

Effectively Responding to FDA-483's and Warning Letters: Avoiding Subsequent Action

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Effective Enforcement and Benefit to Public Health

“...an effective enforcement strategy creates public confidence in FDA oversight...which in turn keeps trust in the safety of FDA regulated products from eroding. Such confidence is critical to the long term interest of both consumers and industry.”

Margaret Hamburg, M.D.
Commissioner of Food and Drugs
August 6, 2009

FDA-483's : List of Observations

- Issued at the conclusion of an inspection, the items listed are the significant observations of the Investigator(s) made during the inspection
 - Do not minimize importance of issues identified that were **not** on the 483. They will be included in the report.
- Items are listed in descending order of importance
- Findings are not intended to be an “all inclusive list” of problems at a site. An inspection is only a “*snapshot in time*”
- It is your responsibility to ensure you are compliant with *all* laws and regulations
- Generally use Turbo EIR to populate findings
- Repeat findings will generally be identified

The Close Out Meeting

- **What is the Company's Purpose**

- Sending the appropriate message to the investigator
- Understanding the observations and assuring their accuracy
- Seeking annotations or corrections where appropriate
- Understanding the broader message that FDA is sending
- Identify and discuss any errors

- **What is FDA's Purpose**

- Ensuring that senior management at the company has notice of the nature and seriousness of the findings
- Ensuring that the Company understands the issues identified in the observations
- Confirming that the facts underlying the observations are correct and that relevant documentation has been collected (if the inspection is of a serious nature)

Understanding the Observation(s)

- Have a meaningful discussion about each observation
- Understand the basis for each observation, and the underlying facts supporting them
- If a device firm, be sure to annotate the findings when applicable (corrected, corrected and verified, etc.)
- If you disagree with an observation, or it is inaccurate, discuss those issues during the close-out meeting
- Demonstrate awareness of the applicable regulations and consult with legal counsel as necessary to ensure the company has a thorough understanding of the applicable requirements

Understanding the Observation(s) (cont'd)

- What aspect(s) of the company's operations were deficient. The deficiencies should be listed in the response.
- If you are confused about the meaning of an observation, raise it during the close-out meeting, or consider contacting FDA to seek oral clarification – but be quick! Do not wait until response is due!
- During the conversation, do not put the official on the defensive as to his or her work product
- Do not state in the written response that the company is confused. This may signal that the company is being combative rather than seeking to fix the problem, especially if FDA believes the claim of confusion to be unreasonable.

First Steps After Receiving an FDA-483

- **Within the Company**

- Assemble a team to work on 483 response
- Fact finding with respect to individual observations
- Drafting the response
- Ensuring timelines for getting response to FDA include time for internal and external vetting

- **At FDA**

- Reviewed by District
- Classified as NAI, VAI or OAI
- May be reviewed by Center

FDA-483 Response Deadline

Federal Register / Vol. 74, No. 153 / Tuesday, August 11, 2009 / Notices 40211

NIECD, NIH, Executive Plaza South, Room 400C, 6120 Executive Blvd., Bethesda, MD Drive, Bethesda, MD 20892 (Telephone Conference Call).

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2009-N-0335]

Review of Post-Inspection Responses

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing a program to support public health protection by facilitating the timely issuance of warning letters. The program establishes a timeframe for the submission and agency review of post-inspection responses to inspectional

Name of Committee: National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

Date: September 16, 2009.

Open: 8:30 a.m. to 12 p.m.

Agenda: To discuss administrative details relating to the Council's business and special Reports.

Place: National Institutes of Health, Building 31, 31 Center Drive, Conference Room 6, Bethesda, MD 20892.

Closed: 1 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, Building 31, 31 Center Drive, Conference Room 6, Bethesda, MD 20892.

Contact Person: Susana Serrato-Sztein, MD, Director, Division of Skin and Rheumatic Diseases, NIAMS/NIH, 6701 Democracy Blvd., Suite 800, Bethesda, MD 20892-4872, (301) 594-6032. ssztein@mail.nih.gov.

Any interested person may file written comments with the committee by forwarding the statement to the Contact Person listed on this notice. The statement should include the name, address, telephone number and when applicable, the business or professional affiliation of the interested person.

