FDA Inspection and Management

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PACT
Production Assistance for Cellular Therapies

Hosting a FDA Inspection

- Preparing for an inspection
- Management of the FDA inspection process
- Inspection response

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Assignment Process

- District or headquarters will send assignment to field inspectors
  - will include pertinent documents (e.g.:IND, Drug Master File, copy of complaint, adverse event reports)

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Types of FDA Inspections

- Compliance Audit – Unlicensed Product
  - 361 product
  - Manufacturer of devices (e.g.: infectious disease test kits, Isolex)
  - Testing laboratory (e.g.: donor screening, microbiological cultures)
  - licensed product
- Biomedical Monitoring (BioMo)
  - Clinical trials - IND or IDE
- Biologics License Application (BLA) pre-licensure
  - review data used to support the application

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Categories of Inspections

- For Cause = Directed
  - Not a routine inspection
  - May be based on;

  a) product complaint/problem reported by the PI or other entity

  b) adverse events too many or too few (as compared to other investigational sites)

  c) patient complaint

  d) sponsor reports concerns about investigator

  e) too may research subjects enrolled (as compared to other investigational sites)

  f) employee notification of “problems”

- Routine = Surveillance

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FDA Inspections of Facilities*

	2008	2009
Cord Blood and Peripheral Blood	19	42

Trends show approximately 30% of inspections resulted in the issuance of a 483

*Mary Malarkey, Director OCBQ, CBER
6th Annual FDA and the Changing Paradigm for HCT/P Regulation

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Inspection Classification

- (NOI): No Action Indicated. Most observations fall into this category.
  - Favorable outcome
  - No objectionable practices were identified
- (VAI): Voluntary Action Indicated
  - Objectionable conditions were identified
  - Regulatory actions not required
- (OAI): Official Action Indicated
  - Warning letter

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FDA Inspection Results
Cord Blood and Peripheral Blood

	NAI	VAI	0AI
2008	15	4	0
2009	28	10	4

*Mary Malarkey, Director OCBQ, CBER
6th Annual FDA and the Changing Paradigm for HCT/P Regulation

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A FDA Form 482 versus a 483

FDA Form 482

- Notice of Inspection
  - FDA has the authority to inspect your facility

FDA Form 483

- The report of inspection findings
  - Presented to person of most authority
  - Not a final determination regarding compliance

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Be Prepared

- Successful inspections are a result comprehensive preparation
  - Ensure you facility is compliant with regulatory requirements
  - Have procedures that define the process for hosting the inspection
  - Have procedures for responding to inspection report

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Prepare in Advance (BIOMO advanced notice)

- Notify all pertinent staff (and others)
- Reserve dedicated room
- Prepare materials:
  - Protocol
  - Investigator brochure and consent form
  - FDA Form(s) 1572 and CV(s)
  - IRB approval
  - SOPs
  - Case report forms
  - Study related correspondence
  - Table of organization

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FDA Methods of Inspection

- Observation
- Interviewing staff
- Reviewing documents (SOPs, records)
- Examining facility, equipment, raw materials, labels, packaging, final product
- Collecting Samples (obtain receipt)
  - Finished product
  - In-process or intermediate product
  - Raw materials
  - Labeling
  - Packaging

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FDA Methods of Inspection

- Ensure SOPs meet FDA regulations
- Establishment follows SOPs

  - *If it isn't in a SOP, you don't have to do it*
- Documentation/records collaborate procedures are being followed

  - *If you didn't document it, you didn't do it*

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Off Limits to FDA

- Internal audit reports
- Financial data
- Personnel personal data (other than qualifications)
- Non-IND research data

- May not breach sterility or impede production

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Audit Management

- Follow your internal SOPs on audit management
- Review inspector credentials
- Relegate inspectors to dedicate room
- Understand scope and potential length of audit

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Example Procedure

1. Upon arrival of a FDA inspector, the **first contact person** will:
- Greet the investigator and get his or her name and ask the purpose of the visit.
-Escort him to an open meeting room Page the PI or whoever the FDA wants to see *(insert your site's language re how to find the PI)* and notify him/her of the
2. Contact the Facility Director, Medical/Scientific Director and Director of Quality Assurance. Where applicable, the PI should be contacted.
3. The Principal Investigator and/or most senior member greets the inspector and:
- review their credentials.
4. Determine the purpose of the visit
-For cause or routine inspection
5. Notify all staff of the FDA's presence in the facility
6. For management of audit refer to SOP #234

SOP# 123, version C Effective 00/00/2010

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Inspection Process

- Opening meeting. Provided/request from the agency:
  - FDA Form 482
  - Scope of inspection (Directed versus For Cause)
  - Anticipated length
  - Staff expected to be needed
  - Facilities that will be involved
  - Review process: will they do summary at end of each day?

