Mastering Regulatory Compliance

FDA Drug Educational Forum

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Thomas J. Arista
Investigator
National Expert – Pharmaceutical / Biotechnology
Office of Regulatory Affairs
Division of Field Investigation
Dallas, Texas (214) 253-4920
thomas.arista@fda.hhs.gov

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- **A Question -**
  - Who runs the shop?
  - Who oversees the operations?
  - Who has final authority and approval?

Organization / Department ?

- Production
- Validation
- Engineering
- Quality Control Unit
- Regulatory Affairs

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- Let us consider your Shop - *Home town, the Great Republic of Texas*
  - *Small shop*
  - *Not to large shop*
  - *One of the big guys*

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- Type of finished products e.g.,
  - Sterile or non-sterile
  - Solid oral dosage
  - Liquids
  - Large volume or small volume parenterals
- Type of manufacturing operations e.g.,
  - Active pharmaceutical Ingredient, (API)
  - Aseptic filling
  - Isolator technology
  - Mixing, Blending, Isolation, Purification

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- Some of the manufacturing steps are:
  - Critical steps ?
  - Important steps ?
  - Less important steps ?
  - Required steps?

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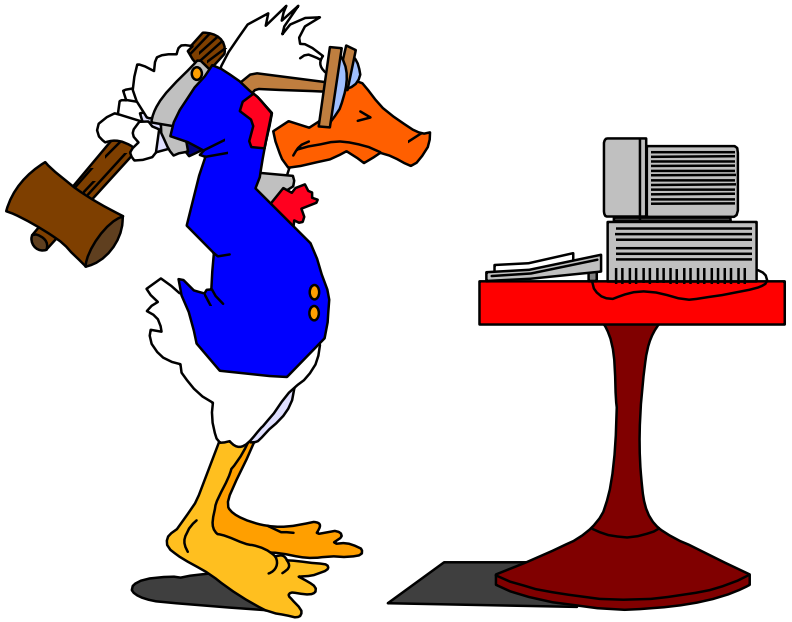
- Does your process use computer assisted automation?
  - Fully - automated
  - Semi - automated
  - Non - automated



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- What are the Quality Control analytical test requirements?
  - In-process control checks
  - Chemistry/Microbiology
  - Finished product QC test requirements / specifications
  - Stability Tests

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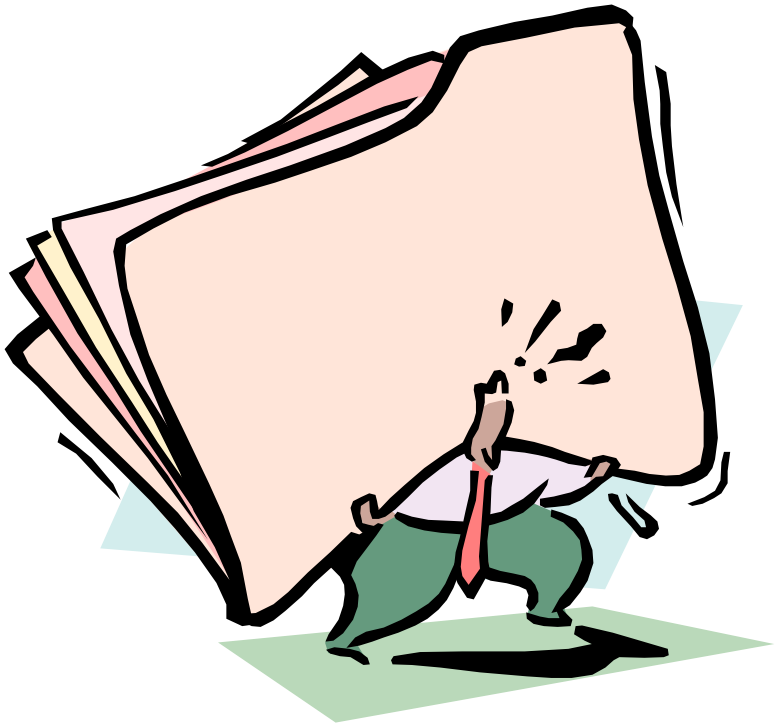
- How much information is needed?
- Type of info / data e.g.,
  - Process Validation
  - QC analysis
  - Data to support manufacturing operations