In the interest of security, NIH has instituted stringent procedures for entrance onto the NIH campus. All visitor vehicles, including taxicabs, hotel, and airport shuttles will be inspected before being allowed on campus. Visitors will be asked to show one form of identification (for example, a government-issued photo ID, driver's license, or passport) and to state the purpose of their visit.

(Catalogue of Federal Domestic Assistance Program Nos. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research; 93.701, ARRA Related Biomedical Research and Research Support Awards, National Institutes of Health, HHS)

Dated: August 4, 2009.

Jennifer Spaeth,
Director, Office of Federal Advisory Committee Policy.
[FR Doc. E9-19219 Filed 8-10-09; 8:45 am]

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Effective Sept. 15, 2009

If 483 response is received within 15 days, FDA will respond to the adequacy of the proposed corrections

After 15 days, FDA need not respond

Once the FDA-483 issues...tick-tock, tick-tock

- There is no legal requirement to respond to the FDA-483 in writing
- Firm's have 15 business days to respond to FDA-483's.
 - Aim for 13 days to anticipate unforeseen problems
- Failure to respond in 15 days, the agency will not consider your response in their decision on subsequent action
- Your response must be complete, thorough and be based on objective evidence to demonstrate you are operating in a state of control and are compliant.
 - Identify changes already implemented
 - Identify plan for longer term items with schedule for completion

Deadline: April 2010 Warning Letter FDA 483 Response



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

UPS

Dear

Between December 21, 2009 and January 6, 2010, Ms. Karen Bryerton Cooper, and Mr. Craig Rybus, representing the Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at the . The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), parts 50 and 56. These regulations apply to clinical investigations of products regulated by FDA. We are aware that at the conclusion of the inspection, our investigators presented and discussed with , Pharmacy Director, Ms. **(b)(6)**, Study Coordinator, and Ms. **(b)(6)**, Pharmacy Operations Clerk, a Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We acknowledge Dr. , IRB Chairman's written response dated February 3, 2010, to the Form FDA 483. However, because this written response was received more than fifteen business days after the Form FDA 483 was issued, the response has not been considered. We plan to evaluate Dr. written response to the Form FDA 483 along with any other written material provided as the direct response to this letter.

Why a Warning Letter?

“When it is consistent with the public protection responsibilities of the agency and depending on the nature of the violation, it is the Food and Drug Administration’s (FDA’s) practice to give individuals and firms an opportunity to take voluntary and prompt corrective action *before* it initiates an enforcement action.

Warning Letters are issued to achieve *voluntary compliance* and to establish *prior notice*.”

*FDA Regulatory Procedures Manual
Chapter 4: Advisory Actions*

Significance of a Warning Letter

“The agency position is that Warning Letters are issued *only* for violations of regulatory significance. Significant violations are those violations that *may lead to enforcement action if not promptly and adequately corrected.*”

A Warning Letter is the agency’s principle means of achieving prompt voluntary compliance with the Federal Food, Drug and Cosmetic Act (the Act).

*FDA Regulatory Procedures Manual
Chapter 4: Advisory Actions*

General Information about a Warning Letter

- Warning Letters are not final agency action
 - “...failure to correct may result in subsequent action such as seizure, injunction, civil money penalties, prosecution”
 - They are informal and advisory in nature
- Commitments to correct an observation at the conclusion of an inspection (FDA-483) may not preclude a Warning Letter
- Typically addressed to top management to ensure they know the seriousness by which FDA considers these observed violations
 - It is management’s responsibility to ensure adequate resources are available to fully correct the violations and prevent their recurrence
 - It is management’s responsibility to ensure all requirements of the Act are being adhered to – not just those identified in the Warning Letter

Types of Warning Letters

- **'Typical' Warning Letter** may be based upon:
 - Inspectional observations or headquarters concerns
 - Compliance with Quality Systems issues
 - Compliance with MDR
 - Compliance with Corrections and Removals
 - Pre-market issues (510(k)'s, PMA's, IDE's, Supplements
 - Bio-research Monitoring (BioMo) inspections
 - Advertising and promotion activities
 - Any other violation of the Act that failure to comply could result in enforcement action

May be issued by District Office or headquarters

Types of Warning Letters (con't)

