U.S. Department of Health and Human Services
Food and Drug Administration

Progress Towards the "Desired State"- Where are We Now?

Ali Afnan, Ph.D.

Office of Pharmaceutical Science, CDER, FDA

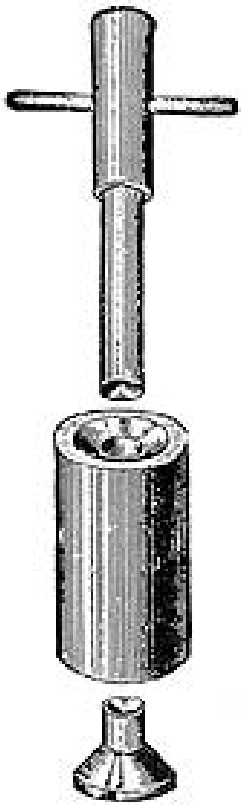
Concept Heidelberg

24 Oct 2007

At the Turn of the Century

At the Turn of the Century

Remington Tablet Machine
circa 1875



Our Industry- The Practice

- **Finding a NCE or NBE**
- **Develop the product**
- **Develop the process**
- **Get regulatory approval**
- **Begin Manufacture**
- **Market and reap the benefits as fast as possible**
  - **Avoiding mishaps (e.g., rejects, 483, warning letter, recall, consent decree, generics entry)**
- **Almost no innovation in manufacturing**

Our Industry- Product Trends

- **Market life short and getting shorter**
  - **“Me-too’s”**
  - **Patent expiry**
- **Cost of manufacturing**
- **Consumer purchasing options increasing**
- **Consumer knowledge of & demand for Q increasing**
- **Declining R&D productivity**
- **Return on investment dictating board room decisions**
- **Potency on the up, forcing dosage down**
- **Almost no innovation in manufacturing**

Product Quality and Process σ

Sigma (σ)	ppm Defect	Yield	Cost of Quality
2	308537	69.2%	25-35%
3	66807	93.4%	20-25%
4	6210	99.4%	12-18%
5	233	99.98%	4-8%
6	3.4	99.99966%	1-3%

Pharmaceutical

Semiconductor

Current (old) Paradigm

- Sampling regime not representative
- Tests based on Pharmacopeial standards
- Little Process control
  - Time
  - Documents ("validate and document")
- Optimization Not Possible
  - Process nor Product
    - Many barriers, few incentives
- Root Cause Analysis of errors usually futile
- Regulator the surrogate for the patient/ customer
- The Mindset
  - Satisfied with 2 sigma processes

Current (old) Paradigm

- **SOP driven**
  - **Knowledge Deficient (KDD)**
  - **“sameness” driven**
- **Little Process control**
  - **Time**
  - **Documents (“validate and document”)**
- **Art and not Science**

Control through Documentation

Specification: (ICH Q6a)

A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.

It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

Current (old) Paradigm

The Mindset

- "The Remington Press of 1875"
- Satisfied with 2 sigma processes
- 5 sigma QC labs
  - ⇨ Sample size non-representative
- Art rather than Science
  - ⇨ Little (if any) use of engineering principles

Compendial Based Product Release?

Test Results, Statistics, and Standards—Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to ensure that the article will indeed comply with compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply.

Compendial Based Product Release?

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for *Dissolution* and *Uniformity of dosage units,* require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.

USP NF, 2007 , Vol 1, page, page 9

Design Space (ICH Q8-R1)

The linkage between the process inputs (materials and process parameters) and the critical quality attributes can be described in the design space.

A design space is of most value where assessments have demonstrated the possibility of interactions between input variables and/or process parameters. Where it is clear that interactions are unlikely, then it can be simpler/easier to work with univariate experimentation and proven acceptable ranges. Movement within approved proven acceptable ranges is not considered to be a change. It is up to the applicant to decide

A design space can be defined in terms of linear ranges of input variables or parameters, or through more complex mathematical relationships. It is possible to define a design space as a time dependent function (e.g., blending time), or as a combination of variables, such as principle components of a multivariate model. Scaling factors can also be included if the design space intends to span multiple operational scales.