FDA defines Process Validation

- *Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre- determined specifications and quality characteristics.*

Another way of saying a similar thought might be….

- *Process validation* might also be a collection and evaluation of data, from the process design phase throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality product

Process Validation

- Or, let's put the legal jargon aside for a moment.
- I like simplicity. How about the following thought?

Validation

"*In today's pharmaceutical industry, whether you are thinking about a computer system, a water treatment systems, or a manufacturing process, validation means nothing more that well-organized, well-documented* common sense*."*

Kenneth Chapman

Director Quality Assurance Pfizer, Inc.

A *History of Validation in the United States*

Pharmaceutical Technology - 10/91

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- I have the easiest job in the Agency..
- When you go back to your shop ask your staff, (e.g., operator/analyst), *3 easy questions*.

3 easy questions

- What do you do?
- How do you do it?
- Can you show me?

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- Question #1- ***What do you do?***

  Specifically, what needs to be executed to accomplish the manufacturing steps or QC analysis?

- ***Examples -***
  - Weight out raw materials;
  - Maintain proper operation of the Water System;
  - Perform qualifications of production or laboratory equipment;
  - Aseptic processing
  - QC Analysis

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- Question #2 – ***How do you do it?***

  Specifically, how do you perform the manufacturing steps or QC analyses that need to be accomplished?

- ***Examples –***
  - Follow Standard Operating Procedures
  - Written Protocols
  - Pharmacopoeia methods
  - National or International Standards, (e.g., AAMI, ISO)

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- Question #3-
  - ***Can you show me?***

- That is:
  - ***Show me*** what you do
  - ***Show me*** how you do it
  - ***Show me*** the data to support successful execution of the manufacturing steps
  - ***Show me*** the analytical data

what does the question do for you?

Question #1-

What do you do?

For, the individual who did the work, (e.g., Operator, Analyst, Technician).

1. Individuals will describe their normal day-to-day operation.
2. This also assist to demonstrate the individuals' level of knowledge and comprehension of their respective jobs.
3. Or, they may describe some inconsistencies with current established procedures.

what does the question do for you?

<u>Question #2 –</u>

How do you do the work?

For, the individual who did the work, (e.g., Operator, Analyst, Technician).

1. The written SOP describe the specific work required to be performed.
2. The SOP is complete and accurate.
3. The SOP may not be current and does not accurately describe the steps performed.

what does the question do for you?

Question #2 cont. –

How do you do the work?

For, the individual who did the work, (e.g., Operator, Analyst, Technician).

1. Individuals are executing the specified operations as described in established protocols.
2. The manufacturing steps are successfully executed with the required specifications and acceptance criteria achieved.
3. Individuals may be performing the requisite operations in an inconsistent manner as described in the protocols.

what does the question do for you?

<u>Question #2 –</u>

Can you show me?

For, the individual who did the work, (e.g., Operator, Analyst, Technician).

1. The data supports the manufacturing steps and QC analysis.
2. The data supports the successful execution of the defined specifications described in protocols.
3. Or, the data documents manufacturing inconsistency, or does not support the requisite production steps and the QC analysis.

has this ever happened to you…

Sometimes, the SOPs are written just short of the preamble to the Constitution.

for example…

April 21, 2006 3:09pm

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HealthWatch
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E-MAIL THIS STORY PRINTABLE VERSION

Car Seat Instructions Too Hard To Read

CHICAGO, March 3, 2003

Many adults are stumped when it comes to the right way to install and use car seats. Above: checking a child car seat to make sure it is securely attached. **(AP)**

QUOTE

Many city police and fire departments offer help in installing child seats.