- **Corporate Wide Warning Letter**
 - Generally inspection driven
 - Requires Center concurrence
 - Appearance of corporate culture of non-compliance
 - Pattern of similar current and past findings at different corporate locations
 - Focuses on management controls
- **Recidivist Warning Letter**
 - “In and Out” of compliance with quality systems or MDR
 - Requires third party independent expert to certify compliance to FDA before FDA confirmatory inspection
 - Tight timeframes for compliance; costly

Types of Warning Letters (con't)

- **Warning Letter with Automatic Detention**
 - Typically for foreign firms
 - Based on inspectional information and/or continuing problems with a product upon offered for entry into U.S.
 - Based on *appearance of adulteration or misbranding*, product is refused entry
 - Warning Letter provides notice of FDA concerns
 - Requires FDA re-inspection to confirm adequacy of promised corrections
 - Due to resource constraints at FDA, re-inspection may take some time

Warning Letter vs. Regulatory Meeting

- FDA can invite top corporate management to a meeting either at the District Office or Center with the goal of emphasizing their concern(s) with ongoing operations
 - May hand deliver a Warning Letter at the meeting
 - May verbally advise management that the meeting is in lieu of written correspondence but should be taken as seriously

Consequences of a Warning Letter

- Impacts Class III PMA reviews if based on QSR
- Prior Notice
 - “May” be last chance to voluntarily comply before enforcement action filed with Dept. of Justice
- Corporate reputation is tarnished
 - Warning Letters publically available
 - May be posted on FDA website
 - Shopped by competitors/seen by customers
 - Raises questions about quality and integrity
 - Especially difficult to defend during litigation
- Government contracts
 - Federal and State contracts may be halted
- Exportability
 - Issuance of certificates requires compliance with QSR

When a Warning Letter is NOT Appropriate

- Violation reflects a history of repeated or continual conduct of a similar or substantially similar nature during which time the individual and/or firm is aware of FDA's concerns
 - Such violations should be considered as “systemic” issues
 - i.e., continuing QSR or MDR issues
- The violation is identified as intentional or flagrant
- The violation represents a reasonable probability of injury or death
- When adequate notice has been provided by other means and the violations have not been corrected or are continuing
- The violations, under Title 18 U.S.C 1001 are intentional and willful acts that once having occurred cannot be retracted

FDA will use other enforcement tools available!

How Effective was Your Response to FDA

- Response should tell the whole story and stand on its own! Allow a “fresh set of eyes” to review before submission to FDA!
- Should acknowledge commitment to compliance and seriousness taken to address findings
- If effective, FDA will follow-up during next inspection
 - Stay abreast of all commitments and notify FDA of any ‘slippage’
 - Be sure all past commitments are complete
- If less than effective, subsequent action may be taken
 - If responding to FDA-483, may generate a Warning Letter
 - If responding to Warning Letter, may result in enforcement action
 - Response may not have been thorough
 - May not have expressed a sense of urgency
 - May result in field corrective action

FDA's Assessment of Your Firm's Response

- Is it timely and understandable?
- Has the Company adequately addressed the nature and seriousness of the inspection observations?
- Has the firm provided objective evidence of correction
- Does the response address only the observations or does it also address the broader issues implicated by the observations?
- Does the Company appear to have an understanding of the issues?
- Does the Company appear to have an adequate remediation plan?

FDA's Assessment of the Response : Understanding

- Corrective Action Plan
 - The plan should show to the agency that the company thoroughly understands what is needed to correct the immediate problem
 - The plan should address the “systemic issue” – not simply the observation
 - More importantly, the plan should show that the company understands the general “good practices” that should govern long-term
 - If a correction is made before the response is submitted, objective evidence should be attached to the response
 - If a correction cannot be made before the response is submitted, the company should provide the agency with a timeline for completion

FDA's Assessment of the Response : Commitment

- The company cannot simply assert that it is committed to addressing the deficiencies identified and maintaining compliance. The company must prove this commitment to FDA by providing objective evidence when available.
- Include comprehensive, thoughtful, and detailed plan for addressing the deficiencies in a manner that will obtain and maintain compliance
- Include a timetable with specific and realistic milestone dates. Provide updates to FDA as needed.
- Include timely and appropriate effectiveness checks

FDA's Assessment of the Response: Accuracy and Tone

- The response itself should give FDA confidence in the company's actions and that it takes the issues identified seriously
- The response should be complete, well-organized, supported with appropriate documentation, easy to understand, and grammatically correct and proof-read
- Each factual assertion in the response ***must be accurate***—each fact should be verified within the company before the response is submitted to FDA
- At best, sloppiness will indicate to FDA that the company is not taking the identified issues seriously. At worst, sloppiness may raise with FDA the question of fraud.

