Proposal of ICH Harmonisation on Quality Management

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"Pharmaceutical GMP's for the 21st Century": FDA's New Initiative on Drug Product Quality

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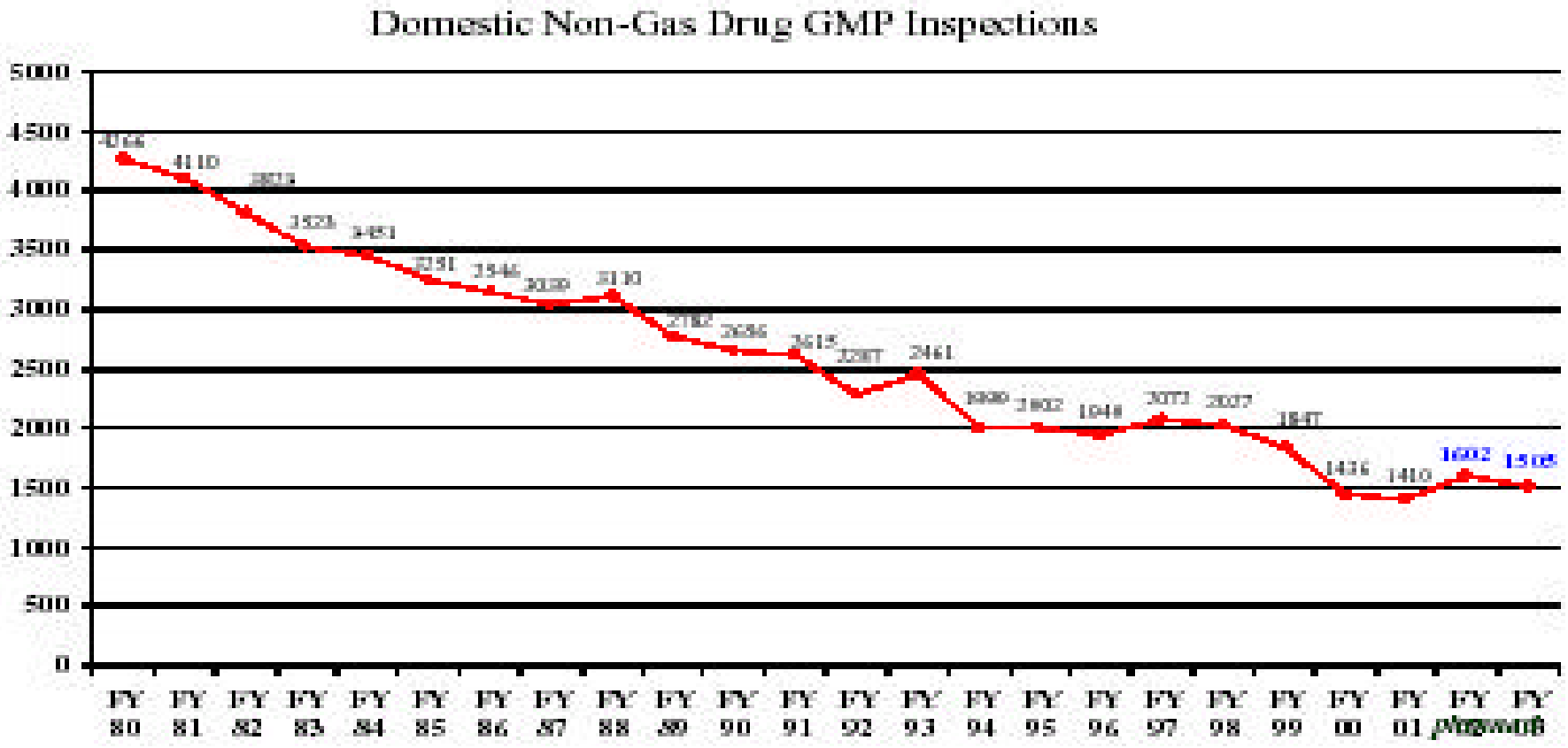
March 3, 2003

Background: Significant changes in pharmaceutical environment have occurred in last several decades

- More approved medicines - greater role in healthcare
- Advances in pharmaceutical sciences & manufacturing technologies
- Advances in science & management of quality
- Application of biotechnology
- Globalization of industry

Background: FDA's Physical Presence has Decreased due to Resource Constraints



Major Themes and Principles

- **Risk-based orientation**
  - Put resources against highest risks
  - Requirements commensurate with risk
- **Science-based regulation**
  - Scientific risk assessments
  - Recognize & facilitate scientific and technological advances

CGMP Compliance in the 21st Century

Arden House
January 25 -30, 2004

Joseph C. Famulare

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What are the Risk Management Goals of the CGMP Initiative?

- Implement systematic risk management approaches to all aspects of drug quality regulation, including:
  - Standard-setting;
  - Review;
  - Inspection; and
  - Regulatory action decision making

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Applying Risk Management to Drug Quality Regulation

- Industry can demonstrate to FDA that reduced regulatory scrutiny is justified by the science/data
- Cannot individually examine GMP requirements in isolation from the system of which they are a part
  - The whole is greater than the sum of its parts
  - Indirect risks to drug quality cannot be ignored

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Risk Management and Resource Allocation (cont'd)

- Product-type factors
  - What are the intrinsic properties of products such that their deficiencies in quality would have more adverse public health impact than others?
    - Narrow therapeutic range
    - sterile
    - Rx vs. OTC
    - Route of administration
- Mining recall data can help weight product factors (e.g., product or dosage form associated with prevalence of serious recalls?)

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Risk Management and Resource Allocation (cont'd)

- Facility-type factors
  - Are some manufacturers or particular manufacturing facilities more likely to produce a product with quality problems?
    - Effectiveness of quality systems and process capability
    - Inspectional record and compliance history
    - Exposure: volume produced at facility
      - Product sales volume
      - Special/sensitive populations
    - Other characteristics?
      - New Registrants?
      - Macher and Nickerson study will help identify

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Proposal made at ICH Washington Meeting

"Quality Management: Utilization of science and risk-based systems to enable post-approval change and improvement".

