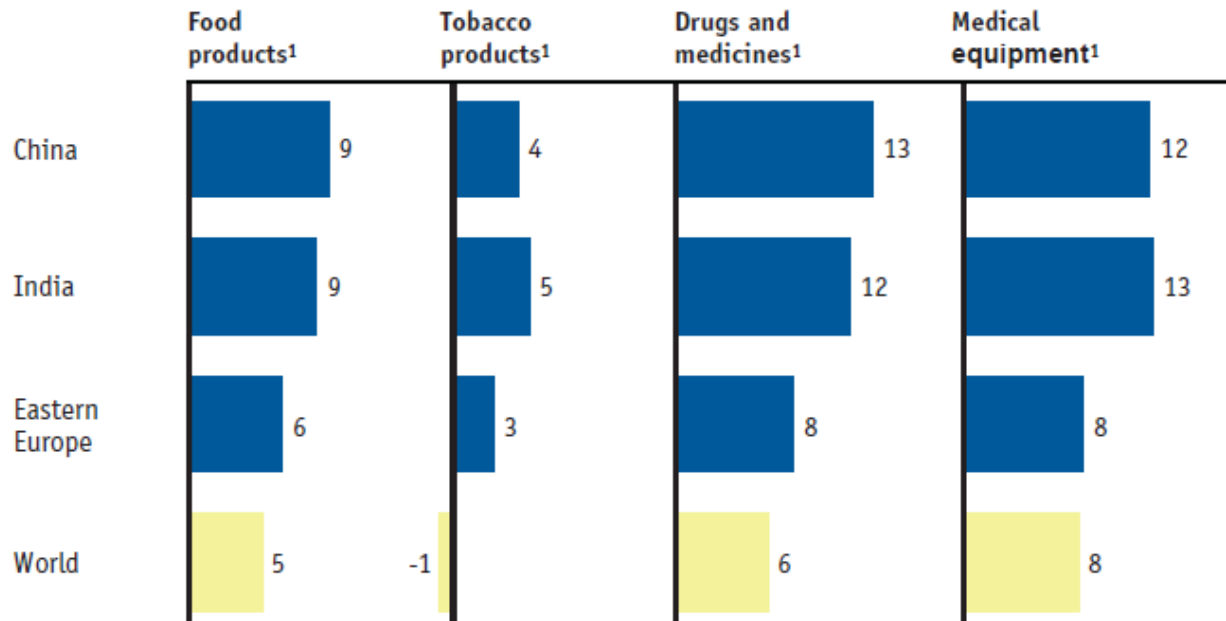
The great rebalancing - continued

- Two cycles at play:
 - Declining dependency ratios – reflecting an increase in the overall proportion of a population that is working age. All major emerging markets are undergoing demographic shifts well-proven to unleash an economic shift: simultaneous labor force growth and rapidly declining birth rates.
 - Largest urban migration in history: 1.5 million people move to cities each week, almost all in developing markets.
 - Economic impact is a rapid increase in output per worker.
 - China and India are seeing labor productivity grow at more than five times the rate of most Western countries

Growing exports of FDA-regulated products from emerging economies

Emerging economies are expected to grow their exports of FDA regulated products faster than the worldwide growth in exports.

Forecast growth in worldwide exports and exports from China, India, Eastern Europe, 2010-20
Percent; CAGR



¹ Categories based on IHS Global Insight do not perfectly mirror FDA regulated products and centers.