FDA's Expectations of Your Response

Listen for your **D.R.U.M.** beat!

- **Direct** – address the items directly raised in the Warning Letter
- **Related** – go beyond those to potentially related problems (systemic approach)
- **Universal** – expand your efforts to identify and address same or similar issues company wide
- **Monitoring** – describe how you will address the issues, assure sustainability and provide assurance management is involved

Meeting with FDA

- When should a company seek a meeting?
 - What if FDA is non-responsive?
- Who should attend?
 - From FDA
 - From the Company
- Setting the Agenda
- The Materials
- The “message” you want to be delivered
- “Take aways” from the meeting
 - Action items
 - Commitments

Warning Letters : Examples

“This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations.”

“You are responsible for investigating and determining the causes of the violations identified by the FDA.”

“You must promptly initiate permanent corrective and preventive action on your...”

“Federal agencies are informed about the Warning letters we issue...so that they may consider this information when awarding government contracts.”

Warning Letters - Examples

“These serious violations of the law *may* result in FDA taking regulatory action without further notice to you.”

“No requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected”

“No premarket submissions for Class III devices to which the QS/cGMP deficiencies are reasonably related will be cleared for approval until the violations have been corrected.”

Warning Letters – Corporate wide

“We realize (redacted) has multiple locations. This letter is an official notification that FDA expects all of your locations to be in compliance. We recommend all of your locations be evaluated and that corrective action be taken corporate-wide if deficiencies are found.”

“The purpose of this letter is to apprise to management of your inadequate corporate wide corrective action plan as evidenced by the continuing serious deficiencies identified at each of these (redacted) facilities and to remind you of your responsibility to ensure that all facilities continuously comply with the Act and all pertinent regulations.”

Warning Letters – Inadequate Responses to FDA -483's

“Your responses continue to be specific spot fixes and have failed to achieve the necessary systemic approach to comprehensively address the violations.”

“We acknowledge the receipt of your firm’s responses to our Investigators’ FDA -483 dated... (4 responses over 8 months). We do not consider your responses to be adequate because of the following...”

“The cGMP deficiencies need more timely and comprehensive corrections than the actions you have proposed or taken.”

“You do not address why you failed to take appropriate action at the time of this incident to assess the scope of the problem and implement appropriate corrective action to prevent recurrence of this potential contamination issue”.