The complexity in implementation of post-approval changes has been identified as one of **the biggest areas of "pain"** currently experienced by industry, primarily because the regulators regulate locally, while industry operates globally.

Frequently, highly dissimilar data, regulatory reporting and inspection requirements are necessary to satisfy the different regulatory systems for evaluation and approval of changes around the world.

A more effective change management system would encourage companies to make desirable changes and improvements more efficiently and in a more timely manner.

Quality Management System

Demonstration of self-control through robust Change Management System and Process Review System of Industry as well as improved Industry's accountability for post approval changes and improvements are crucial not only to attain an imminent effect of reduced review time, but also to realize ultimate goal of reduced necessity for post approval change supplements.

Quality Management System (cont'd)

For Industry: Adoption of cutting-edge technologies and an implementation of improvement to the products, including existing products, can be fostered, and submission of post approval change supplement to 3 regions can be made efficient because of enabled use of common data. As the result of efficient manufacturing operation as well as effective utilization of resources, economic loss such as rejects and reworks which currently occur due to the postponed improvements can be alleviated.

For Agency: Review / Inspection burden can be reduced providing the rationale to apply flexibly post approval change regulations, based upon risk management principle, to the firms with well implemented Quality Management System and favorable compliance track record.

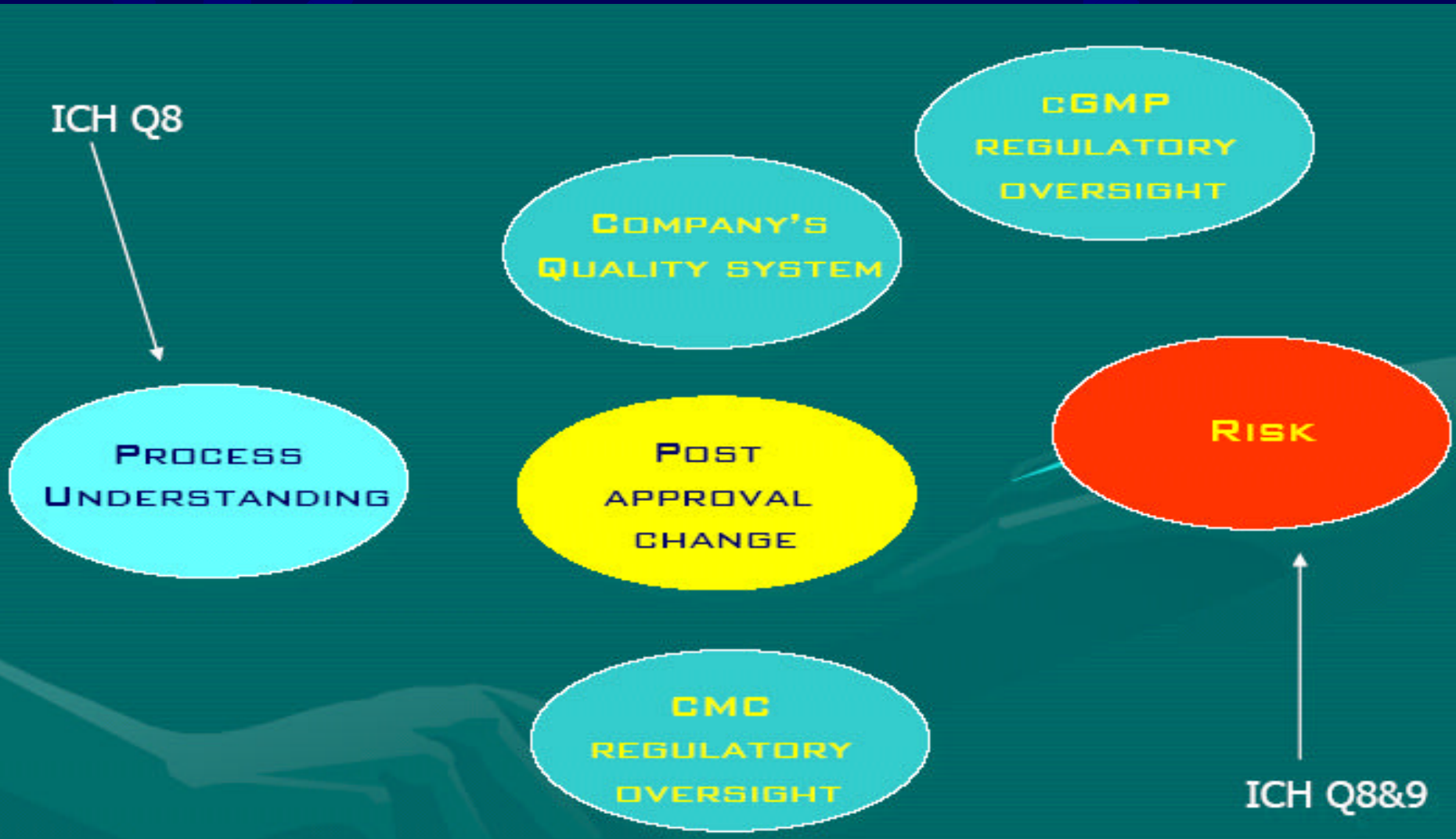
Conclusion of ICH Washington Meeting

The SC agreed, in principle, that this topic can be progressed further as a new ICH topic and to proceed with the development of a Concept Paper and a Business Plan by a six-party EWG.

Due to resources issues, progress with this topic will be deferred until the moment that Q8 and Q9 have reached *Step 2*.