(AP) Instructions for installing child safety seats in cars are written in language too difficult for many adults to understand, researchers say.

Such manuals are written at a tenth-grade reading level on average, according to a new study, while data suggest that nearly a quarter of U.S. adults read at or below a fifth-grade level, and at least 25 percent read at about an eighth-grade level.

The findings are cause for concern because motor vehicle collisions are a leading cause of death and injury for infants and children. About 80 percent of car safety seats are improperly installed or misused, the study found.

what are the problems…

- 90% in Illinois installed incorrectly;
- Instructions are difficult, and some confusing;
- Instructions written at 7th to 12th grade reading level;
- Reading difficulty tied to the number of words with 3 or more syllables;
- Use shorter sentences;
- Write instructions at a 5th grade level, which is optimum for understanding health-related information;

some times…

- The established procedures are not followed.
- The SOP is not complete or accurate.
- Specifications established in protocol acceptance criteria are not met.

so then….

- Assure that the written procedures and protocols are complete and accurate;
- Assure that personnel understand what needs to be done by following all of the requisite manufacturing steps as described in the SOP or protocols;
- Assure that laboratory analyst are performing the appropriate methods of analysis, (e.g., pharmacopeias compendia).

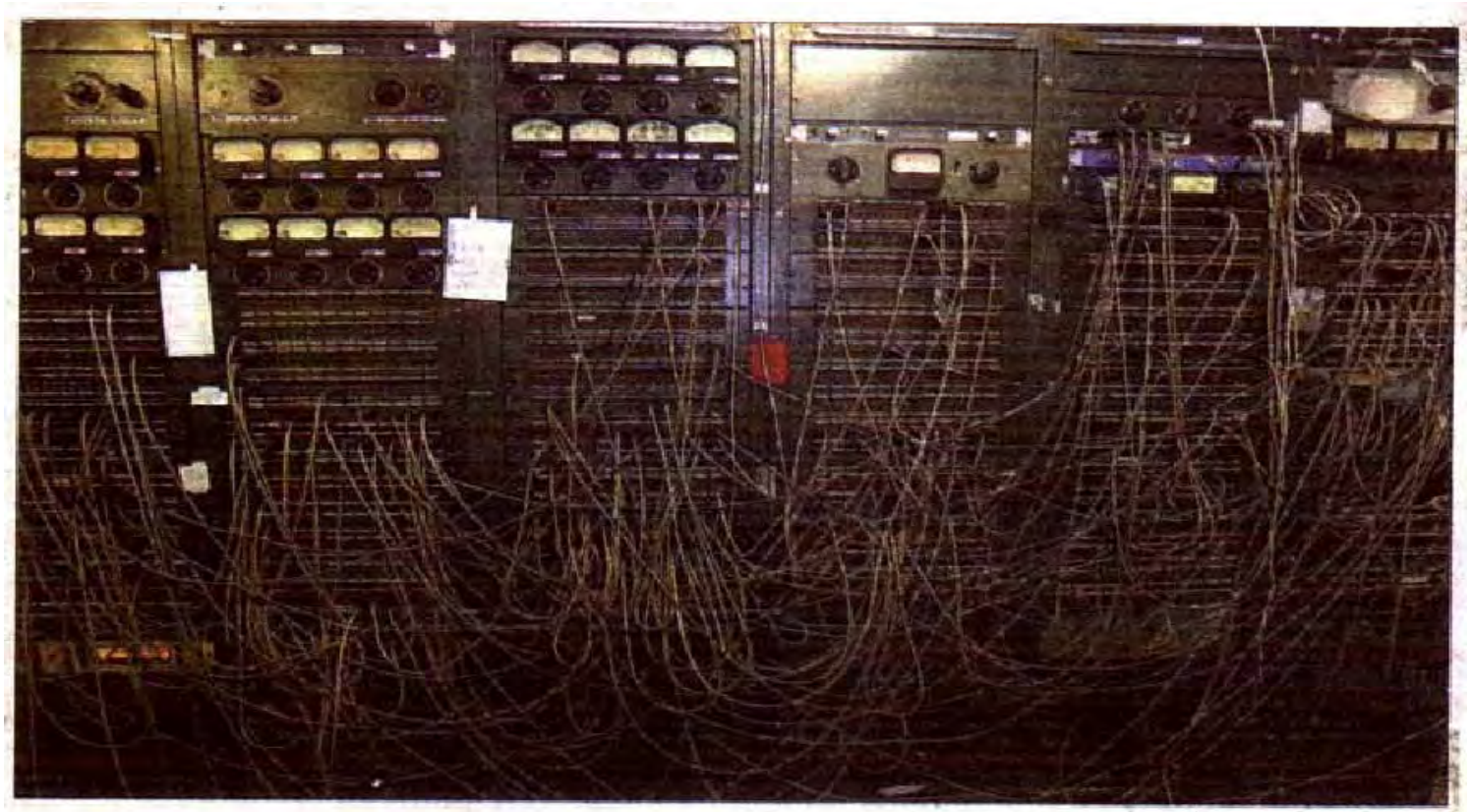
some times
we drop the ball…it happens

- How do we correct the issues or concerns?
- In response to the issues or concerns, were the corrective actions appropriate?
- Are concerns or deviations addressed within a reasonable period of time?

changes

- There may be changes, (e.g., adjustments, refinements), to the manufacturing operation.
  - *Minor*
  - *Major*

in the event of some adjustments…?



Photos by RUTH FREMSON/The New York Times

A maze of old, cloth-covered cables makes up a switchboard system in the Audio Master Control room at the United Nations in New York City.

e.g., might be attributed to communications…?

- Large part of the fuselage arrived with wire harnesses; though the ***wires within the harnesses were not connected properly***;
- Workers were ***unable to thread the wires through the fuselage***;
- The ***workers had to stop final assembly of the full aircraft*** and spend days pulling together and testing the wiring;

- *International Herald Tribune, June 26, 2006*

