



Planning Your Quality System

**From Development to
Commercialization**



10,000 Feet

(Get out your oxygen masks)

- The FDA defines the general quality system components for both medical devices and drugs.
 - Medical Devices: 21CFR Part 820 Quality System Regulation.
 - Drugs: 21 CFR Part 211 Current Good Manufacturing Practices for Finished Pharmaceuticals
 - Nutritional Supplements: 21 CFR Part 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements



10,000 Feet

(Get out your oxygen masks)


- The expectations and organization of your quality system will be largely the same regardless of the regulatory environment you face.
 - Medical Devices: Regulations emphasize structure and organization of the quality unit.
 - Drugs: Regulations are much more specific about the required elements to be included in your quality system.
 - Nutritional Supplements: Organized similar to the drug cGMPs, with more “wiggle” room.

It gets more complicated still...

- Because these industries all use the term “current” in their manufacturing description the actual meaning or intent of the rules is expected to change as technology changes. For example:
 - 21 CFR Part 11: Software signatures evolved from highly onerous, with intense scrutiny into software security and lengthy validation protocols to a less severe interpretation. The actual wording of Part 11 did not change.
 - Validation: The proposed new guidance document is radically different from the existing guidance with a new emphasis on capability studies and risk management. The reference to validation in 21CFR Part 820 did not change, and the first actual reference to validation was added to 21 CFR Part 211 this year even though it has been in general practice and an FDA requirement for approval for several decades.
 - Nutritional Supplements: New response by the FDA to the challenge of managing the nutritional supplement industry, which has found many potent compounds which meet the food requirement. (Hormone analogs present in food, etc) Not many guidance documents out, but expect this to evolve quickly over the next few years as new products and risks emerge.

If this is how the regulations work, how can you plan for the future?

- Remember that quality and regulatory compliance are not synonymous
 - “Quality” means those features of products which meet customer needs and thereby provide customer satisfaction. In this sense, the meaning of quality is oriented to income. The purpose of such higher quality is to provide greater customer satisfaction and, one hopes, to increase income.
 - Joseph M. Juran and A. Blanton Godfrey, *Juran’s Quality Handbook* (McGraw-Hill, 1999) 2.1—2.2
- Quality systems have been a subject of extensive study, and a number of valuable resources exist to help you implement the correct practices. Emphasize the proper practices and the details will (hopefully) follow.



Review – Quality Systems are impacted by or Quality is . . .

- Cost
- Regulatory Compliance
- Ability to meet the expectations or needs of the customer
- Profit



With some hard work . . .

- It is possible to comply with the cGMP requirements. Small companies routinely do this for Class I medical devices, nutraceuticals, and over-the-counter drugs.
- Biologics and potent drug compounds are more challenging, and require a larger investment to build the appropriate quality system.
- In both cases, planning and resource management are important to meeting a compliant state.

How do you manage cost?

- Think end product. How large / small will the quality department need to be?
 - A medical device quality system is not the same burden as a potent drug compound's quality system.
 - How risk adverse is your company? Inversely, how nimble?
- Be judicious in the development of complicated or expensive systems. Plan to eventually have an MRP or document management system that can help support your system. But ensure that you understand the requirements of each program before you try to go electronic.
- Be judicious in the use of electronic files as your final document, because the final approved copy must meet the requirements of the 21 CFR Part 11 predicate rule.
- Build your program in a logical manner.

How do you manage cost?

- Using a paper-based documentation system is advantageous for a small company.
 - Employees gain a thorough understanding of the different systems (CAPA, Deviations, Change Control) without a computer program automatically prompting the next step.
 - Paper-based systems easily grow with your company.
 - There is no software to maintain or validate.
 - Forms can get lost and not noticed to be missing until an auditor inspects your records.
- Beware the magic bullet of software, well-developed paper systems provide better quality management than a poorly developed electronic system.
 - If you don't have a CAPA system, then it probably is not appropriate to set up an electronic system.



What is a logical manner?

- Good documentation practices support...
- The program for standard operating procedures and training, which supports . . .
- The program for calibration and maintenance of equipment which supports . . .
- The validation program which supports. . .
- cGMP status of facility and products.



Essential Elements

- Establish good document practices early.
- Emphasize good cGMP practices and infrastructure first, add on software and databases when your system is beginning to function.



Warning Letters highlight common mistakes in quality system development

- Issues extracted from FDA warning letters:
 - A report was finalized with missing data. (wasn't in notebook!)
 - Another test notebook showed some data was missing from the same report.
 - Testing SOP was changed/varied from the original validation.
 - Post-Its attached to release paperwork.
 - Non-validated, insecure computer network.
 - Incomplete lab notebook information (signatures, reviews, units, dates, etc...)