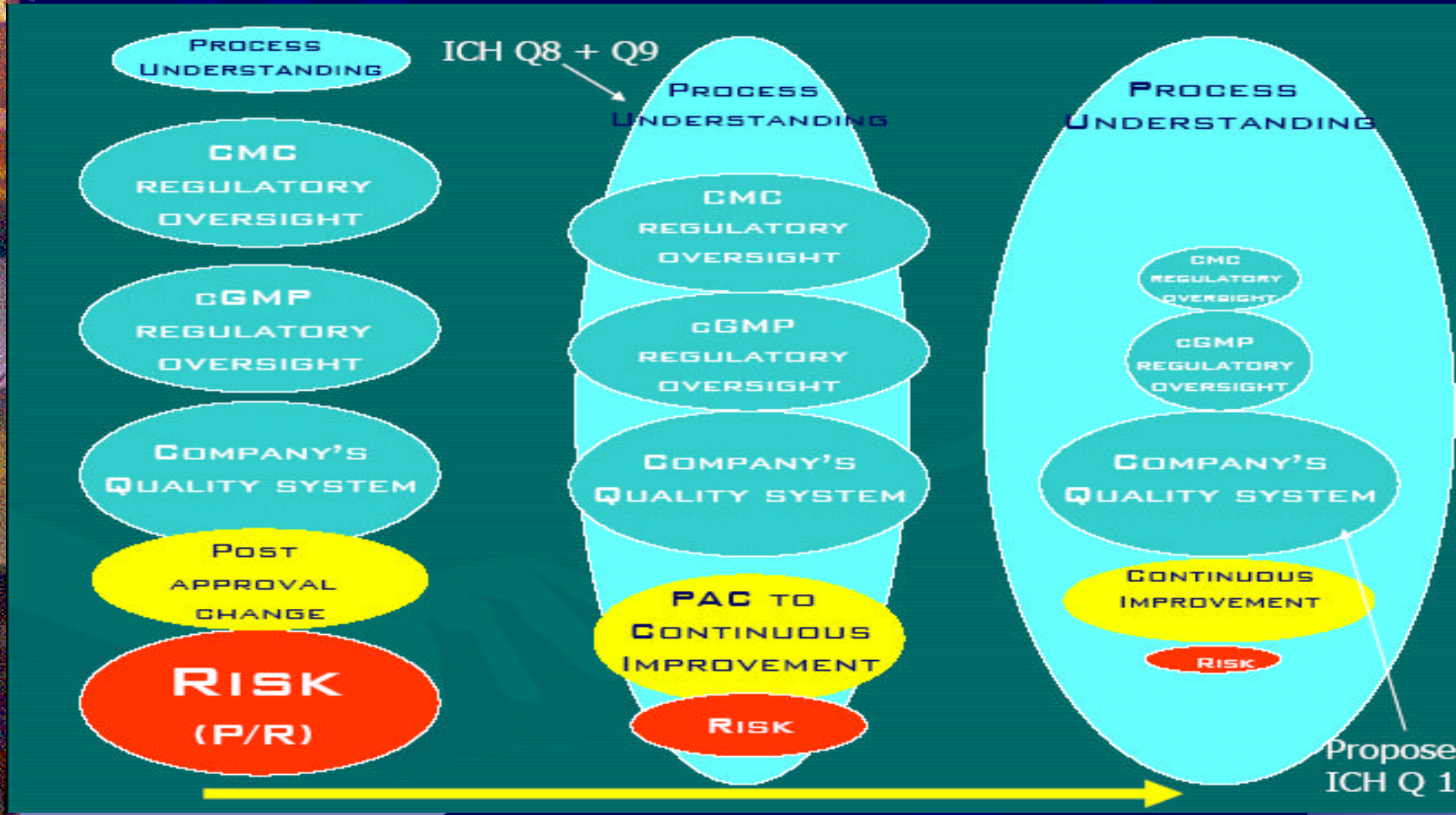
(No QS discussion was made at Yokohama Meeting. Discussion will be re-opened from Brussels Meeting in the next spring.)