Source: IHS Global Insight

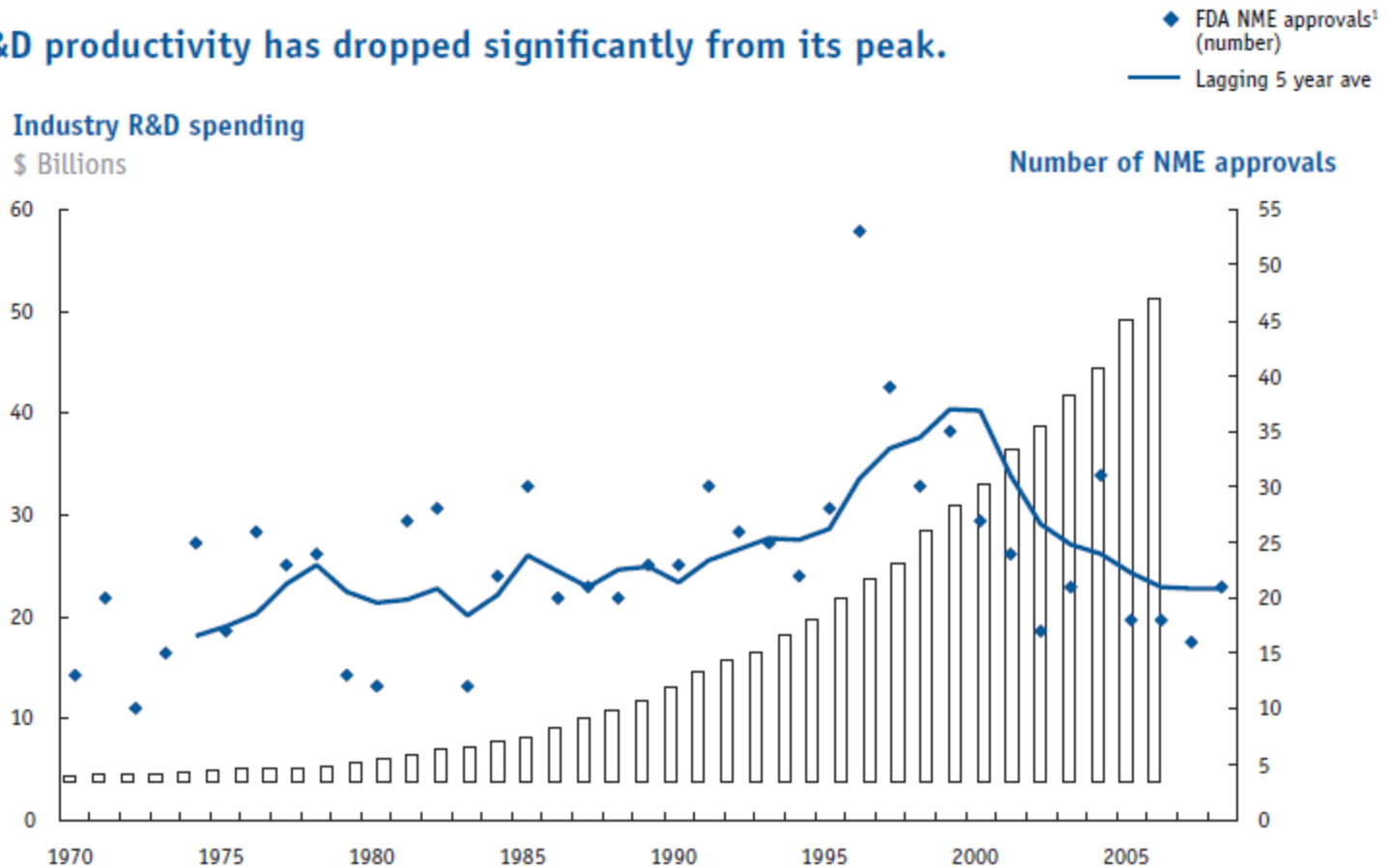
The productivity imperative

- Emerging markets – virtuous growth – larger and younger working populations
- Rich nations – low birth rates and graying work forces
 - Best hope is improved productivity
 - Will lead to increased imports, changes to manufacturing processes and increased pressures to reinvent the manufacturing process



R&D productivity declining

R&D productivity has dropped significantly from its peak.



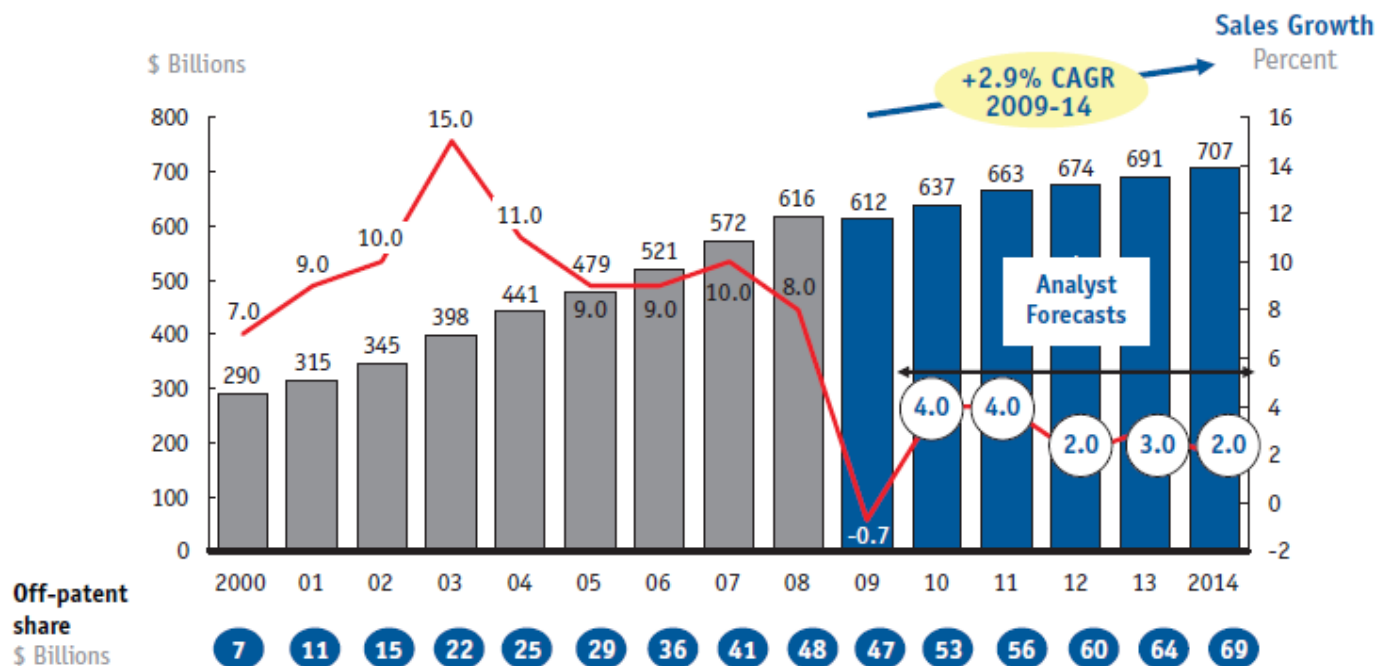
¹ Lagging 5 year average, includes NCEs and BLAs. BLAs included 1986 onward; biologics approvals in prior years assumed negligible.

Source: NME data for 1966 - 1971 from Peltzman, S. (1973) J. of Political Economy 81, no. 5: 1049-91. NME data for 1972-1979 as reported in Hutt, P.B. (1982) Health Affairs 1(2) 624. NME Data for 1980-2007 from Parexel's Pharma R&D Statistical Sourcebook 2009/2010, FDA, and PhRMA. Industry R&D spend data from PhRMA Annual Membership Survey, 2008 and Parexel 2009/2010.

Cost pressures facing pharmaceutical companies

Pharmaceutical company revenues are under pressure and unlikely to regain historical levels of growth.

Worldwide total prescription drug sales 2000-14



- 1 EvaluatePharma focuses on manufacturer's selling price for Top 500 pharma and biotech companies (IMS traditionally higher since it includes all retail/wholesale invoices and excludes rebates).
- 2 Majority of industry estimates more conservative in early 2009; IMS revised in late 2009 to project 4-7% CAGR growth through 2013.

Source: EvaluatePharma April 2009; team analysis

The global grid

- Last 20 years: Rise of networks of unimaginable density and complexity
 - Money, goods, data, and people now cross borders in huge volumes and at unprecedented velocity.
 - Since 1990 – trade flows have grown 1.5 times faster than global GDP
 - Cross-border capital flows expanded at three times the rate of GDP growth
 - Information flows increased exponentially
 - Typical manufacturing company:
 - Relies on more than 35 different contract manufacturers around the world. (Auto/airplane manufacturers rely on tens of thousands)

The global grid - continued

- Trade flows between China and Africa – growing by 30% annually – creating robust commercial networks that barely existed a few years ago
- Asia has supplanted North America and Europe as the Middle East's largest trading partner.
- Emerging-market-to-emerging-market transactions are on the rise



Pricing the planet

Issue: Rapidly rising resource consumption: availability/cost versus environmental sustainability

- The interplay of three forces: growing demand, constrained supply and increased regulatory and social scrutiny will determine:
 - what resources we use
 - how we use them
 - what we will pay for them
- Demand: Will grow
- Supply: Will be constrained
 - will come from harder-to-access, more costly, and more politically unstable environments
- Regulatory/Political scrutiny: Will increase

Government and the marketplace

- Government will likely to play an even larger role in the advance of market capitalism for three reasons:
 - Governments called upon to mitigate negative impact of globalization on citizens
 - Financial crisis itself has prompted large-scale direct government intervention – both through fiscal stimulus and movement toward increased regulation
 - Spread and dispersal of economic power around the world is making it harder to reach consensus on multilateral approaches to setting the rules of global interactions and fostering more bilateral and regional deal-making.