Design space can be predictive or non-predictive in nature. A non-predictive design space includes the region of successful operation, though a quantitative relationship between the design space parameters and CQAs is unknown.

“A Paradigm in Crisis”

THE WALL STREET JOURNAL.

WEDNESDAY, SEPTEMBER 3, 2003 - VOL. CCXLII NO. 45 - ★★★★ $1.00

Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst

The Three-Story Blender

By Leila Abboud
And Scott Hensley

Main points from this:

- High tech in R & D
- Relatively low tech in Manufacturing
- It matters
  - Big Pharma manufacturing costs are $ 90 Bn
  - Significantly more than R&D

Quality by Design: A Challenge to the Pharma Industry

(CAMP, R. Scherzer. FDA Sci. Board. 4/9/02)

Lags behind other industries

- Reflecting back -the most prominent reason is our inability to effectively communicate with each other
  - In a regulatory setting
  - Across disciplinary boundaries
  - Across organizational boundaries

Inability to communicate

- “Guilty until proven innocent”
- “Testing to document quality”
- Our specifications – the so called “zero tolerance”
- Most of us understand “zero tolerance” is a myth
- Dr. Woodcock’s presentation at FDA’s Science Board was not effectively leveraged to end this myth

Linking Critical Product Attributes to Clinical Performance: Is it Possible?

- Currently not known: regulatory standards often highly conservative based on uncertainty
- “Gross excursions” used as examples
  - Failure to inactive virus vaccine (polio)
  - Contamination/substitution (e.g., ethylene glycol)
  - Total in vivo dissolution failure

Clinical Effects of Minor Variations in Content Uniformity (OOS)

- Clinical reviewer: "I don't know, but I'm worried"
- Reviewing chemist: "significant"
- Investigator: "very large"
- Today's presenter: "clinically undetectable in vast majority of cases"

The Desired State

- **Product quality and performance**
  - **ensured through design**
    - **Formulation, product and process**
  - **effective and efficient manufacturing processes**
- **Specifications: Product and process**
  - **based on a *mechanistic* understanding**
  - **how formulation and process factors affect product performance**
- **Continuous *real time* quality assurance**
- **Regulatory policies and procedures: Relevant**
  - **tailored to accommodate … scientific knowledge**

The Goal

- … is to design and develop well understood processes
  - that will consistently ensure a predefined quality at the end of the manufacturing process.
- Such procedures consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns
  - while improving efficiency
  - Allowing continuous improvement
    - ⇨ Process Optimization, Product Improvement

The Goal

- **Currently, most pharmaceutical processes are based on time-defined end points**
  - **time-defined end points do not consider (or manage) physical differences in raw materials**
  - **Even though materials meet pharmacopeial specifications (generally identity and chemical purity**
- **A process end point should *not* be a fixed time; rather it is the achievement of the desired material attribute.**

Catalyst for Change

- **Process Analytical Technology (PAT)**
  - **A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance**
- **Pharmaceutical CGMPs For The 21st Century**
  - **Quality System Guidance**
  - **Process Validation: Guidance for the new Paradigm**
- **PAT Training**
  - **2nd cadre completed course**
  - **Curriculum finalized**
  - **Trainers & Training Centers Identified**
    - **Duquesne & Delaware Universities; Optimal Automation Ltd**
  - **Includes Biotechnology**

Catalysts for Change

- **Pharmaceuticals Inspectorate**
  - **2nd Cadre completing in training**
- **Office of Pharmaceutical Science**
  - **Implementation of internal Quality System**
- **ONDC Restructured to form ONDQA**
  - **Manufacturing Science Group**
- **Quality by Design Initiative**
  - **Initiated dialogue**
  - **QBD Pilot (11 NDA's- ONDQA)**

What is Quality by Design (QbD)?