Elements relevant to the Quality



Ajaz S. Hussain at FDA Pharmaceutical Inspectorate August 5, 2004

Interrelation of Q8、Q9 and Q10



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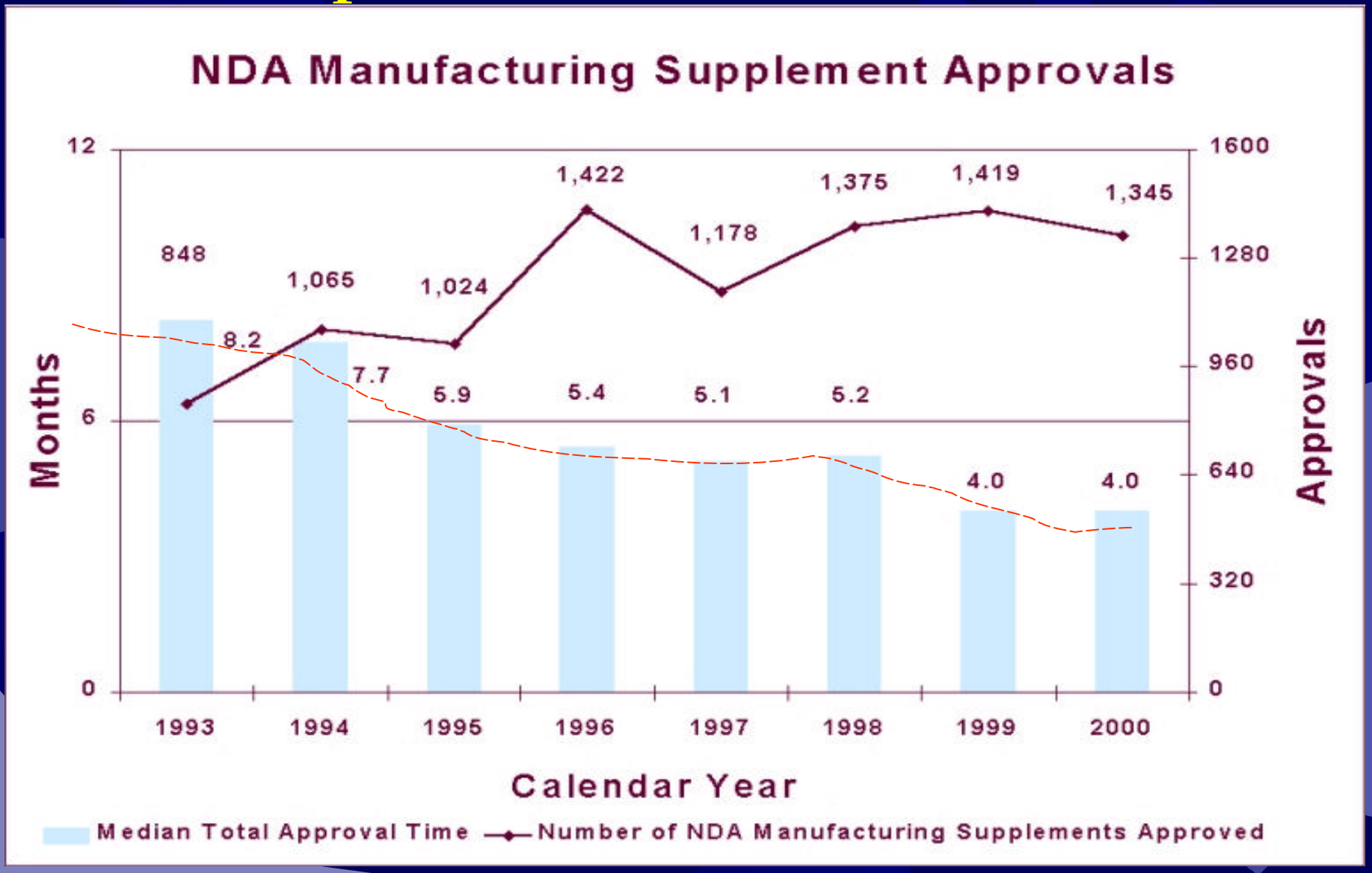
CDER Report to the Nation