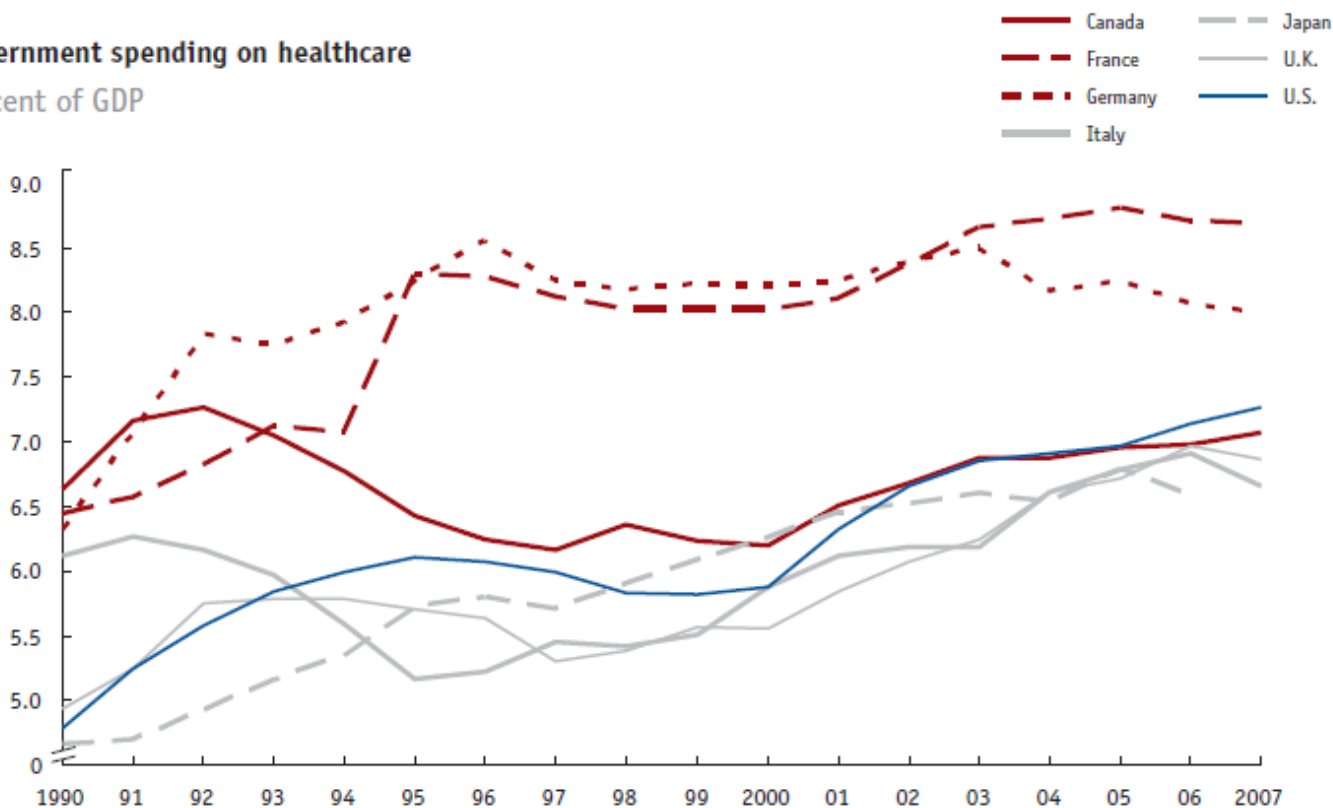
THE COMING CHANGES WILL MAKE FDA'S PRODUCT SAFETY AND QUALITY RESPONSIBILITIES FORMIDABLE AND MORE GLOBAL IN THE YEARS AHEAD

- Global changes will have significant implications for the manufacturers and products that FDA regulates
 - Increasing pressure to reduce costs and increase productivity
 - Greater government influence in healthcare markets
 - Growing globalization of production of FDA-regulated products leading to growth in imports
 - Increased risk of counterfeiting and other fraud

Increase in government healthcare spending

Most countries are seeing increases in healthcare spending.

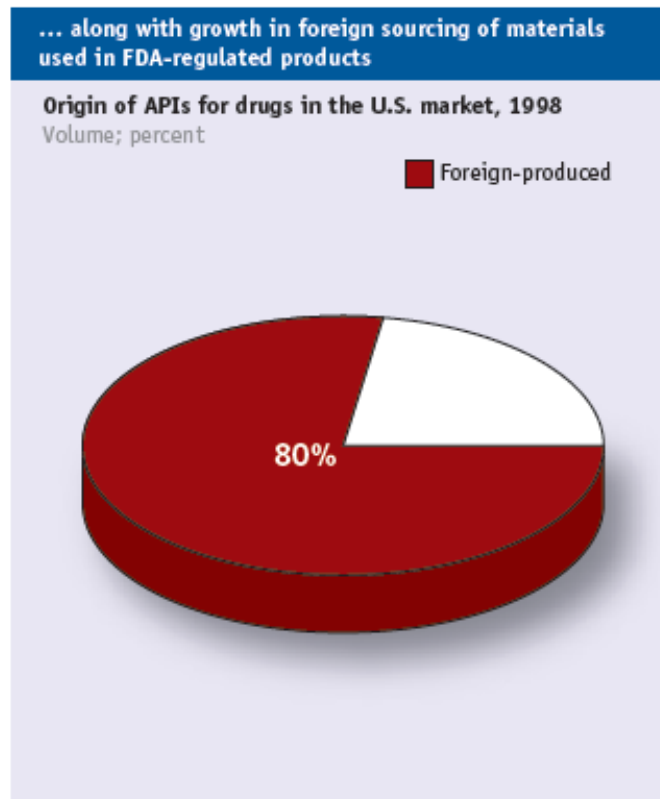
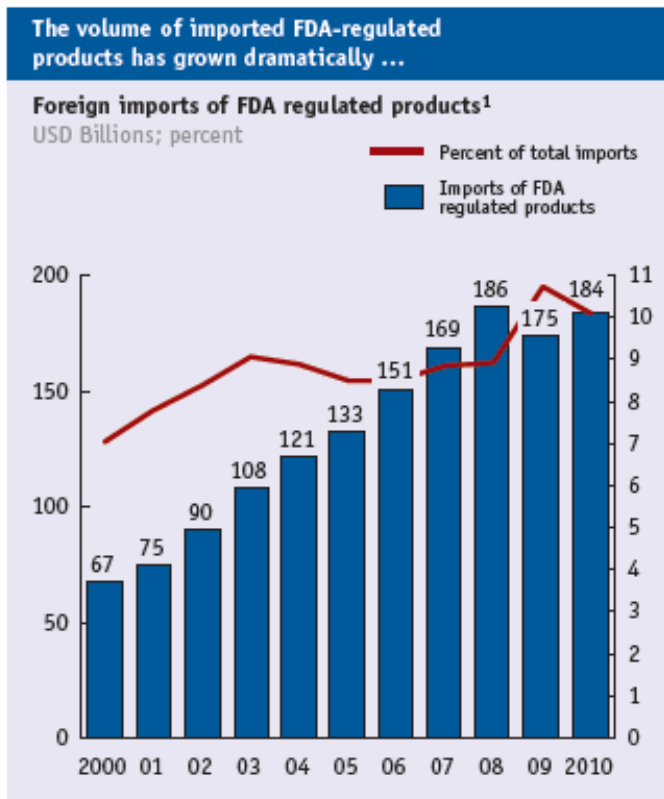
Government spending on healthcare
Percent of GDP



