Predicting

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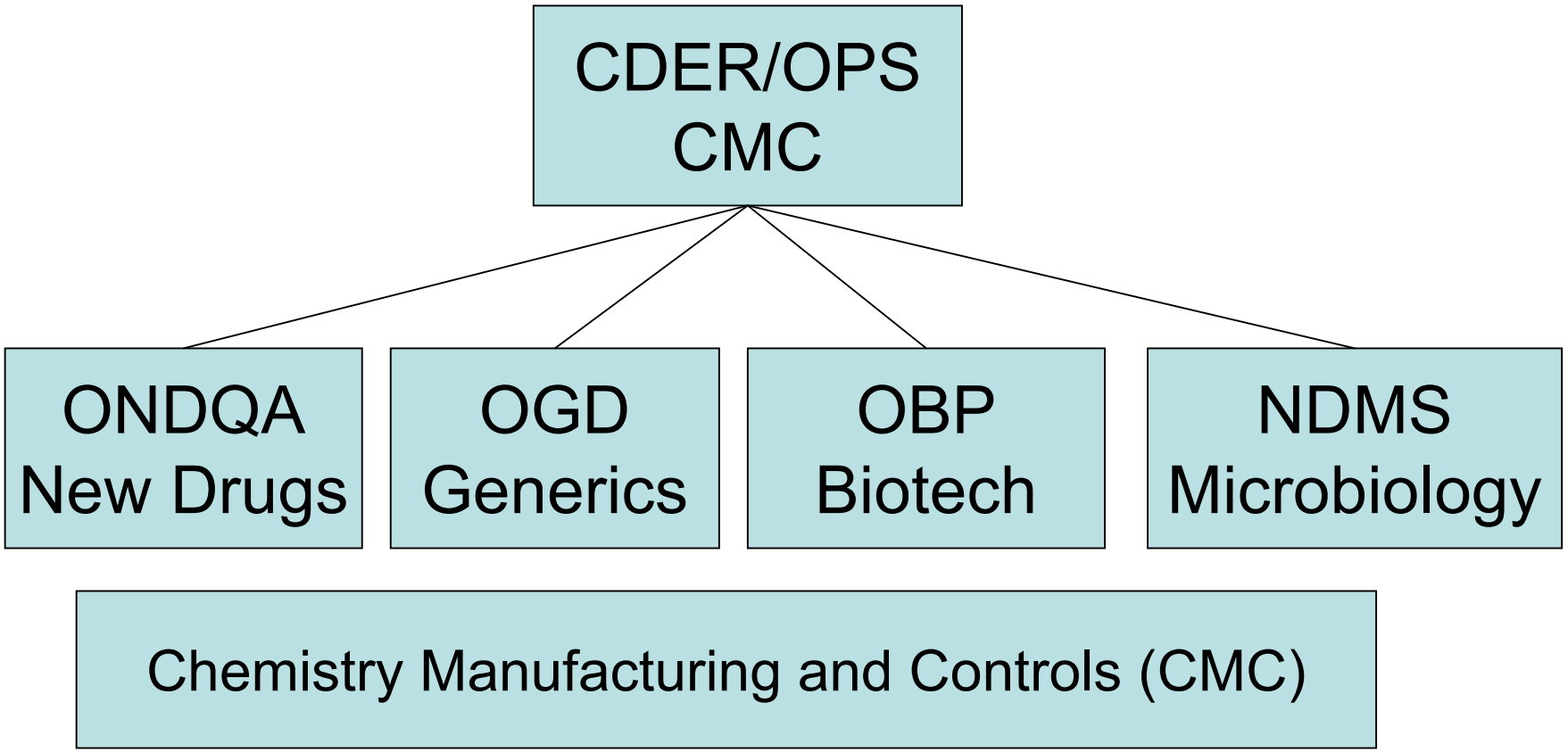

What have we heard?

- Call for change to our practice
- Application of risk analysis and QbD principles to technical problems
  - Analysis; API; Product Manufacturing
- Shewart Cycle still works
  - Plan; Do; Check; Act
  - QbD is Our 6σ
  - Measurement; Variability;

What have we heard?

- Focus specification on the patient need
- Control the raw material properties!
- I can do it, so can you!
  - Yes we can!
- No regulator is holding us back
  - Quite the contrary
- We know the difficulties
- We have the tools
- Others have gone before us

Is this a requirement?

- No, not yet…
  - But survival is also not required
- We have plenty of advice…
  - But nobody will tell us what to do

Future Direction

- Continued convergence
  - Previously separated concepts evolve to the same solutions
  - Accountability for decisions drives us toward more common and defensible procedures

Opportunities to Shape the Future

- Standards development requires your help
- Application of statistical tools to the problems of batch release is inevitable
- Get involved

SDO Code of Practice

- Open
  - All interested parties are invited to participate
  - Transparent proceedings
- Balanced
  - No sector can dominate (user, producer, government)
- Due Process
  - All positions are considered
  - Appeal process is available
- Relevant and Coherent
  - Avoid duplication of effort
  - Provide added value

Some Organizations

- American Society of Mechanical Engineers (ASME); www.asme.org
- ASTM International; www.astm.org
- International Organization of Standardization (ISO); www.iso.org
- International Electrotechnical Commission (IEC); www.iec.ch (Switzerland)
- Innovation and Technology Commission (ITC); www.itc.gov.hk (Hong Kong SAR)

Important Documents in US

- Congressional Act
  - National Technology Transfer and Advancement Act
  - Empowers NIST to track use of standards
    - National Institute for Standards and Technology
  - Empowers OMB concepts for NGO leadership
- Executive Branch Directive
  - Office of Management and Budget
  - OMB Circular A-119
  - http://www.whitehouse.gov/omb/circulars/a119/a119.html

OMB A 119

- Most concise document explaining the government approach to:
  - Non Government Organizations (NGO)
  - Consensus Standards Organizations (CSO)
  - Government participation in these organizations

What about Government authority?