e.g., might be attributed to communications…?

Final notes:

- Delay costs $6.1 billion over the next four years;
- Implementation of business improvements results in a €2.1 billion in cost reductions, and,
- A two year delay for aircraft delivery commitments
  - *Seattle Post-Intelligencer – October 3, 2006*

in the event of changes…

- Are the changes major or minor?
- How do you determine if the changes are major or minor?
- Who do you ask?
- There are knowledgeable individuals who can determine if changes are major or minor.

in the event of changes…

- Do the changes impact upon the finished product or manufacturing process?
- How do you determine the impact of changes?
- There are knowledgeable individuals who can determine if major or minor change impact the finished product or manufacturing process.

in the event of changes…

- The individual changes, when considered collectively, do they present a departure from the validated process or equipment qualifications?
- Who do you ask?
- There are knowledgeable individuals who can determine if the changes, collectively, do not impact upon the validated process or equipment qualifications.

in the event of changes…

- Do the changes require a Supplement to be sent into the Center?
- Or, can the changes be included in an annual product review?
- Who do you ask?
- There are knowledgeable individuals who can determine if a supplement is required.

changes require assessment

- Who do we ask in order to answer the questions?
- The knowledgeable individuals;
  - Production
  - Validation
  - Engineering
  - Quality Control Unit
  - Regulatory Affairs

changes require assessment

- The knowledgeable individuals may employ a variety of evaluation tools to determine impact of the changes and if there are operational or regulatory risks.
- For example:
  - Faulty Tree Analysis, (FTA)
  - Failure mode and effect analysis, (FEMA)
  - Hazard Analysis Critical Control Points, (HACCP)

changes require assessment

- What if there is no formal evaluation tools, (i.e., the examples in the preceding slide)?

not to worry…

- You currently perform;
  - Evaluations
  - Assessments
  - Determine the impact and/or risks
  - Provide recommendations
  - Implement corrective measures

not to worry…remember..

- What you do, how you do it, and the supporting data is in a *Change Control* documents…it's all written out in an SOP or protocol.
- The document describes and answers many questions concerning the ***evaluation process*** and ***rationale*** to support the *major* or *minor* changes and there impact upon the manufacturing process.

