Revisions to 21 *CFR* 314.70

Supplements and Other Changes to an Approved Application

PhRMA Perspective

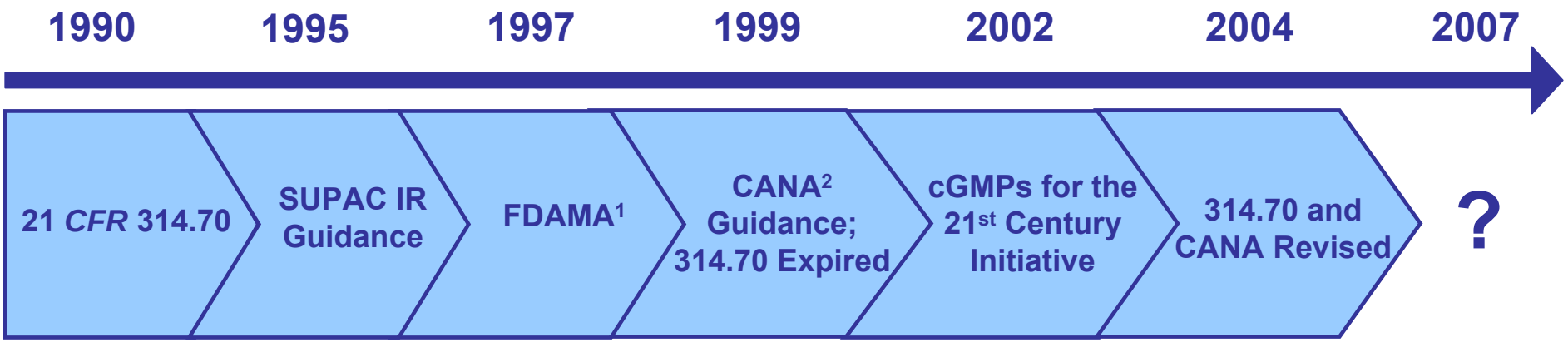
FDA Public Meeting – 7 Feb 2007

Revisions to 21 *CFR* 314.70 - Outline

- Historical Perspective
- Recommendations
- Concepts
- Global Alignment
- Parallel Activities
- Summary

Revisions to 21 *CFR* 314.70 - Historical Perspective

CMC Post-Approval Changes



1. Food and Drug Administration Modernization Act of 1997
2. Guidance for Industry: Changes to an Approved NDA or ANDA

Revisions to 21 *CFR* 314.70 - Historical Perspective

PDUFA Metrics- Manufacturing Supplements

Fiscal Year	1999[1]	2000[2]	2001[2]	2002[2]	2003[2]	2004[2]
Total	1459	1438	1474	1759	1696	1616
Prior Approval	900	684	579	602	618	539
Changes Being Effected	559	754	895	1157	1078	1077
Percentage						
Prior Approval	62	48	39	34	36	33
Changes Being Effected	38	52	61	66	64	67

1. FY 2000 Performance Report to Congress
2. FY 2004 Performance Report to Congress

PhRMA supports revision of 21 *CFR* 314.70 if :

- Reduces the number of manufacturing supplements
  - Many current supplements are non-value added
  - Drains resources from both industry and FDA
- Addresses “conventional” submissions
  - Rewards application of prior knowledge (product history & track record) and risk-based approaches
  - Acknowledges that full implementation of QbD will take years
- Establishes the foundation for QbD
  - QbD will be less complex and easier to accomplish
  - Demonstrates the longer-term reward of investing in manufacturing science of unit operations

Revisions to 21 *CFR* 314.70 - Recommendations

- Reduce or remove “Reporting Categories” that are not necessary
  - Reduce the number of, or eliminate Changes Being Effected Supplements (0 and 30 Day)
- Remove “Change Categories” considered low risk
  - Eliminate site-change supplements for packaging and testing
  - Provide for adoption of equivalent or superior analytical methods without a supplement
- Revise statements not consistent with risk-based approach
  - Eliminate phrases such as “that may affect” (21 *CFR* 314.70 b.2.iv)

Revisions to 21 *CFR* 314.70 - Concepts

- Re-evaluate format and content of NDA Annual Reports
  - Streamline the requirements by including only an Index of Changes with supporting data available upon FDA inspection
  - Explore integration of NDA Annual Report and Annual Product Review

NDA Annual Report & Annual Product Review

Regulation	314.70	211
FDA Branch	Pharmaceutical Science	Compliance
Interval	Annual	Annual
Batch History	No	Yes
Summary of Changes	Yes	Yes
Stability Profile	Yes	Yes
Tool for Continuous Improvement	No	Yes

Revisions to 21 *CFR* 314.70 – Concepts (cont.)