Source: OECD Health Data 2009

Growth in FDA imports

Increases in global trade are increasing the exposure of U.S. consumers to foreign products and source materials.



¹ IHS Global Insight industry categories were used to compute these figures; categories do not exactly match FDA-regulated products.

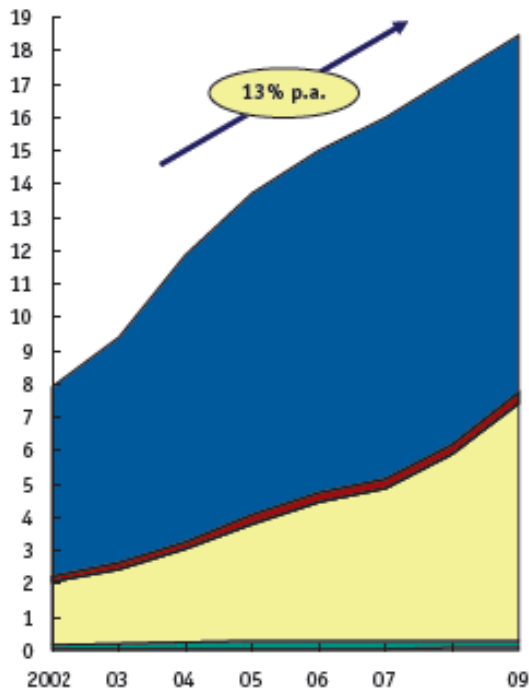
Source: IHS Global Insight, Frost & Sullivan, GAO: Improvements Needed in the Foreign Drug Inspection Program

Import lines of FDA-regulated products

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

Imported lines¹(millions)

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



CAGR

2002-09 Explanation of center's products

Category	CAGR	Explanation of center's products
Foods	9.5%	<ul style="list-style-type: none"> • Food products for human, animal, pet use, except meat and poultry • Articles for cleansing, beautifying, promoting attractiveness of body
Drugs	12.9%	<ul style="list-style-type: none"> • Prescription and OTC drugs for human
Devices	20.8%	<ul style="list-style-type: none"> • Medical devices for human use • Products that emit radiation (e.g., microwaves, lasers, x-ray machines)
Veterinary products	6.7%	<ul style="list-style-type: none"> • Drugs, devices, and food additives for animals and pets
Biologics	15.8%	<ul style="list-style-type: none"> • 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.

Proportion of FDA-regulated products that are imported

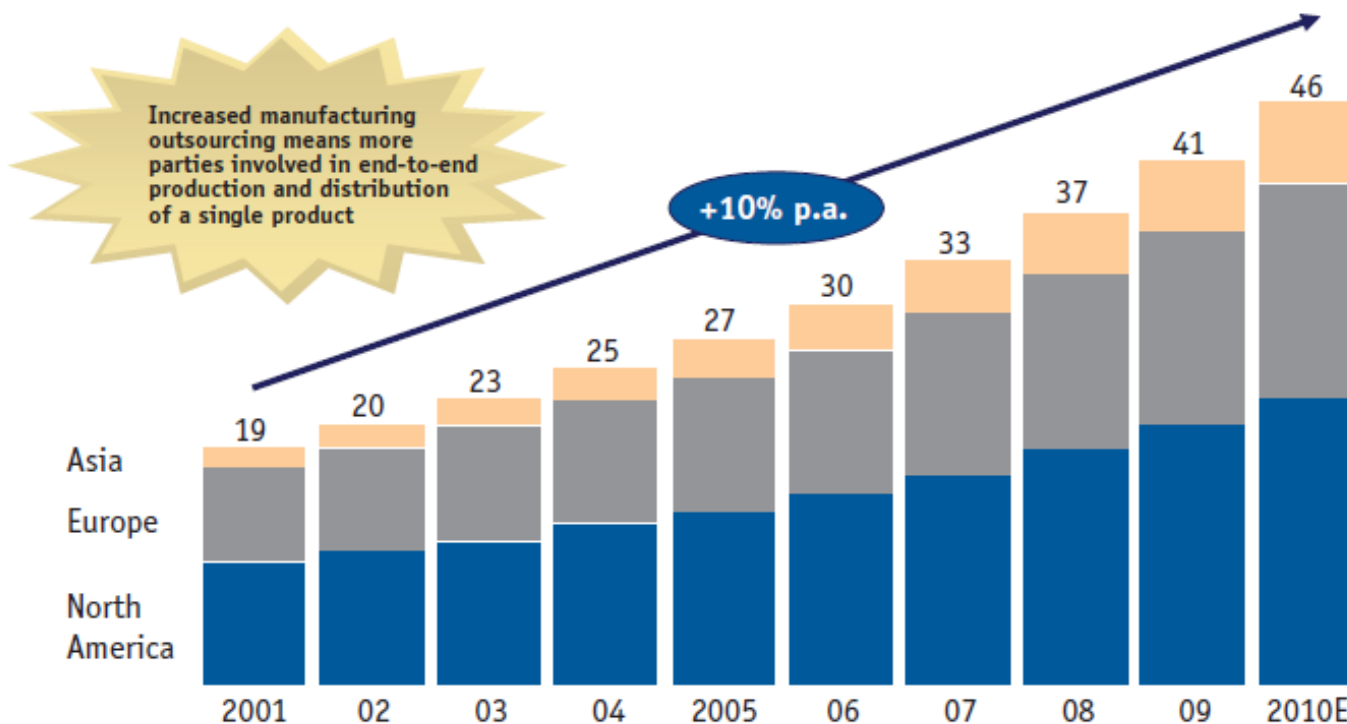
	Number of import lines in (2009)	Proportion of total spend met through imports (2010)
Food	10.7 million	10-15
Medical Devices	7.1 million	52
Drugs	0.35 million	28

Source: FDA Import Data, IHS Global Insights

Market for Contract Manufacturing Outsourcing

Increased fragmentation of regulated producers adds a new challenge to the FDA's safety assurance efforts both domestically and abroad.