- **In a Quality-by-Design system:**
  - **The product is designed to meet patient requirements**
  - **The process is designed to consistently meet product critical quality attributes**
  - **The impact of starting materials and process parameters on product quality is understood**
  - **Critical sources of process variation are identified and controlled**
  - **The process is continually monitored and updated to allow for consistent quality over time**

Catalysts for Change

Office of Generic Drugs

- **QbR (Question Based Review)**
  - **80% of ANDA using this format**
  - **Initiated change**
  - **The QbR will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment that incorporates and implements the concepts and principles of the FDA's *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach* and *Process Analytical Technology* initiatives.**

The main objectives of this enhanced review system are to:

- **assure product quality through design and performance-based specifications,**
- **facilitate continuous improvement and reduce CMC supplements through risk assessment,**
- **enhance the quality of reviews through standardized review questions,**
- **reduce CMC review time when sponsors submit a quality overall summary that addresses the QbR.**

QBR Initiative

FDA's Woodcock Suggests Extending Question-Based Review to New Drugs

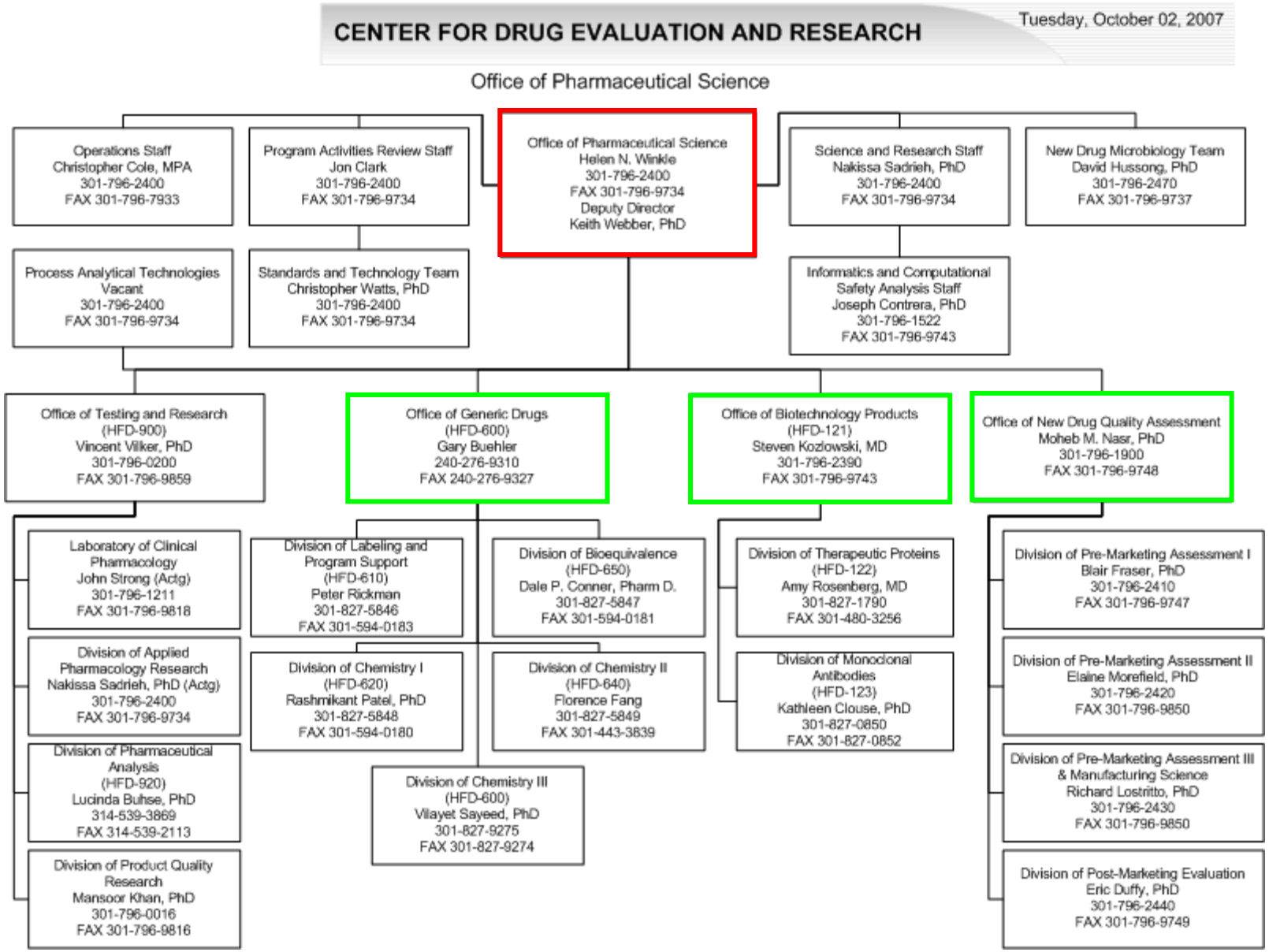
The FDA question-based review initiative that is being embraced by the generic drug industry is a step in the right direction toward streamlining the assessment of drug product quality and should be extended to the innovator drug industry as well.