- Re-evaluate format and content of NDA Annual Reports
  - Streamline the requirements by including only an Index of Changes with supporting data available upon FDA inspection
  - Explore integration of NDA Annual Report and Annual Product Review

- Borrow from experience of FDA Office of Compliance
  - "Risk-Based Method for Prioritizing CGMP Inspection of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model" (Sept 2004)

Revisions to 21 *CFR* 314.70 – Concepts (cont.)

- Re-evaluate format and content of NDA Annual Reports
  - Streamline the requirements by including only an Index of Changes with supporting data available upon FDA inspection
  - Explore integration of NDA Annual Report and Annual Product Review
- Borrow from experience of FDA Office of Compliance
  - "Risk-Based Method for Prioritizing CGMP Inspection of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model" (Sept 2004)
- Apply experience of FDA Office of Post-Marketing Evaluation
  - Complete data-mining of risk-based review practices

FDA Review Strategy – A Risk Based Approach

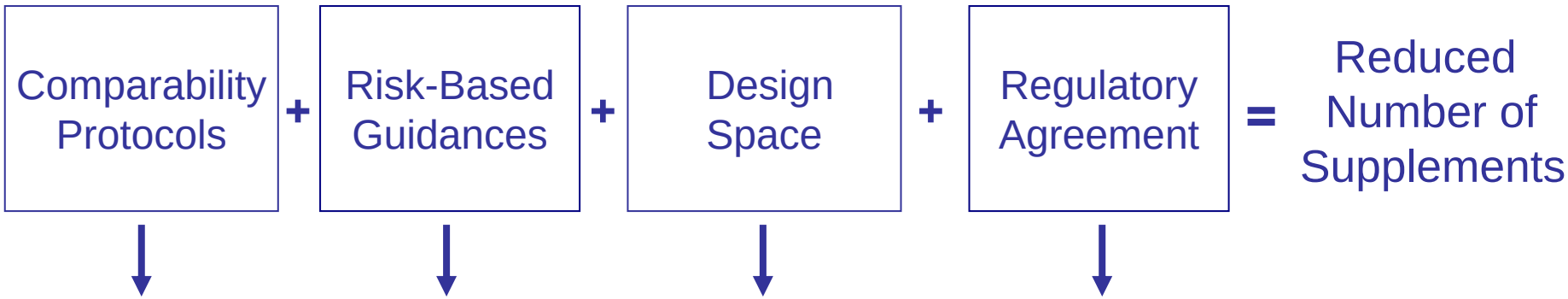
"We wish to advise you that changes such as these should not be submitted as a supplement. Such changes should be described in the annual report. Therefore it will not be accepted as a supplement but will be retained in the files. Please refer to this submission in your next annual report." – *excerpt from FDA Acknowledgement Letter*

FDA determined that change was low risk – no supplement needed

Revisions to 21 *CFR* 314.70 - Concepts (cont.)

- Consider a different approach to classifying manufacturing sites
  - Based on Quality System rather than dosage forms
  - Empirical Experience / Dosage Form → Prior Knowledge & Risk-based Approaches / Quality Systems
- Utilize research outcomes
  - e.g., PQRI – Container/Closure Group
    - Evaluate packaging changes based on moisture-vapor transmission rate per unit rather than stability data
- Continue to change emphasis of Guidance Documents from prescriptive to conceptual
  - SUPAC IR Guidance → PAT Guidance
  - Retain current Guidance Documents that serve conventional submissions
- Focus on the conventional but lay the groundwork for QbD

Revisions to 21 *CFR* 314.70
Laying the Foundation for QbD



Establishes agreed criteria for changes

Reduces number of changes required to be reported based on risk assessment

Utilizes QbD principles & tools (PAT, DoE)

Identifies life-cycle commitments based on QbD

Revisions to 21 *CFR* 314.70 – Global Alignment

Global Manufacturing Site

US
(sNDA)

EU
(Variation)

Canada
(sNDS)

Japan
(sJNDA)

Number of Filings: Variable

Time to Approval: Weeks to Years

Global regulatory environment presents a hurdle to continuous improvement & technical innovation

Revisions to 21 *CFR* 314.70 – Global Alignment

EFPIA Position on Variations

- Promotes a risk and science-based approach
- Builds upon the concepts of ICH Q8, Q9, and Q10
- Should encourage and enable innovation and continuous improvement in manufacturing processes
- Based on 2 variation categories:
  - Minor changes which require only a notification
    - either as immediate notification or annual reportable
  - Major changes requiring prior assessment
- Introduces the concept of a Regulatory Agreement

Timely opportunity to work toward an aligned US and EU regulatory system for CMC post-approval changes