Pharmaceutical contract manufacturing outsourcing market
USD Billions

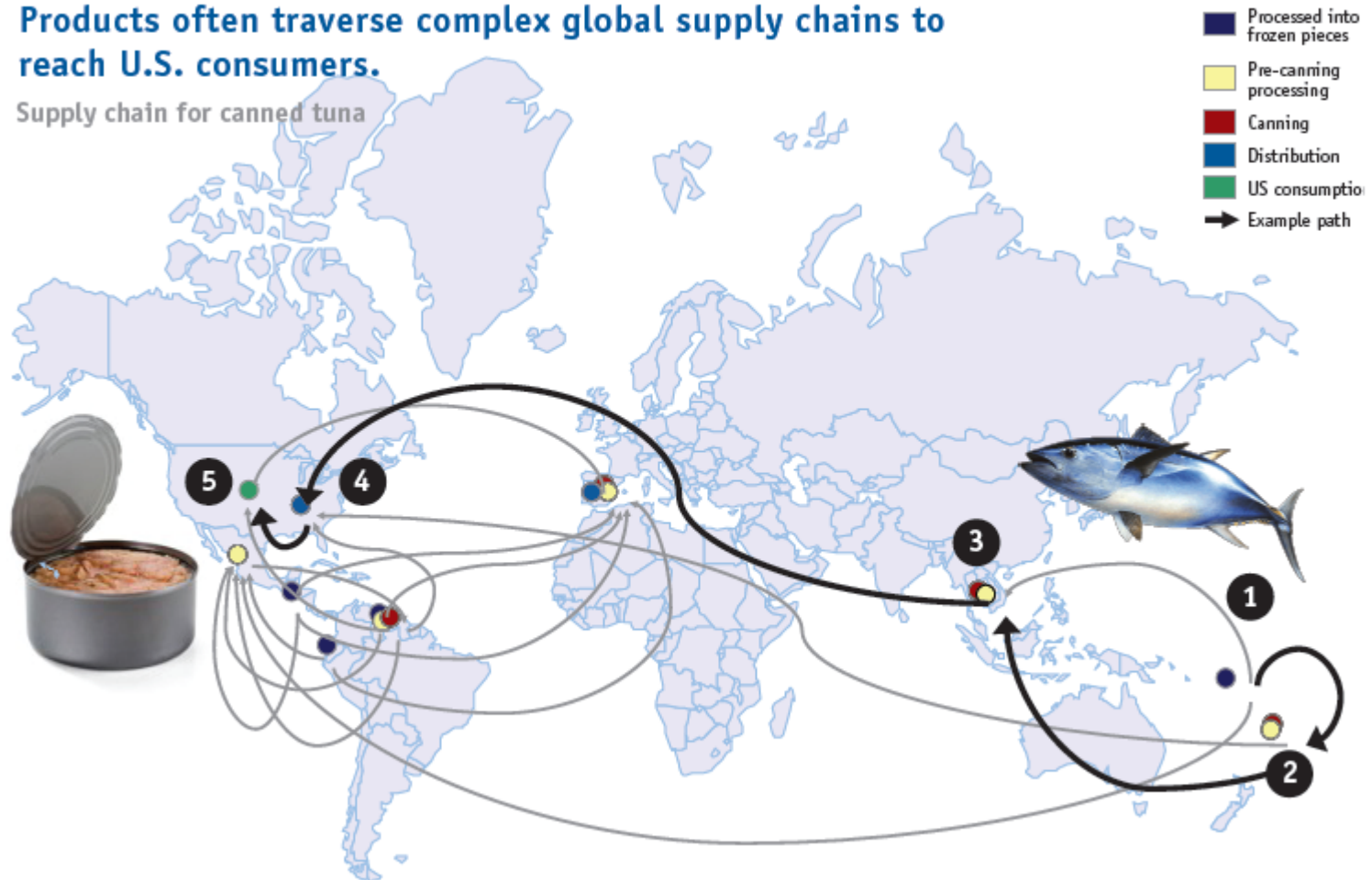


Source: Frost & Sullivan

Illustrative supply chain for canned tuna

Products often traverse complex global supply chains to reach U.S. consumers.