This assertion was made by Janet Woodcock, the deputy commissioner and chief medical official for FDA, at a Sept. 3 policy meeting sponsored by the Generic Pharmaceutical Association in Washington, D.C.

The use of QbR in the innovator drug industry should "minimize the number of pre-approval supplements… This should conserve regulatory resources."

Woodcock noted that QbR is part of FDA's 21st century initiative launched four years ago to modernize regulatory oversight of new and generic drugs.

"The Gold Sheet"


CENTER FOR DRUG EVALUATION AND RESEARCH
Tuesday, October 02, 2007
Office of Pharmaceutical Science
Operations Staff
Christopher Cole, MPA
301-796-2400
FAX 301-796-7933
Program Activities Review Staff
Jon Clark
301-796-2400
FAX 301-796-9734
Office of Pharmaceutical Science
Helen N. Winkle
301-796-2400
FAX 301-796-9734
Deputy Director
Keith Webber, PhD
Science and Research Staff
Nakissa Sadrieh, PhD
301-796-2400
FAX 301-796-9734
New Drug Microbiology Team
David Hussong, PhD
301-796-2470
FAX 301-796-9737
Process Analytical Technologies
Vacant
301-796-2400
FAX 301-796-9734
Standards and Technology Team
Christopher Watts, PhD
301-796-2400
FAX 301-796-9734
Informatics and Computational Safety Analysis Staff
Joseph Contrera, PhD
301-796-1522
FAX 301-796-9743
Office of Testing and Research
(HFD-900)
Vincent Vilker, PhD
301-796-0200
FAX 301-796-9859
Office of Generic Drugs
(HFD-600)
Gary Buehler
240-276-9310
FAX 240-276-9327
Office of Biotechnology Products
(HFD-121)
Steven Kozlowski, MD
301-796-2390
FAX 301-796-9743
Office of New Drug Quality Assessment
Moheb M. Nasr, PhD
301-796-1900
FAX 301-796-9748
Laboratory of Clinical Pharmacology
John Strong (Actg)
301-796-1211
FAX 301-796-9818
Division of Applied Pharmacology Research
Nakissa Sadrieh, PhD (Actg)
301-796-2400
FAX 301-796-9734
Division of Pharmaceutical Analysis
(HFD-920)
Lucinda Buhse, PhD
314-539-3869
FAX 314-539-2113
Division of Product Quality Research
Mansoor Khan, PhD
301-796-0016
FAX 301-796-9816
Division of Labeling and Program Support
(HFD-610)
Peter Rickman
301-827-5846
FAX 301-594-0183
Division of Bioequivalence
(HFD-650)
Dale P. Conner, Pharm D.
301-827-5847
FAX 301-594-0181
Division of Chemistry I
(HFD-620)
Rashmikant Patel, PhD
301-827-5848
FAX 301-594-0180
Division of Chemistry II
(HFD-640)
Florence Fang
301-827-5849
FAX 301-443-3839
Division of Chemistry III
(HFD-600)
Vilayet Sayeed, PhD
301-827-9275
FAX 301-827-9274
Division of Therapeutic Proteins
(HFD-122)
Amy Rosenberg, MD
301-827-1790
FAX 301-480-3256
Division of Monoclonal Antibodies
(HFD-123)
Kathleen Clouse, PhD
301-827-0850
FAX 301-827-0852
Division of Pre-Marketing Assessment I
Blair Fraser, PhD
301-796-2410
FAX 301-796-9747
Division of Pre-Marketing Assessment II
Elaine Morefield, PhD
301-796-2420
FAX 301-796-9850
Division of Pre-Marketing Assessment III & Manufacturing Science
Richard Lostritto, PhD
301-796-2430
FAX 301-796-9850
Division of Post-Marketing Evaluation
Eric Duffy, PhD
301-796-2440
FAX 301-796-9749