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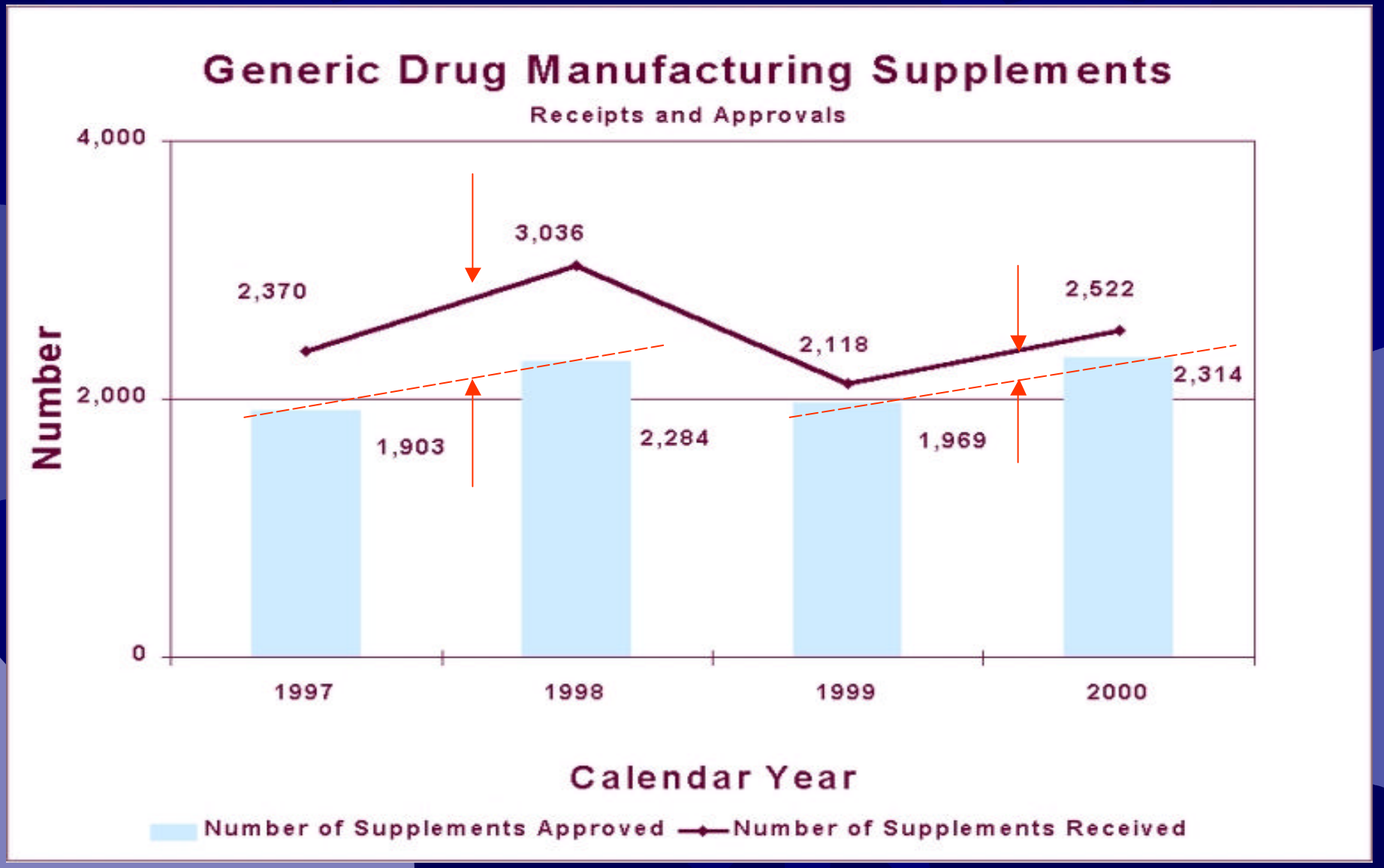
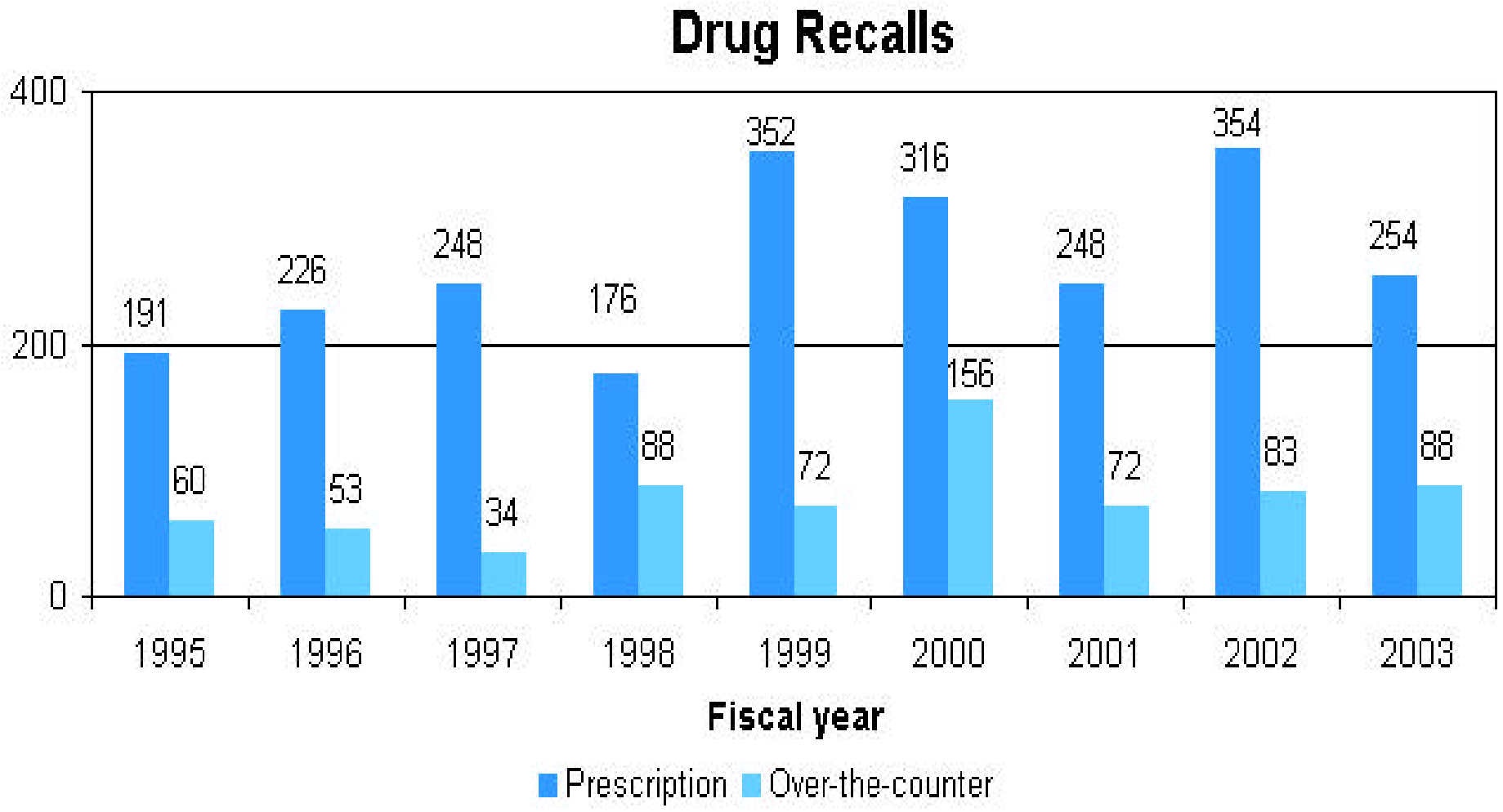
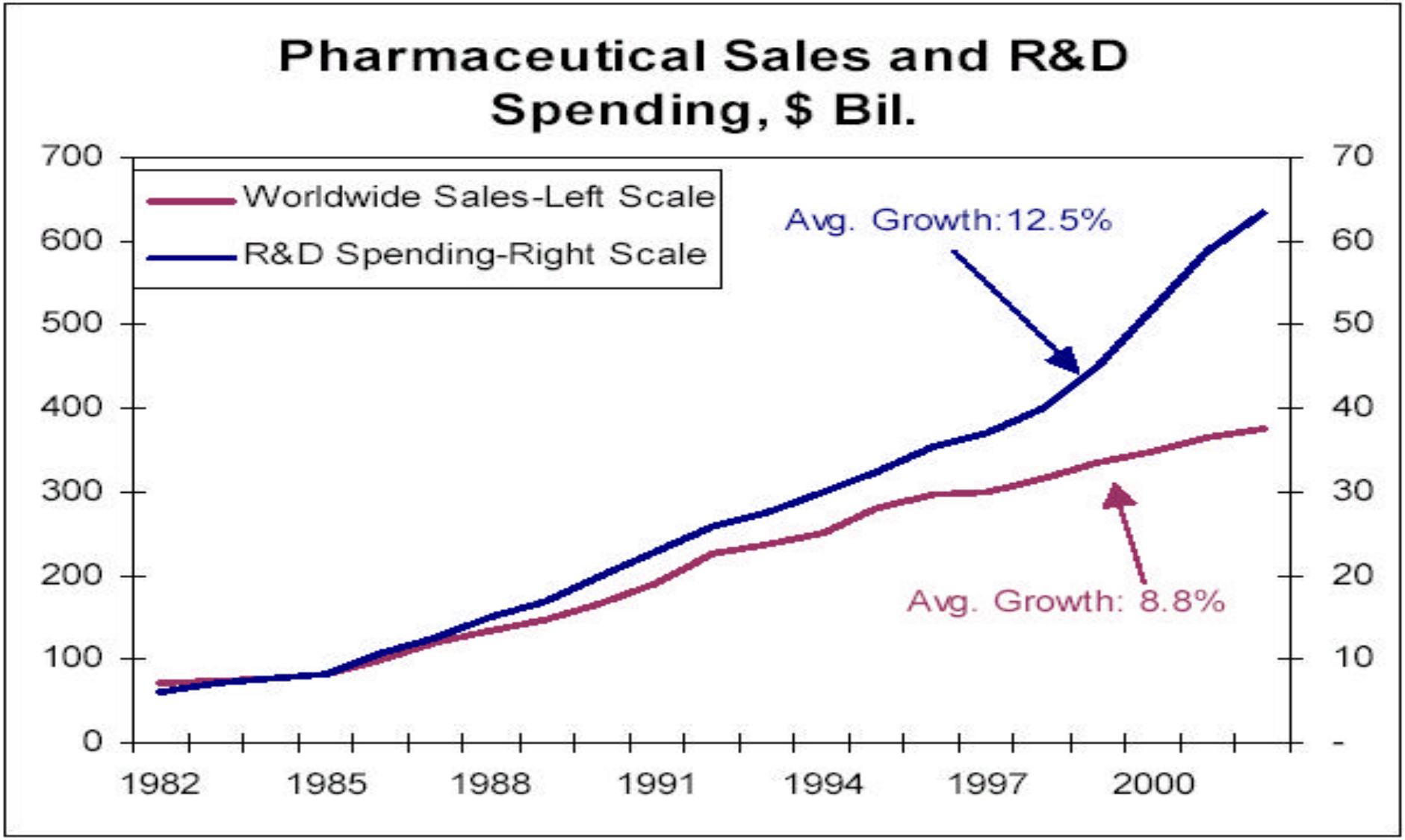