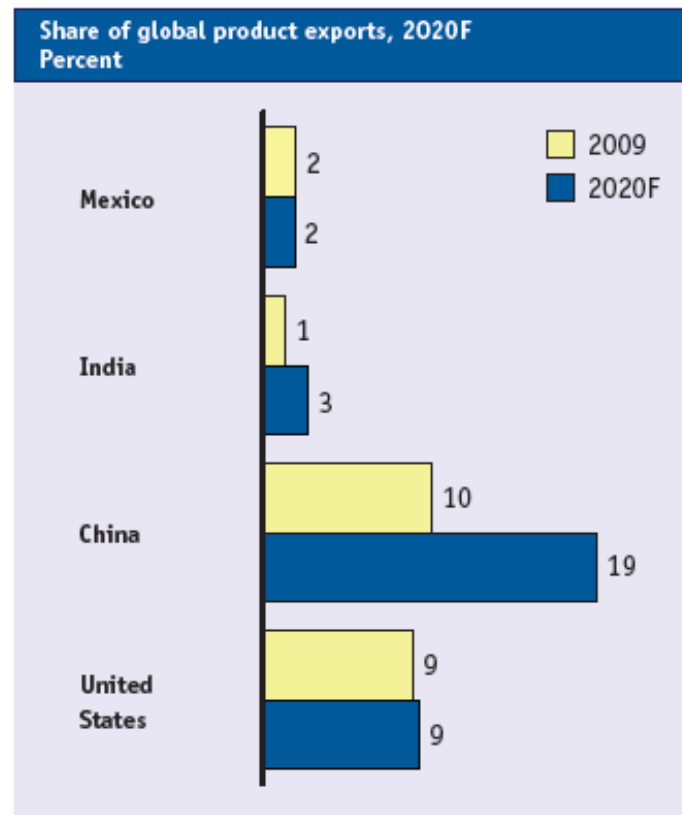
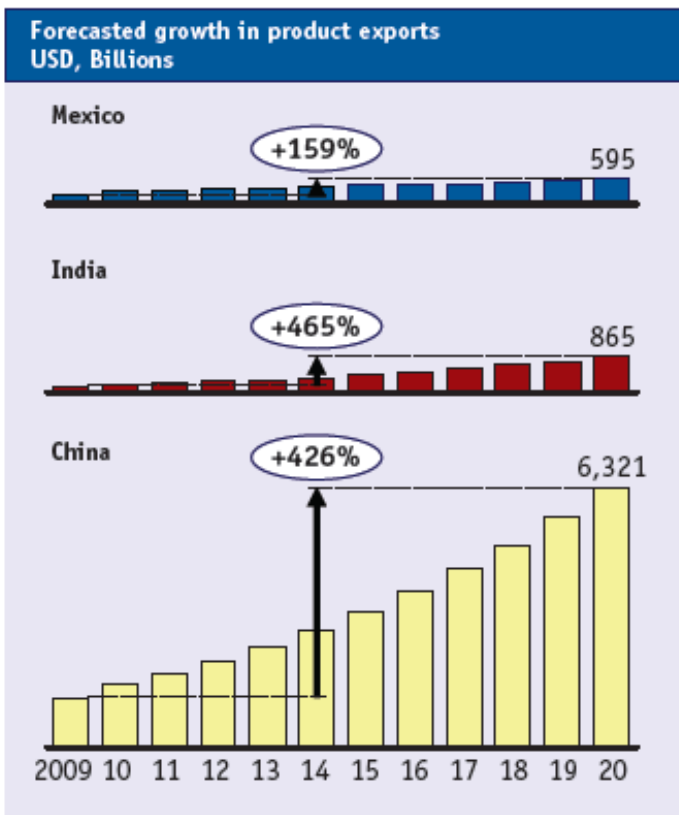
Supply chain for canned tuna



Source: <http://www.ilo.org/public/english/dialogue/sector/techmeet/tmfce07/tmfce-r.pdf>

Increase in total foreign exports from developing countries

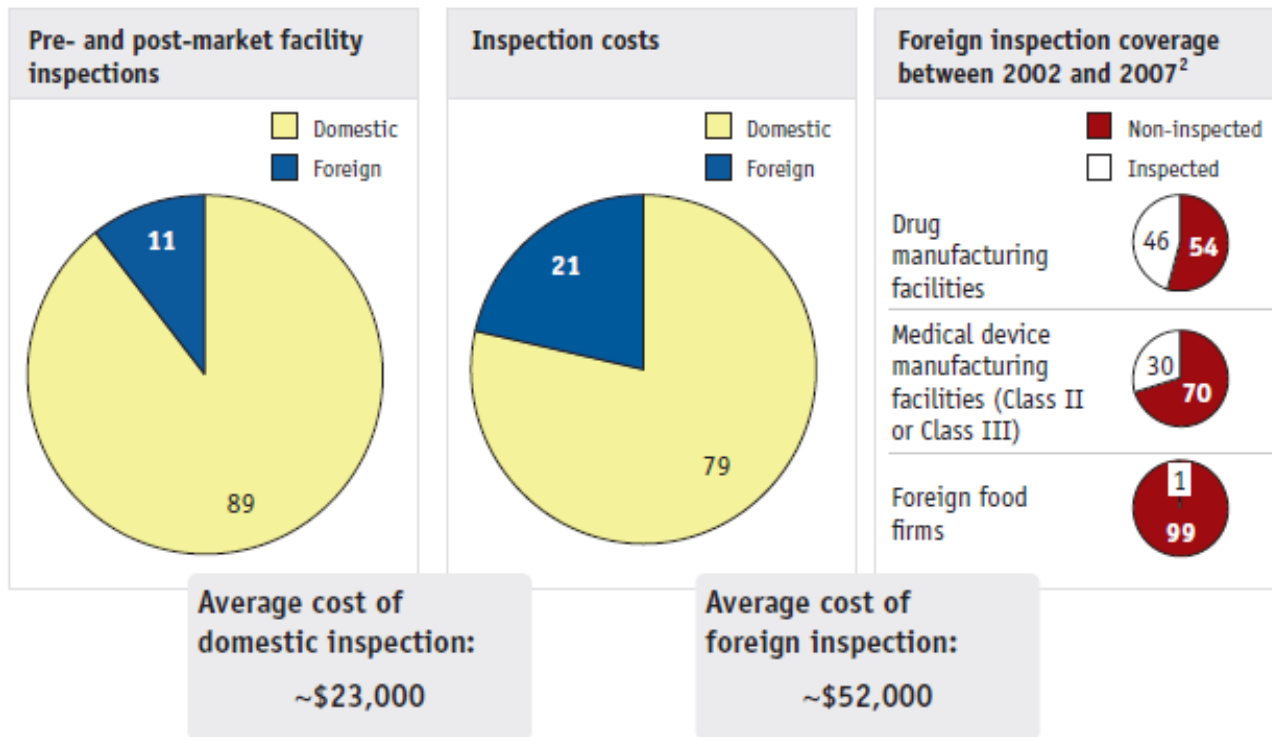
A significant portion of the increase in foreign products will come from developing countries.



Source: McKinsey Global Insights

Cost and coverage of foreign inspections

The average cost of foreign inspections is two times the cost of a domestic inspection but there is a significant gap in foreign inspection coverage.



1 FDA entry reviewers conduct document reviews on nearly all import lines. A subset of those lines that are reviewed are also sampled.

2 Food inspections calculated from 2001 through 2007.

Four core building blocks:

1. FDA, in close partnership with foreign counterparts, will assemble global coalitions of regulators dedicated to building and strengthening the product safety net around the world.
2. With these coalitions, FDA intends to develop a global data information system and network in which regulators worldwide can regularly and proactively share real-time information and resources across markets.
3. FDA will continue to expand its capabilities in intelligence gathering and use, with an increased focus on risk analytics and thoroughly modernized IT capabilities.
4. FDA will effectively allocate agency resources based on risk, leveraging the combined efforts of government, industry and public- and private-sector third parties.