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Control the Inspection

- Ensure all staff know the FDA is in your facility
- Limit idle business conversation by all staff
  - Do not want FDA to overhear any information that is not pertinent to the inspection
- Accompany inspector at all times when they are in your facility

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How to Answer Questions

- Truthfully
- Don't elaborate beyond direct question
- OK to say "I don't know", but I'll get you the answer
- OK to ask for clarity related to question
- OK to disagree and provide a clarification or example (provide documentation, where applicable)
- Polite

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Audit Management

- Maintain a copy of all documents provided
- Keep notes
- Maintain a list of documents provided to the agency, which they take with them
- Obtain a receipt for products, materials, packing/labeling taken by the FDA
- End each day with a synopsis with the FDA of findings/concerns
- Meet with staff to see what corrections/clarity can help with remaining audit time
- Generate potential corrective action immediately to present to FDA the following day

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Handling 483

Response not “required”

- But, lack of response is viewed as a lack of concern

Immediately respond to report

- Response within 15 days can result in revised 483s (to your benefit)

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483 Response

- Factual
  - do not speculate
- Describe interim controls
- Demonstrate evaluation of root cause and systems that may have contributed to problem
- Provide comprehensive description of corrected system controls
- Address impact to past previously distribute product
- Address impact to quarantine product inventory
- Address prevention of future problems
- Provide dates for completion of all corrective action

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Inaccurate Observation Findings

- Demonstrate where finding is incorrect
  - provide documents and/or references

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Establishment Inspection Report (EIR)

A detailed narrative of the inspection. Includes lists of all records reviewed, what aspect of the facility was audited. A detailed summary of the inspection. Includes identification of specific records reviewed, identification of participating staff, staff comments

- Available to inspected establishment after inspection process is *closed*
- Available to pubic through *Freedom of Information Act*

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Example EIR

SUMMARY OF FINDINGS:

This inspection of a medical association Institutional Review Board (IRB) was conducted as follow-up to an inspection assignment dated 9/27/99 from Patricia A. Holobaugh, Center for Biologics Evaluation and Research, Bioresearch Monitoring, HFM-650. The assignment requests an unannounced, directed inspection of the referenced IRB and its operations. Additionally, the assignment requests specific information/documentation associated with the IRB's operations. Included in this request was the review of the files for at least six (6) studies that have been reviewed by the IRB. Three of the study files audited were specified in the inspection assignment while an additional three were selected from the IRB's list of studies approved since 1996 (*see Exhibit 1*). *The IRB files that were audited as part of this inspection were* associated with the following studies:

1. [redacted] (note the inspection assignment refers to this study and the Gene Activated Therapy or GAT study as two separate studies. However, this inspection revealed that the referenced studies were actually the same study);
2. [redacted]. Investigational Proposal for the Study of [redacted]
3. [redacted] (note-this study was never approved by the IRB as the Clinical Investigator (CI) never submitted all information needed to review the research proposal.);

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FOI

- The Freedom of Information Act (FOIA) and FDA's regulations governing disclosures require release of inspection information to the public
  - List of inspectional observations (FDA-483)
  - EIR (attachments and exhibits are excluded from requirement)
  - Warning letters communication with the regulated establishment must be disclosed upon request by any member of the public
- Mandate publicly accessible "electronic reading rooms" with electronic search and indexing features

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FOI- Requests

Requests must be in writing (do not accept e-mail)

- **A**. Requestor's name, address, and telephone number.
- **B**. A description of the records being sought. The records should be identified as specifically as possible. A request for specific records that are releasable to the public can be processed much more quickly than a request for "all information" on a particular subject. Also fees for a more specific and limited request will generally be less.
- **C**. Separate requests should be submitted for each firm or product involved.
- **D**. A statement concerning willingness to pay fees, including any limitations.