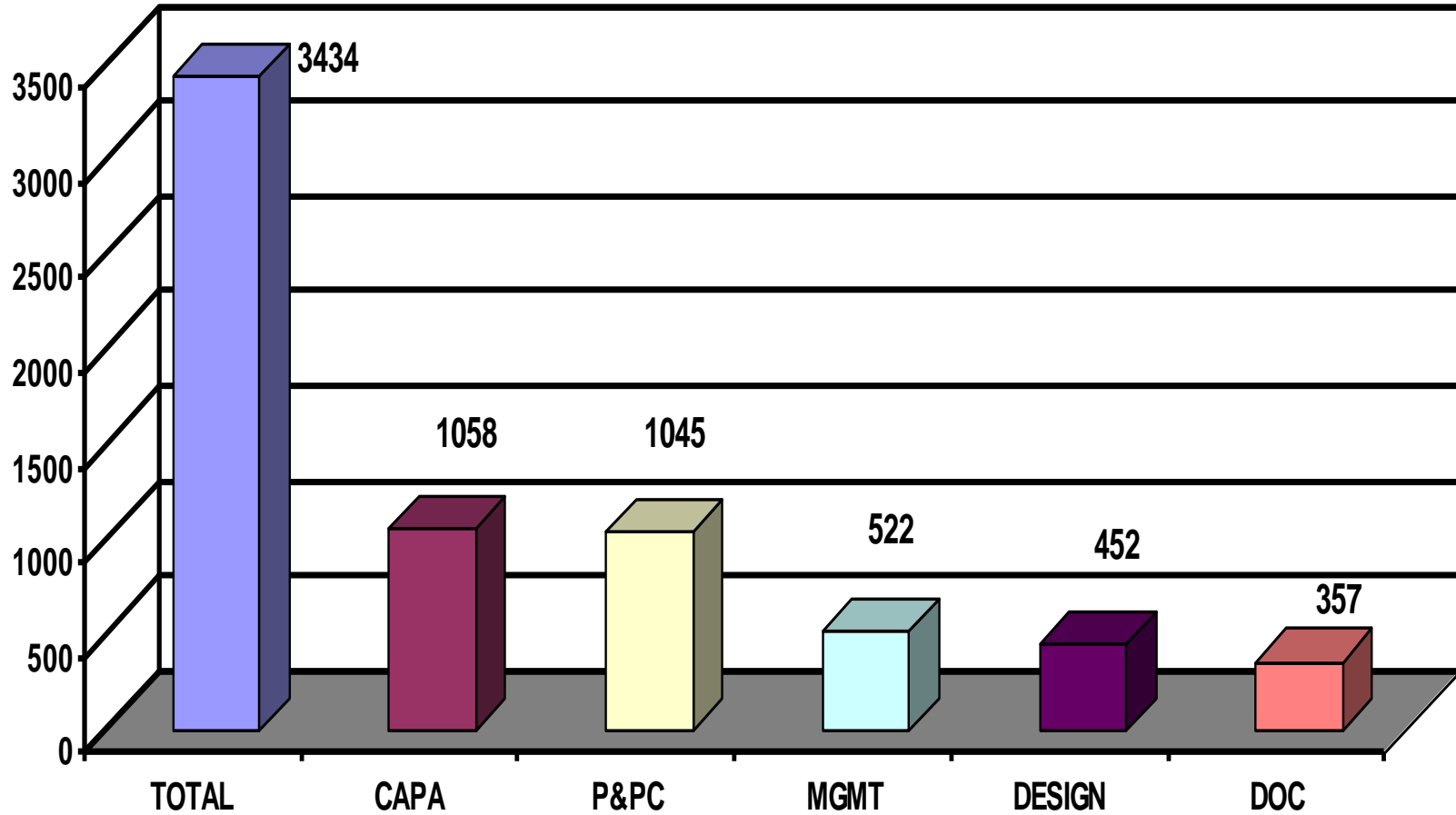
FDA Warning Letters : FY 11 (thru 8/11)

Center	FY 2010	FY 2011
CDRH	201	(154)
CDER	173	(95)
CFSAN	192	278
CBER	15	(7)
CVM	71	(48)
Tobacco	21	631
TOTAL	673	1213