Regulatory Compliance

- Early planning saves pain and problems later.
- For regulated industries, certain aspects of routine functions: product testing, manufacture, and labeling can rapidly become complicated.
- Difficult to outsource this too much, because no one knows your product or field as well as yourself.
 - Outside resources can definitely accelerate your learning curve.

Expected Reading (no, really)

- [Bar Code Label Requirements--Questions and Answers](#)Final10/5/2006
- [Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information](#) Draft9/3/2003
- [Compressed Medical Gases](#)Final2/1989
- [Computerized Systems Used in Clinical Investigations](#)Final5/10/2007
- [Current Good Manufacturing Practice for Combination Products](#)Draft9/29/2004
- [Current Good Manufacturing Practice for Medical Gases](#)Draft5/6/2003
- [Current Good Manufacturing Practice for Phase 1 Investigational Drugs](#)Final7/14/2008
- [Expiration Dating and Stability Testing of Solid Oral Dosage Form Drugs Containing Iron](#) Final6/27/1997
- [Expiration Dating of Unit-Dose Repackaged Drugs: Compliance Policy Guide](#)Draft5/27/2005
- [Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP](#)Final11/11/2006
- [General Principles of Process Validation](#)Final5/1987
- [Good Laboratory Practice Regulations Questions and Answers](#)Final 3/2/1998
- [Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities - FDA Public Health Advisory](#) Final4/5/2001
- [Guidance for IRBs, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research \(21 CFR 50.24\)](#) Draft released for comment Draft8/29/2006
- [Guideline for Validation of Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices](#) FinalPosted 3/2/1998
- [Investigating Out-of-Specification Test Results for Pharmaceutical Production](#)Final10/11/2006
- [Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients](#) Draft4/17/1998
- [Marketed Unapproved Drugs -- Compliance Policy Guide](#)Final6/8/2006
- [Monitoring of Clinical Investigations](#) FinalPosted 3/2/1998
- [Nuclear Pharmacy Guideline Criteria for Determining When to Register as a Drug Establishment](#) FinalPosted 3/2/1998
- [Part 11, Electronic Records; Electronic Signatures — Scope and Application](#)Final9/3/2003
- [PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance](#) Final9/29/2004
- [PET Drug Products - Current Good Manufacturing Practice \(CGMP\)](#)Draft9/15/2005
- [Pharmacy Compounding -- Compliance Policy Guide](#) Final5/2002
- [Possible Dioxin/PCB Contamination of Drug and Biological Products](#) Final8/23/1999
- [Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment](#) [Revised Attachments](#) Draft11/2003
- [Preparation of Investigational New Drug Products \(Human and Animal\)](#) Final11/1992
- [Prescription Drug Marketing Act — Donation of Prescription Drug Samples to Free Clinics](#)
- [Prescription Drug Marketing Act \(PDMA\) Requirements- Questions and Answers](#) (Issued and Posted 11/13/2006) Final 3/2006
- [Process Validation: General Principles and Practices](#).Draft11/17/2008
- [Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations](#) Final9/27/2006
- [Questions and Answers on Current Good Manufacturing Practices \(cGMP\) for Drugs](#)Final8/4/2004
- [Review of FDA's Implementation of the Drug Export Amendments of 1986](#) Final11/1989
- [Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice](#)Final 9/29/2004
- [Street Drug Alternatives](#) Final 3/2000
- [Testing of Glycerin for Diethylene Glycol](#)Final5/1/2007
- [The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 - Good Manufacturing Practice \(CGMP\)](#)Draft10/18/2007

Back up to 10,000 ft

- The FDA has created guidance documents to help clarify questions or address particularly challenging issues.
 - Medical Gases
 - Filter testing
 - Aseptic manufacture of sterile products
- Even though these are not identified as cGMP regulations, the FDA has successfully defended the argument it has the authority to interpret the cGMPs and apply them appropriately to the situation. (So unless you have a legal budget the size of your development budget the easiest strategy is to plan to comply.)



Guidance documents

- A surprising amount of information can be gathered from guidance documents.
 - Itemize all the “should” and “verifies” identified in the related guidance documents.
 - Proceduralize or validate as required.
- Expect to find outdated or annoying tasks.