IMPLEMENTING THE PATHWAY TO GLOBAL PRODUCT SAFETY AND QUALITY

- A. Establishing the framework and approach for broader data sharing and use of third parties.

- B. Establishing the Global Coalitions of Regulators
 - Determining the governance structure for the coalitions (roles, mandates, operating model, funding mechanism, etc.)
 - Identifying initial partners, with a goal of expanding over time
 - Conducting discussions with key emerging economies that may not be part of the initial group-
 - Identifying early high priority topics for agreement

Conclusions

- FDA is committed to addressing its challenges and those of the future by implementing a strategy to enhance global product safety and quality.
- The essence of this strategy marries creative international coalitions with cutting-edge investigative tools to continue to provide the consistently high level of safety and quality assurance the public expects – and deserves.
- FDA will continue to partner with other federal agencies, the states, and nations around the world. It will also look to Congress to modernize its antiquated authorities so that FDA's legal tools keep pace with globalization.
- FDA will engage all stakeholders in a process that will unfold over several years. Success will require boldness, creativity, and patience. It will not be easy, but it is imperative – Global supply chains, international trade, foreign sourcing, and terrorism remind us daily that the rest of the world will not stop and wait for regulators to catch up. FDA will engage its international counterparts, industry and stakeholders worldwide to blaze the Pathway to Global Product Safety and Quality.



Analytical Challenges in Product Identification & Adulteration

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September 30th, 2011



Review of Dietary Supplement Regulations



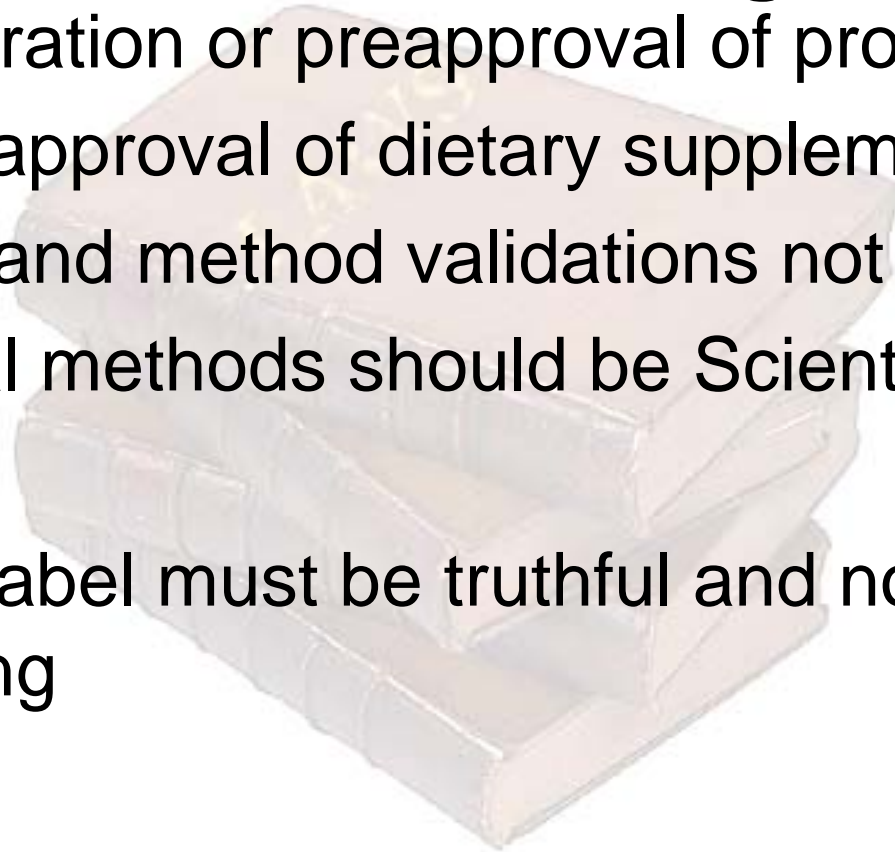
Dietary Supplement Health and Education Act of 1994 (DSHEA)

- dietary supplement or dietary ingredient **manufacturer is responsible** for ensuring that a dietary supplement or ingredient is **safe** before it is marketed
- FDA is responsible for taking action against any **unsafe** dietary supplement product after it reaches the market.
- FDA is responsible to ensure **compliance** of product information, such as labeling, claims, package inserts, and accompanying literature.

DSHEA, cont.

(Differences from Drug GMPs)

- No registration or preapproval of products
- No FDA approval of dietary supplements
- Process and method validations not required
- Analytical methods should be Scientifically Valid
- Product label must be truthful and not misleading



DSHEA, cont.

- FDA Final rule 21 CFR 111 – All foreign and domestic companies that manufacture, package, label or hold dietary supplements including those involved with testing, quality control, and dietary supplement distribution in the U.S., must comply with the Dietary Supplement Current Good Manufacturing Practices (cGMPS) for **quality control**.



- manufacturer, packer, or distributor whose name appears on the label of a dietary supplement marketed in the United States is required to submit to FDA all serious **adverse event reports** associated with use of the dietary supplement in the United States.



FDA Expectations

- Specifications of manufacturing process, components, labels, packaging materials and finished products set by firm must be met and, when not met, conduct material review
- Identity testing of dietary ingredients required
 - C of A from **qualified vendor** is acceptable that includes test methods, limits, lot results with specifications
 - Vendor qualification: confirm C of A through confirmation of tests



FDA Inspections of Dietary Supplements

First inspections began in Summer 2008

FY 2008	7
FY 2009	34
FY 2010**	84
FY 2011(9/13/11)	<u>145</u>
	270+

** 25% official action indicated

General Problem Areas

- Inadequate identity testing
- Failure to establish specifications
- Failure to test products for specifications
- Inadequate records, laboratory testing, Manufacturing Record & Batch Record
- Failure to conduct material reviews
- Lack of adequate corrective action plans





What happens when you go
from this.....