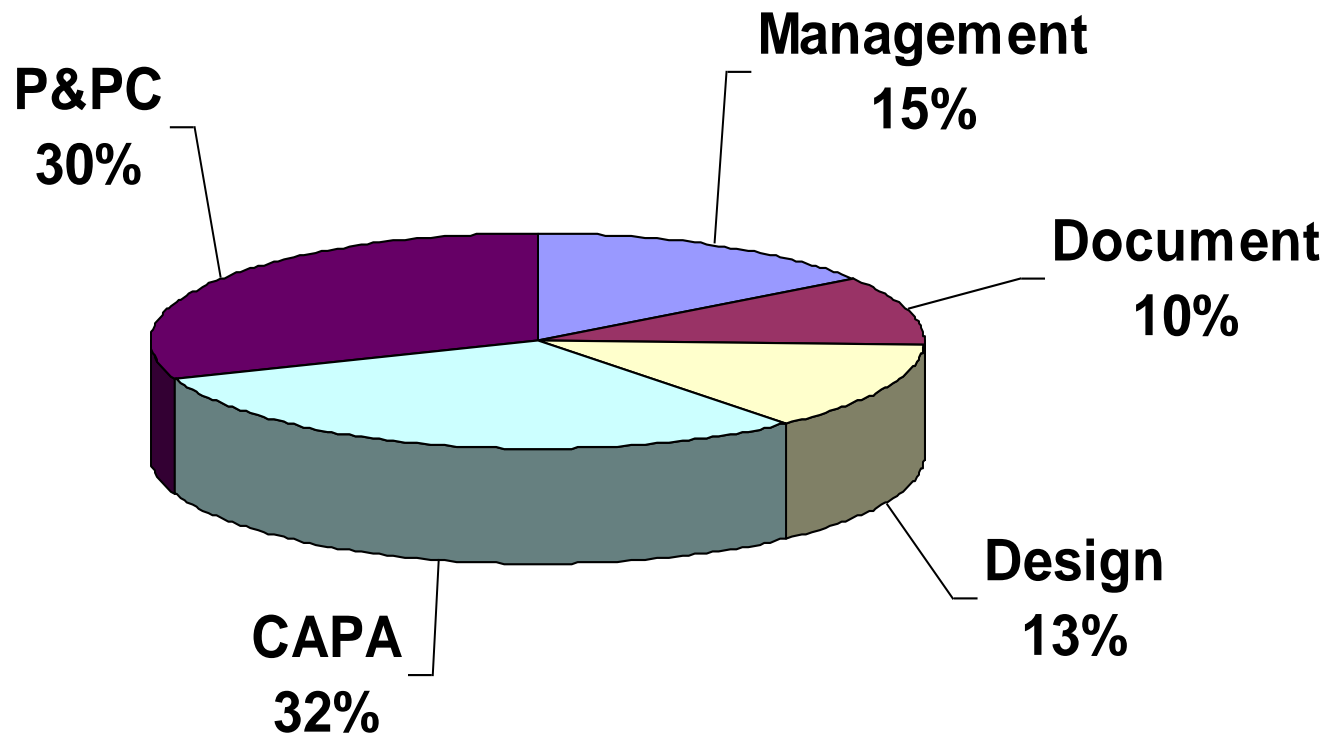
Most Frequent Quality System Warning Letter Cites : 2010

21 CFR 820.198(a)	-	Complaints	42
21 CFR 820.100(a)	-	CA/PA	30
21 CFR 820.75(a)	-	Process validation	28
21 CFR 820.22	-	Quality audits	26
21 CFR 820.184	-	DHR	21
21 CFR 820.20(c)	-	Management review	19
21 CFR 820.30(i)	-	Design changes	18
21 CFR 820.90(a)	-	NCR	18
21 CFR 820.30(g)	-	Design validation	17
21 CFR 820.50	-	Purchasing controls	17

Analysis of 2010 FDA-483 Observations



Analysis of FY 2010 FDA-483 Observations



Questions?

Thank You!

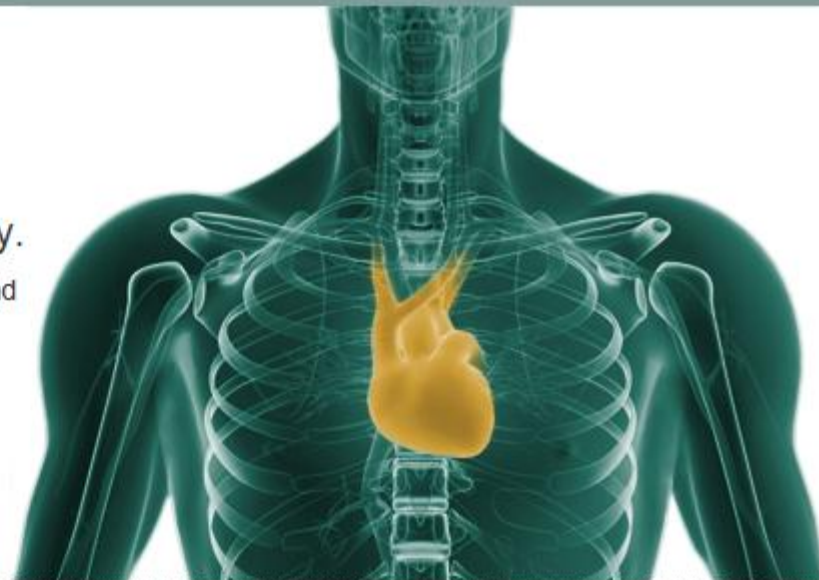
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