Recalls in USA



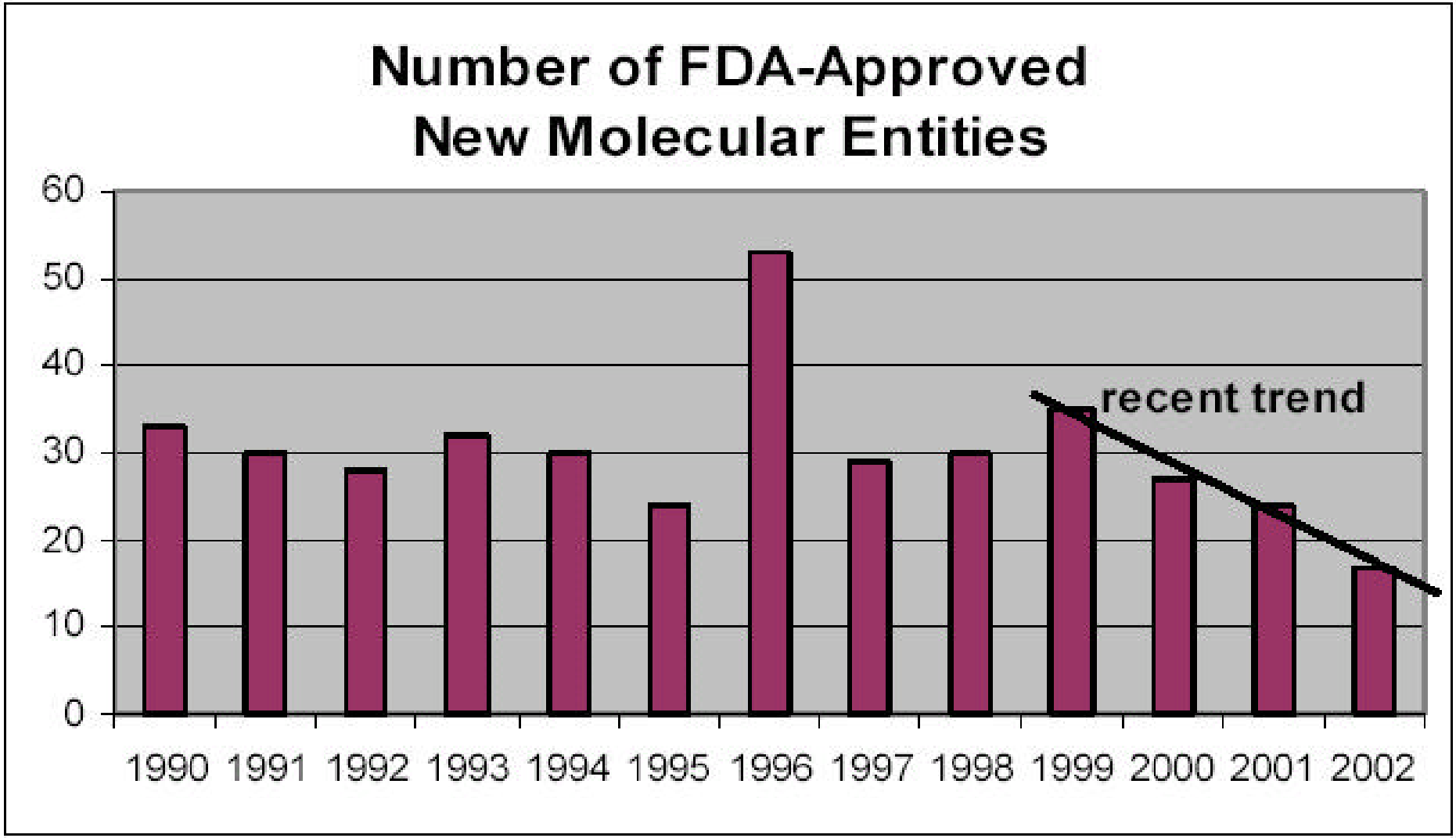
CDER 2003 Report to the Nation

New Drug Development Cost in USA



Source: *Financial Times*, PhRMA

New Drug Approvals in USA



Source: FDA

Background of Proposal

NDA submissions : ca. 200 / year Approvable NDAs : 20-30 / year
NDA/ANDA supplement submissions : ca. 4,000 / year (in USA)

Reduced post approval change supplements review time for existing products and efficient resource use are needed for streamlining of NDA review process.