- "This policy does not preempt or restrict agencies' authorities and responsibilities to make regulatory decisions authorized by statute."

- These authorities include:
  - "Determining the level of acceptable risk"
  - "Setting the level of protection"
  - "Balancing risk, cost and availability of technology in establishing regulatory standards."

Standards Include…

- “Definition of terms;
- Classification of components;
- Delineation of procedures;
- Specification of dimensions, materials, performance, designs, or operations;
- Measurement of quality and quantity in describing materials, processes, products, systems, services or practices;
- Test methods and sampling procedures;
- Descriptions of fit and measurements of size or strength.”

Why move to standards?

- “Eliminate the cost to the Government of developing its own standards and decrease the cost of goods procured and the burden of complying with agency regulation.”
- “Provide incentives and opportunities to establish standards that serve national needs.”
- “Encourage long-term growth for U.S. enterprises and promote efficiency and economic competition through harmonization of standards.”
- “Further the policy of reliance upon the private sector to supply Government needs for goods and services.”

Standards Classification

- Voluntary Consensus Standards
  - Consensus Standard Organizations (CSO)
  - Use ANSI SDO Code of Practice
  - An CSO is accredited by ANSI
- Non-Consensus Standards
  - Company standards
  - Association Standards
  - Not accredited
- Government Unique Standards
  - Guidance
- Standards Mandated by Law
  - USP/NF referenced in 21 U.S.C. 351

FDA Staff Manual Guide

SMG 9100.1

FDA Policy

- FDA adopts appropriate standards when not in conflict with statute or regulation
- Prefer internationally harmonized standards
- Guidance will reference existing standards
- Encourage sponsors to reference standards in product applications
- Use existing promulgation authorities
- Use of standards is otherwise voluntary
- Term “standard” is defined by OMB A-119

Policy

- Employee activity in standard development:
  - Does NOT connote FDA agreement
  - Employee remains obligated to represent and support FDA policy

Regulatory Compliance

- The issue of conformity to a standard in use is NOT the primary concern of the FDA
- As always:
  - Compliance to CGMP is the primary concern
  - CGMP requirements are flexible enough to allow different approaches
  - A person should decide which practice to apply before beginning manufacturing
  - The practice should be justified repeatedly on a periodic basis

Application Approval

- Sponsors are encouraged to reference standards in product applications
- The use of a standard should be justified in terms of the application
  - Similar to justification of:
    - specification
    - formulation
    - process technology
    - overall control strategy

Microbiological Standards Used

- ISO 11137 Sterilization – Radiation
- ISO 17665 Sterilization – Moist Heat
- ISO 11135 Sterilization – Ethylene Oxide
- ISO 11140 General - Chemical Indicators
- ISO 13408 Aseptic Fill – Isolator Systems
- ISO is an CSO

Warning

- When specifying the use of any standard
  - You must justify it at the level of technical practice in your facility in terms of CGMP
  - You must justify the standard in the application in terms relevant to the product under review
- Simply stating the standard is being used is not, alone, justification for its use

ASTM

- ASTM is an CSO (Accredited by ANSI)
- Technical Committee E55
  - Process Analytical Technology (PAT) Management
  - PAT System Implementation and Practice
  - General Pharmaceutical Standards
  - Terminology
- Technical Committee E11
  - Quality and Statistics
  - Emerging Standards on Sampling Plans Specific to Pharmaceutical Industry
- www.astm.org

IPEA

- International Pharmaceutical Excipients Auditing
  - Publishes “common practice” documents
  - Audits companies on request
  - Therefore: Is a standards organization
  - Not CSO
  - Is an Non-Consensus Standard Organization
- www.ipeainc.com

Accountability

- Accountability to NGO standards is voluntary and NOT required
  - FDA may recommend NGO standard in writing
  - Recommendation is like guidance
  - Guidance is not required
- Accountability to CGMP is required
- Accountability to application commitments is required

Advantages for Industry

- Standard may provide a way to meet the requirement with a practice others have already used successfully
- Standard may alert you to concerns that you did not previously consider
- Standard may be easier to implement
  - Less training
  - Less chance of unforeseen consequence

Advice

- Do NOT use the standards industry for:
  - Personal gain
    - Others will sense your motive and not cooperate
  - Resolving trouble with one standard by creating a competing standard
    - It is better to open the issue directly with the existing standard
- Do:
  - Apply standards with cooperation from the regulator
  - Apply standards before compliance issues arise

Summary

- QbD is here to stay
  - It is a phlosophical approach to focus on product quality
- Work to be done
  - There is a lack of detailed advice
  - Not likely to come from the government
  - Most likely to come from standard orgainizations
  - You can, you must, get involved to survive

End

- Say what you do
- Do what you say