FDA web: http://www.fda.gov/RegulatoryInformation/FOI/HowtoMakeaFOIARequest/default.htm

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FDA Letters

Untitled versus Warning- Both Intend to Notify of Practices that Need to be Amended

Warning Letter:

- Expresses FDA's stance (based on statue or rules)
- Not a commitment to enforcement, but a prelude to possible enforcement
- Serious stuff (call your lawyer)

Untitled Letter:

- Intended to induce voluntary compliance with regulations
- Does not include a statement about potential enforcement action

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Warning Letters

- Letter states requirement time-line for response (usually 15 days)
- Letter of closure issued after corrective actions have been satisfactorily addressed

  - applicable to warning letters issued after 9/1/2009

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FDA Letters

FDA posts warning letters on their web site:

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

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[Example of Actual Untitled Letter]

CSL Biotherapies Untitled Letter
Brian McNamee
Chief Executive Officer (CEO)
CSL Biotherapies
45 Poplar Road
Parkville, Victoria 3052
Australia

Dear Mr. McNamee:

The Food and Drug Administration (FDA) conducted an inspection of CSL Biotherapies, located at 45 Poplar Road, Parkville, Victoria 3052, Australia, between April 19 and April 28, 2010. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP) requirements in the manufacture of licensed biological vaccine products and monovalent influenza bulks.

We would like to meet with you and other senior management at CSL Biotherapies to further discuss the issues cited in this letter and how you will address them going forward..

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Regenerative Sciences, Inc
July 25, 2008
CERTIFIED MAIL
RETURN RECEIPT REQUESTED
Christopher J. Centeno, M.D.
Medical Director
Regenerative Sciences, Inc.
11080 Circle Point Road
Building 2, Suite 140
Westminster, Colorado 80020

[Example of Actual Untitled Letter]

Dear Dr. Centeno:

The Food and Drug Administration (FDA) has reviewed your website at Internet address: http://www.regenexx.com and has determined that you are promoting your use of mesenchymal stem cells under conditions that cause these cells to be drugs under section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(g)] and biological products, as defined in section 351(i) of the Public Health Service Act (PHS Act) [42 U.S.C. 262].

We request that you notify this office, in writing, of the steps you have taken or will take to address the violations noted above and to prevent their recurrence. Your response should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 N, Rockville Maryland 20852-1448.

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FDA NEWS RELEASE
For Immediate Release: August 6, 2010
Media Inquiries: Shelly Burgess, 301-796-4651, shelly.burgess@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA
FDA Seeks Injunction Against Colorado Manufacturer of Cultured Cell Product

Example of Actual FDA News Release Regarding Action

The U.S. Food and Drug Administration is seeking an injunction in federal court against Regenerative Sciences LLC, of Broomfield, Colo., citing violations of current good manufacturing practice (cGMP) that cause its cultured cell product to be adulterated. The product is also misbranded due to the lack of adequate directions for use and the failure to bear the "Rx only" symbol.

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm221656.htm

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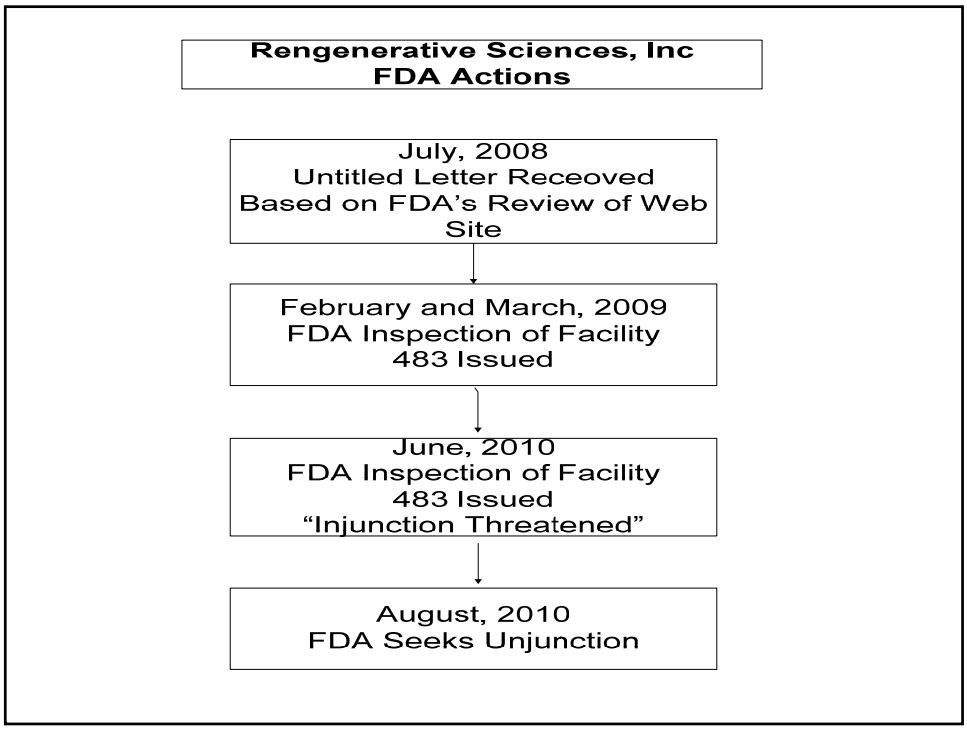