Resources incurred by Industry for submission of post approval change supplements in 3 regions are enormous, too.

Because of different review time before approval in 3 regions, Industry tends to postpone implementation of quality improvement until all 3 regions approve supplements, placing much emphasis on efficiency.

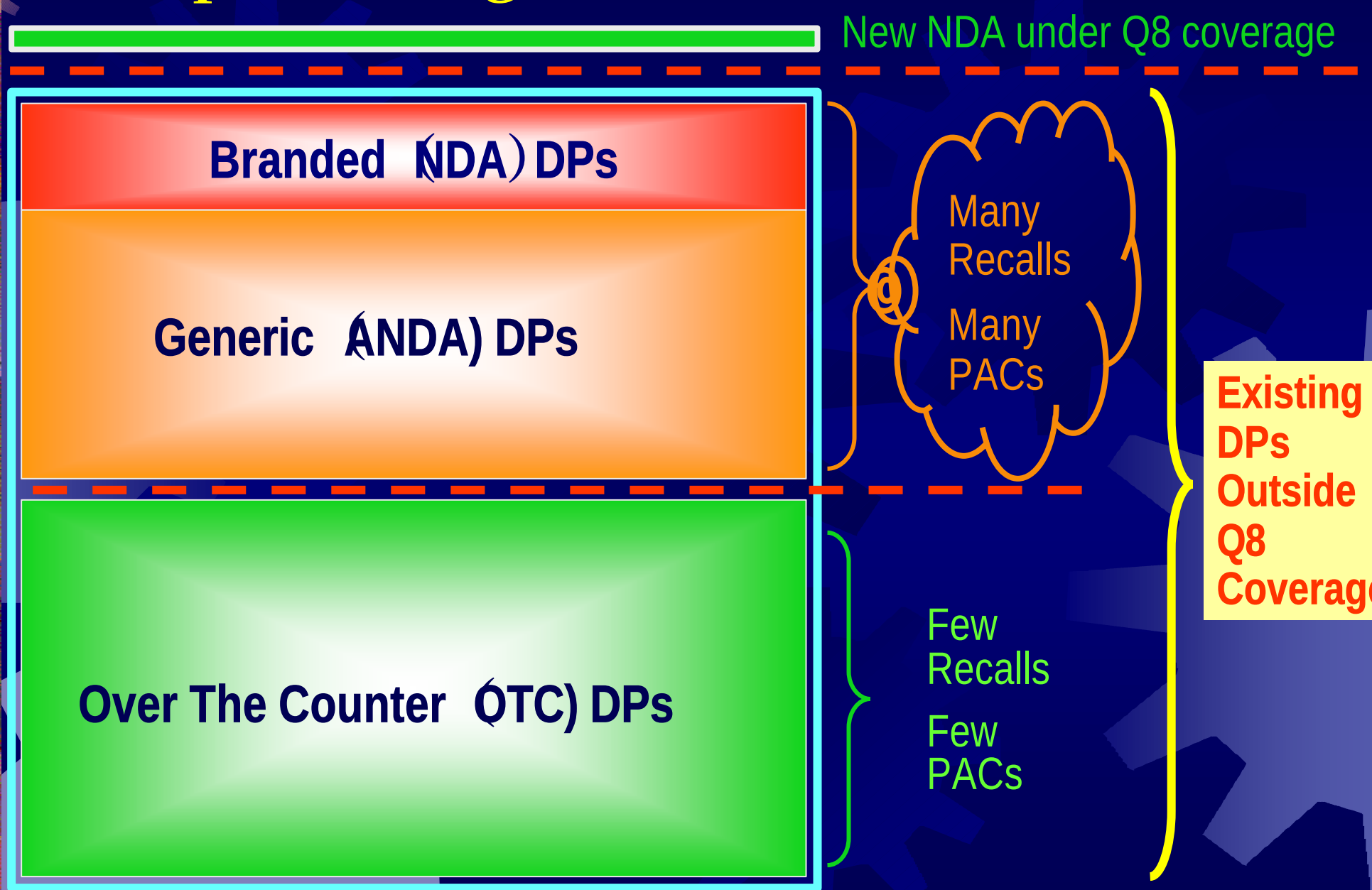
Potentially compromised situation of Patient's benefit.

Reduction in newly approvable products, while ever increasing development costs, Industry has to cope with the cost from existing product mix.