Ability to meet the needs of the customer

- Design Specifications
- Review your design specifications
- Review your design specifications
- Review your design specifications
- Emphasize that your specifications must be properly written. Medical Device industry emphasizes this heavily and that influence is spreading to pharmaceuticals.



The future. . .

- Trends are toward emphasizing systems for risk management.
- Medical Device compliance is becoming more stringent.
- Pharmaceutical companies are beginning to adopt the quality system regulations architecture for their quality system.



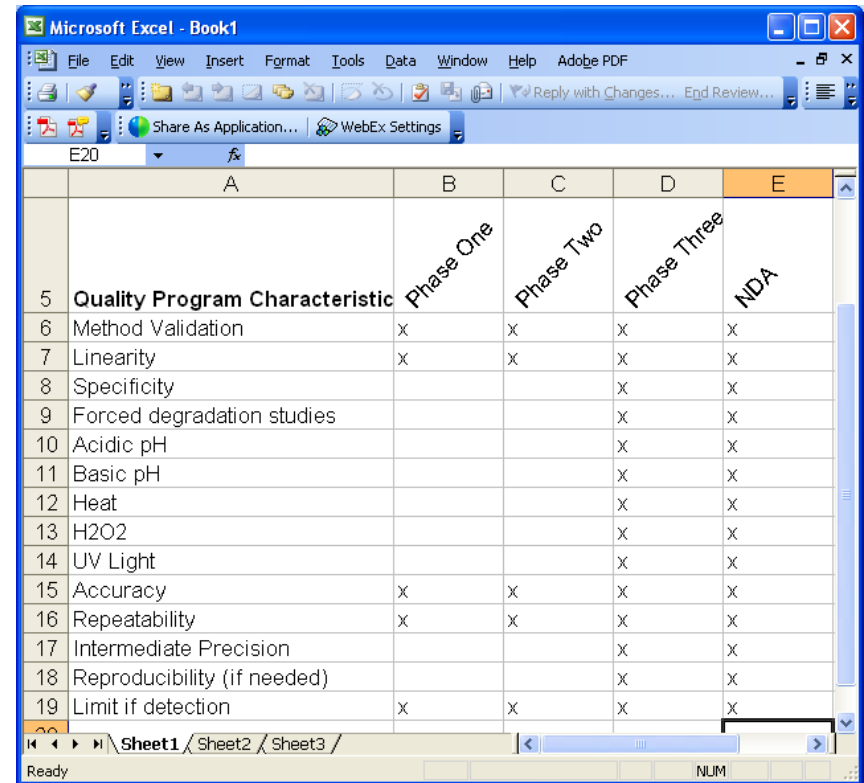
Suggested Strategy for biologics

- Identify the quality systems which will be required to ensure data integrity through the application phase:
 - Quality Manual
 - Employee training
 - Change Control
 - Document management. (this is more than just SOPs!)

Product implementation plan

Identify the characteristics of your product which the FDA expects to be clarified, and at what point in the submission process that should be prepared.

A very good summary of these expectations is available in Agalloco's Validation for Pharmaceutical Processes



	A	B	C	D	E
		Phase One	Phase Two	Phase Three	NDA
5	Quality Program Characteristic				
6	Method Validation	x	x	x	x
7	Linearity	x	x	x	x
8	Specificity			x	x
9	Forced degradation studies			x	x
10	Acidic pH			x	x
11	Basic pH			x	x
12	Heat			x	x
13	H2O2			x	x
14	UV Light			x	x
15	Accuracy	x	x	x	x
16	Repeatability	x	x	x	x
17	Intermediate Precision			x	x
18	Reproducibility (if needed)			x	x
19	Limit if detection	x	x	x	x



Quality Manual

- Expect to revise it.
- In development this will be rudimentary, and should emphasize how you will maintain control of the product development process.
- Establish a culture of record keeping, and cGMP documentation early to avoid pain in the future.
- Establish change control of the process early!



Suggested Reading

- Sidney H. Willig and James R. Stoker, Good Manufacturing Practices for Pharmaceuticals: A Plan for total Quality Control. (Deckker, 1997)
- Joseph M. Juran and A. Blanton Godfrey, Juran's Quality Handbook. (McGraw-Hill, 1999)
- James Agalloco and Frederick J. Carleton, Validation of Pharmaceutical Processes. (Informa, 2008)
- Oliver Schmidt, Pharmaceutical Quality Systems. (CRC Press, 2000)

A decorative graphic on the left side of the slide consists of several overlapping squares of varying shades of orange, arranged in a stepped pattern that ascends from left to right. The squares are semi-transparent, creating a layered effect.

Thank You