Revisions to 21 *CFR* 314.70 – Parallel Activities

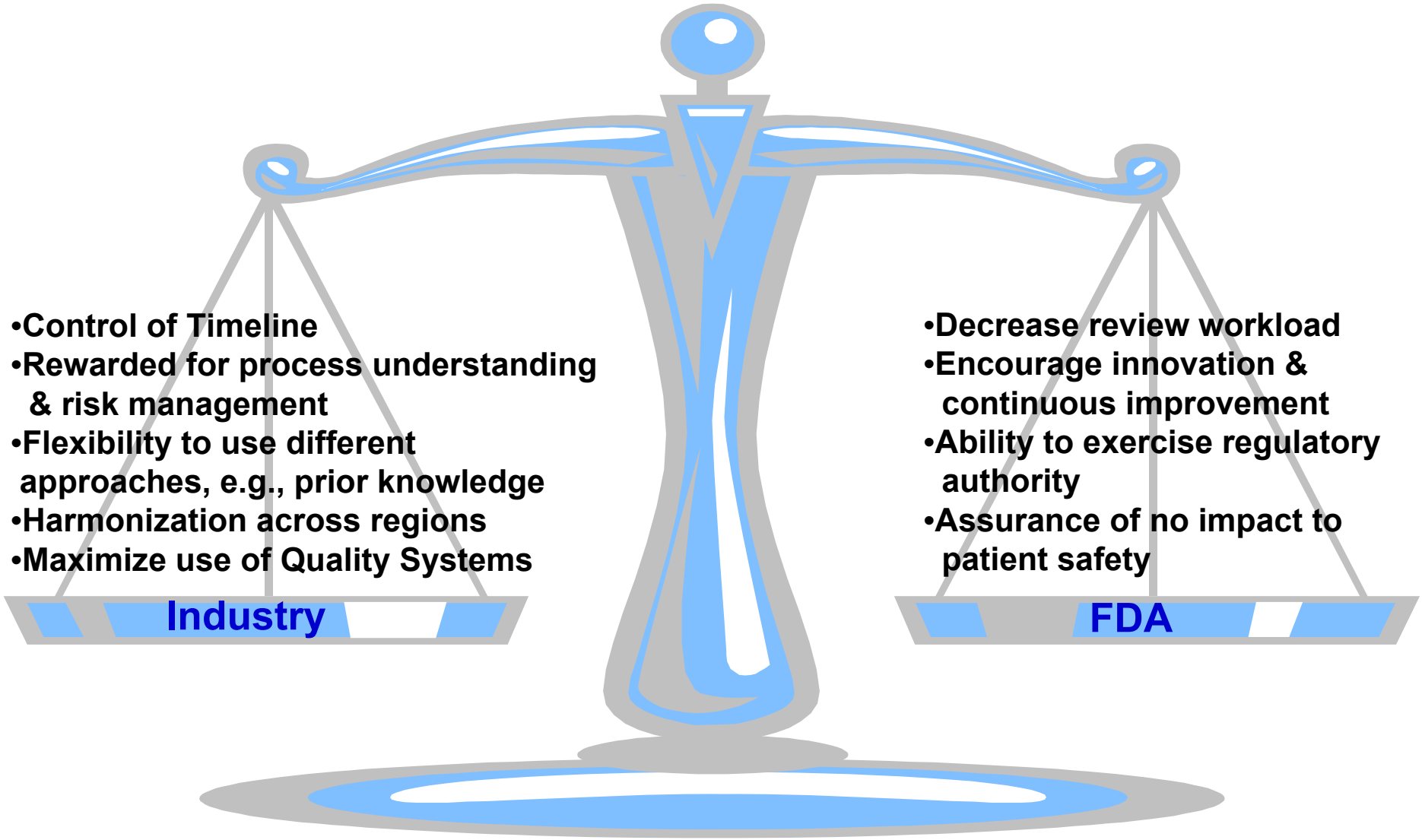
- CMC Pilot Program
- Collaborative Research Agreement – FDA & Conformia
- ICH Q10 and ICH Q8R1
- Additional Guidance Documents, e.g. Comparability Protocols
- Data-mining & track record, FDA Office of Post-Marketing Evaluation
- Risk-based method for prioritizing cGMP inspections, FDA Office of Compliance

Revise 21 *CFR* 314.70 ? - Summary

Worthy of consideration if:

- Decreases the number of manufacturing supplements
- Focuses on conventional submissions
- Rewards application of prior knowledge and risk analysis conducted within a modern Quality System
- Establishes the foundation for QbD
- Builds on ongoing parallel activities, e.g., CMC Pilot Program
- Progresses a step change toward “Achieving the Balance”

Regulating CMC Post-Approval Changes – Achieving the Balance



Acknowledgements

- PhRMA Pharmaceutical Quality Steering Committee
- PhRMA Technical Leadership Committee