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- The Code of Federal Regulations (CFR) describe a number of responsibilities requirements, and oversight activities of...
- The Quality Control, (QC), Unit

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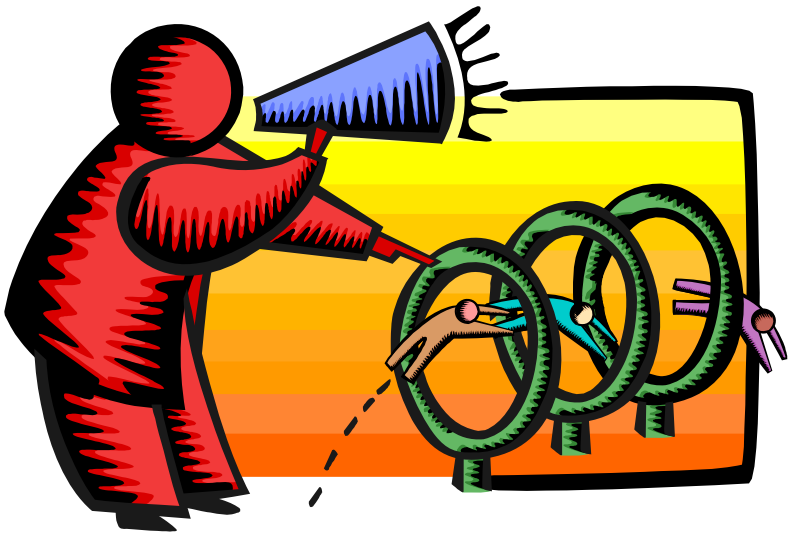

- However, a successful QC Unit obtains assistance, knowledge, and support from e.g.,:
  - Senior Management
  - Production
  - Validation
  - Engineering
  - Quality Control laboratory
  - Regulatory Affairs

which will assists to…

- I believe it's everyone (i.e., Agency & Industry) goal to have no objectionable conditions or other violations of the FD&C Act.
- We (i.e., Agency & Industry) want everyone to be in compliant with CGMP, all commitments made in an application to be true and accurate, and the data used to support the applications are appropriate and acceptable.

Objectionable Conditions & FDA-483

- However, in reality we do document significant objectionable conditions in the FDA-483 form.

- The observations are made when the Investigator's "judgment" conditions or practices observed, indicate that any food, drug, device, or cosmetic have been adulterated or are being prepared, packed, or held under conditions whereby they may become adulterated or rendered injurious to health.
  - *IOM 5.2.3*

Current Top 10 Objectionable Conditions

- #10 – Written procedures are not established followed for the cleaning and maintenance of equipment…*21 CFR 211.67(b)*
- #9 – Employees are not given training in the particular operations they perform as part of their function and cGMP…*21 CFR 211-25(a)*
- #8 - Batch production and control records are not prepared for each batch of drug product produced…*21 CFR 211.118*
- #7 – Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications…*21 CFR 211.165(a)*
- #6 – There is a failure to thoroughly review any unexplained discrepancy, the failure of a batch or any of its components to meet any of its specifications…*21 CFR 211.192*

Current Top 10 Objectionable Conditions

- #5 - There is no written procedure for production and process controls designed to assure that the drug products have the identity, strength, quality , and purity they purport to are represented to possess…*21 CFR 211.100(a)*
- #4 – Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, test procedures designed to assure that components, containers, closures, in-process materials conform to appropriate standard of ISQ&P…*21 CFR 211.160(b)*
- #3 – Control Procedure are not established which monitor the output validate the performance of those manufacturing processes that maybe responsible for causing variability in the characteristics of in-process material and the drug product…*21 CFR 211.110(a)*
- #2 – Written production and process control procedures are not followed in the execution of production and process control functions, documented at the time of performance…*21 CFR 211.100(b)*

Current Top 10 Objectionable Conditions

- Numero Uno
- the Big Kahuna
- the Boss Hog
- the one that gives everyone heartburn

- #1 - The responsibilities and procedures applicable to the quality control unit are not in writing, such written procedures are not followed…*21 CFR 211.22(d)*

?

- Given #1 – What is the Quality Unit responsible for and what exactly are they doing……?

a few points to ponder…for those of us that have some difficulties with sleep…

- If you can't sleep
- Forget the sleep aids
- Don't need a hypnotist
- You don't need any warm milk…or a shot of your favorite cold beverage…
- I have the sure fire cure…
- I guarantee these fine reading materials will put you right to sleep…faster that a debate for a presidential election…
- Go to the following websites…if these don't make you snore…your in real trouble…

FDA Internet addresses

- Human Drugs:
  - http://www.fda.gov/cder
- Biologics:
  - http://www.fda.gov/cber
- Devices:
  - http://www.fda.gov/cdrh
- Vet Drugs:
  - http://www.fda.gov/cvm

Cheers!