Catalysts for Change

- **Re-write of 21 CFR 314.70**
  - **To reduce supplements**
- **Concept of risk mitigation taking hold in Agency**
- **Quality by Design Discussions between OBP and biotechnology product industry**
- **The Process Validation Guidance**
  - **New draft replacing 1987 Guidance progressing**

Catalysts for Change

- **Consensus Standards**
  - **Technical Committee E55**
    - **FDA involved**
  - **The FDA Standards Working Group**
  - **ISO 13485: For the purpose of setting risk-based inspectional priorities, the Secretary shall accept voluntary submissions of reports of audits assessing conformance with appropriate quality systems standards set by the International Organization for Standardization (ISO) and identified by the Secretary in public notice. If the owner or operator of an establishment elects to submit audit reports under this subparagraph, the owner or operator shall submit all such audit reports with respect to the establishment during the preceding 2-year periods. (CDRH)**
- **FDA Staff Manual Guide (SMG) Finalised**

Change

Change (*v*)

1. make or become different.
2. exchange for another.
3. move from one to (another).
4. (change over) move from one system or situation to another.

Change (*n*)

1. the action of changing

Change What?

- **Do we *need* 6 σ- Or is 2 σ *adequate*?**
- **Zero Tolerance- Myth or reality?**
- **Specifications?**
- **Compendial Release Tests?**
- **…**

Change Who?

- FDA?
- Other regulators?
- Industry?
  - Brands
  - Generics
  - Biologics
  - Bio-generics
- Other interested parties?
- Customer (education)?

Definitions of Quality

(ICH-Q8) The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*).

(ICH-Q9) "The degree to which the inherent properties of the product, system or process, fulfill requirements." ***(ICH Q9)***

(ASQ) A subjective term for which each person or sector has its own definition. In technical usage, quality can have two meanings:

1. the characteristics of a product or service that bear on its ability to satisfy stated or implied needs;

2. a product or service free of deficiencies. According to Joseph Juran, quality means "fitness for use;" according to Philip Crosby, it means "conformance to requirements." ***(ASQ Glossary of Terms)***

CFR *implies* Quality to be

Lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

Change?

Ford Model-T (1908)

Powered by the world's first supercharged hydrogen internal combustion engine, equipped with a hybrid electric transmission and pioneering green materials and processes, Model U **is a vision for the future.**

- **The creation of something new is not accomplished by the intellect but by the play instinct acting from inner necessity. The creative mind plays with the objects it loves.**

(Carl Jung 1875-1961)

Change

Change has a considerable psychological impact on the human mind. To the fearful it is threatening because it means that things may get worse. To the hopeful it is encouraging because things may get better. To the confident it is inspiring because the challenge exists to make things better. **(King Whitney Jr.)**

Nothing endures but change. **(Heraclitus 540 BC - 480 BC)**

Acknowledgements

- **Ajaz Hussain**
  - **Sandoz**
- **Keith Webber**
  - **FDA, OPS-IO**
- **Chris Watts**
  - **FDA, OPS-IO**
- **Gawayne Mahboubian-Jones**
  - **Optimal Industrial Automation**
- **Ken Leiper**
  - **Benson Associates**