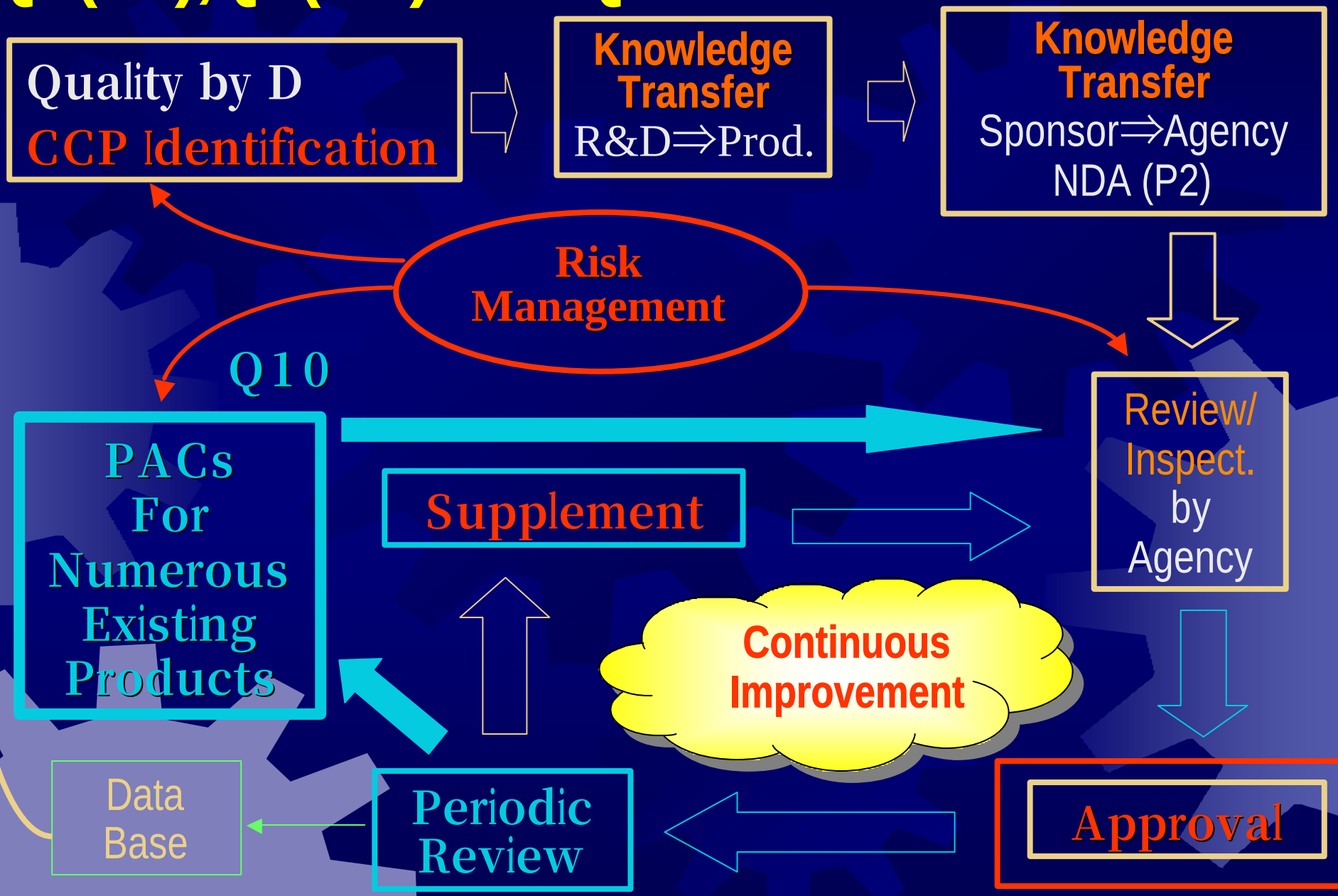
Increase in recall suggests that continuous improvement is also needed for existing products which are not covered by Q8.

Ultimate suppression in numbers of NDA/ANDA supplement is important.

Groups of Drug Products



Q8(PD),Q9(RM) and Q10



Risk-Based Approach Final Report FDA 2004

ONDC Pharmaceutical Quality Assessment System

The Office of New Drug Chemistry (ONDC) within CDER has developed and is implementing a new risk-based pharmaceutical quality assessment system **to replace its current CMC review process.**

This new system should **reduce the need to submit manufacturing supplements and increase first-cycle approval of new drug applications**, thereby making drug products available to patients in a timelier manner.

Risk-Based Approach Final Report FDA 2004

Risk-Based Approaches

The risk-based approach will be applied to the review, compliance, and inspectional components of FDA regulation. The intensity of FDA oversight needed will be related to several factors, including the degree of a firm's product and process understanding and the robustness of the quality system.

Process changes with critical variables that have not been sufficiently defined (e.g., processes for many older products) may require the submission of additional data or comparability protocols.

Other considerations, such as public health impact and the compliance status or compliance history of the manufacturer**,** will continue to influence the intensity of FDA oversight.

The frequency and/or scope of inspections will be reduced for firms that FDA determines have acquired sufficient process understanding and have succeeded in implementing effective quality systems approaches.

Risk-Based Approach Final Report FDA 2004

Risk-Based Approaches (cont'd)

FDA hopes that this approach will create **positive incentives for other firms to implement effective quality systems** at their manufacturing sites.

The Agency will continue to apply risk-based principles to the product quality review process (i.e., the product quality aspects of the investigational new drug (**IND**); **preapproval** chemistry, manufacturing, and controls (**CMC**); and **postapproval supplement review** processes).

The new assessment system has the potential to reduce the regulatory burden in proportion to the manufacturer' efforts to achieve continuous improvement and manufacturing process optimization.

FDA's regulatory strategies will be **based on the degree to which an application reflects a manufacturer's understanding of manufacturing process, process control, and quality systems.**

Cooperation with International Regulatory Partners

While Q8 and Q9 continue to progress, **ICH will begin to pursue Q10**, a document that will cover life-cycle management for process and system control. Q10 is **intended to promote post-approval improvements to manufacturing processes to address current pressures felt by both regulatory authorities and industry with respect to post-approval changes.**

Risk-Based Approach Final Report FDA 2004

Cooperation with International Regulatory Partners (cont'd)

For the regulatory authority, there is **a need to reduce the burden of supplement review and provide review oversight to only certain changes** using a risk basis.

For manufacturers, **the regulatory process should not delay implementation of improvements in manufacturing processes once a product has been approved** for marketing.

To further advance its collaboration with international partners and strengthen its oversight of non-U.S. drug manufacturing sites that produce FDA-approved pharmaceuticals for Americans, FDA will be seeking membership in the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

Risk-Based Quality System and Q10