GMP Facilities

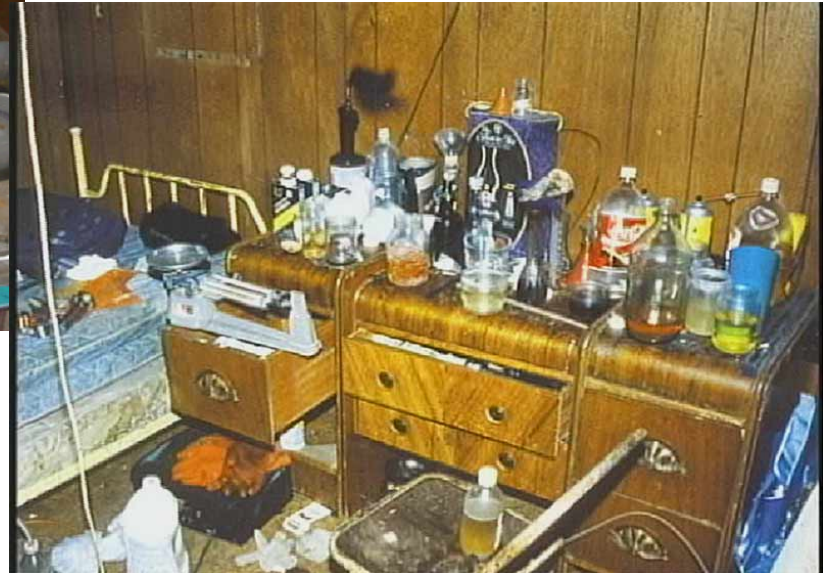


Quality Control





To this.....



Continuing Challenge

- Illegal products claiming to be dietary supplements
- Mostly non-traceable:
 - portable operations – if detected, just move operation to new location and name
 - “kitchen sink” manufacturing – non-industrial, using household appliances at small scale out of garages or homes
 - foreign manufacturing – Internet marketing, so-called “Canadian Pharmacy”

Pharmaceuticals disguised as Dietary Supplements

Common categories of these illegal products

- [Weight loss products](#) – containing sibutramine
- [Body-building products](#) –
- -containing anabolic steroids or steroid analogs
- [Sexual enhancement products](#) –contain the approved drugs Viagra, Cialis, and Levitra or an analog of the active ingredient



Tainted Products Marketed as Dietary Supplements

On Dec. 15, 2010, the Food and Drug Administration (FDA) took new steps aimed at keeping consumers safe from harmful products that are marketed as dietary supplements and that contain undeclared or deceptively labeled ingredients.

FDA has found that these products are often promoted for weight loss, sexual enhancement, and bodybuilding.

The new steps FDA has taken include:

- A letter from Commissioner of Food and Drug Administration Hargrove to the dietary supplement industry emphasizing their legal obligations and responsibility to prevent tainted products from reaching the U.S. market.

- A new rapid public notification system on its website to more quickly warn consumers about tainted products marketed as dietary supplements.
- A mechanism for industry to alert FDA about potentially tainted products and about the firms that make them.

A History of Action

Among the substances found in products that are marketed as dietary supplements and that contain hidden or deceptively labeled ingredients are:

- the active ingredients in FDA-approved drugs or their analogs (closely related drugs)
- other compounds, such as novel synthetic steroids, that do not qualify as dietary ingredients.

When FDA investigations have discovered tainted products marketed as dietary supplements, the agency has issued warning letters and conducted seizures and criminal prosecutions.

FDA has also alerted consumers to hundreds of products with these often deceptively labeled and harmful ingredients, including more than 80 products related to sexual enhancement, more than

70 products marketed for weight loss, and more than 80 products marketed for bodybuilding.

Advice for Consumers

Michael Levy, director of FDA's Division of New Drugs and Labeling Compliance, says labeling of these tainted products may claim that they are "alternatives" to FDA-approved drugs, or "legal" alternatives to anabolic steroids. "Consumers should avoid products marketed as supplements that claim to have effects similar to prescription drugs," Levy says. "Consumers should also be wary of products with labeling only in a foreign language or that are marketed through mass e-mails."

In all, consumers should look out for these potential warning signs of tainted products marketed as dietary supplements:

- Products claiming to be alternatives to FDA-approved drugs or claiming to have effects similar to prescription drugs.
- Products claiming to be a legal alternative to anabolic steroids.
- Products that are marketed primarily in a foreign language or those that are marketed through mass e-mails.
- Sexual enhancement products promising rapid effects such as working in minutes to hours, or long-lasting effects such as 24 hours to 72 hours.
- Products that provide warnings about testing positive in performance enhancement drug tests.

Generally if you are taking or considering



using any product marketed as a dietary supplement, FDA suggests that you:

- check with your health care professional or a registered dietitian on any supplements you may need in addition to your regular diet.
- ask yourself: Does it sound too good to be true?

- Be cautious if the claims for the product seem exaggerated or unrealistic.
- Watch out for extreme claims—for example, "quick and effective," "use all," "cure or cure disease," or "totally safe."
- Be skeptical about anecdotal information from personal "testimonials" about incredible benefits or results obtained from using a product.

ask your health care professional for help distinguishing between reliable and questionable information from

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Diverted Mail Shipments

- International Mail Facilities
- Screening by Customs & Border Patrol
- Pharmaceuticals referred to FDA

Pharmaceuticals in Mail Order Dietary Supplements

- Sibutramine
- Desmethyl- & Bisdesmethyl-sibutramine
- Phenolphthalein
- Nicotine
- Terazosin – bitter melon powder
- Sildenafil (Viagra)
- Sulfoildenafil
- Tadalafil (Cialis)
- Aminotadalafil





Counterfeits

- Counterfeit Cialis – contained Sildenafil (Viagra)
- Counterfeit Xanax – contained melatonin
- Counterfeit ExtenZe – contained sildenafil & tadalafil
- Counterfeit Ativan – Lorazepam



Others

- Nicotine
- Resveratrol
- Epimedium
- Yohimbe alkaloids
- ECGC (green tea)
- Arginine



Other concerns

- Toxic Metals (Pb, Se, Cr, Cd)
- Weight loss
- Steroids
- Erectile dysfunction drugs/analogues
- Truthful labeling

Conclusions

- Ingredient identity and product labeling continuing to be problems – adulteration, counterfeiting continuing
- **FDA Foods and Veterinary Medicine Program Strategic Plan 2012 – 2016:** Continue executing a science-based regulatory program that fully implements the Dietary Supplement Health and Education Act of 1994, and other relevant statutes and regulations. (September, 2011)



FDA Foods and Veterinary Medicine Program Strategic Plan 2012 – 2016

Program Goal 5 :

Improve the safety of dietary supplement products and the supply chain

Objective #5.3:

- Develop and implement strategic, risk-based, and innovative compliance and regulatory strategies to address dietary supplement safety issues.
- Advance post-market surveillance systems in the regulation of dietary supplements.
- Advance pre-market oversight of dietary supplements by finalizing and implementing new dietary ingredient (NDI) guidance.