Enforcement

- Recalls
- Injunction

  - a civil action to prevent cease production and/or distribution
- Seizure of final product
- Fines
- Consent decree

  - an legal agreement to correct. Details exact requirements.
- Criminal investigations

  - allows FDA to hold employees legally liable for their actions

http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm

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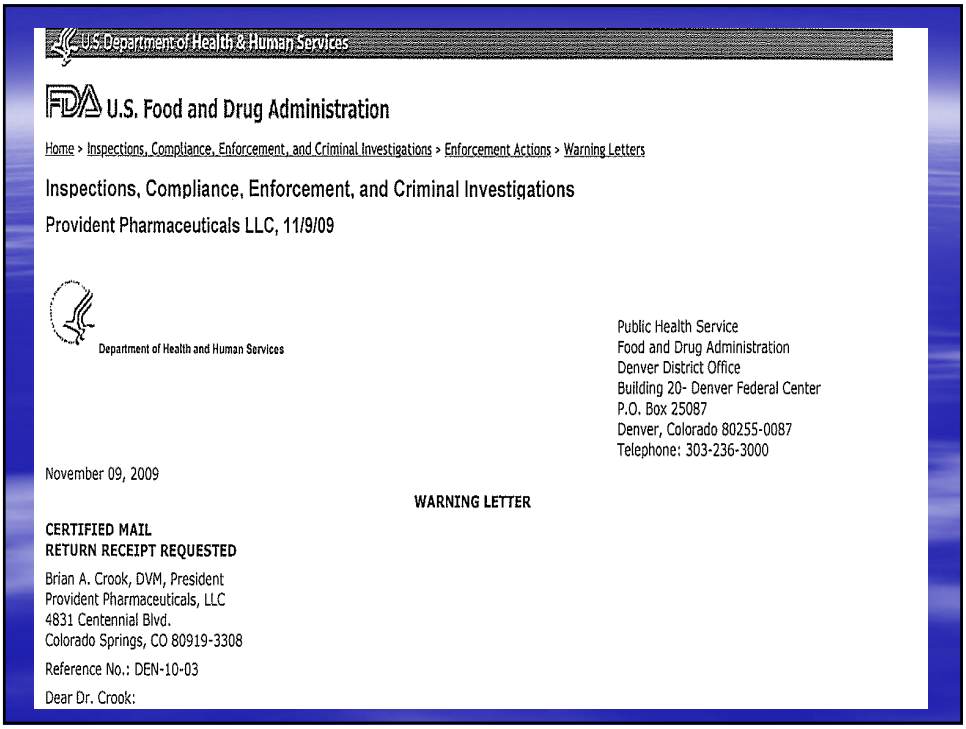

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Home > Inspections, Compliance, Enforcement, and Criminal Investigations > Enforcement Actions > Warning Letters

Inspections, Compliance, Enforcement, and Criminal Investigations

Provident Pharmaceuticals LLC, 11/9/09

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Denver District Office
Building 20- Denver Federal Center
P.O. Box 25087
Denver, Colorado 80255-0087
Telephone: 303-236-3000

November 09, 2009

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Brian A. Crook, DVM, President
Provident Pharmaceuticals, LLC
4831 Centennial Blvd.
Colorado Springs, CO 80919-3308

Reference No.: DEN-10-03

Dear Dr. Crook:

Dr. Cook Warning Letter

- We acknowledge your July 2009 response and commitment to develop a **(b)(4)**. Please provide a copy of your **(b)(4)**.
  - X In addition, if not included in the **(b)(4)** provide corrective actions to prevent similar deviations from recurring.
  - X Note that failure to have an adequate number of qualified personnel is not justification to circumvent your adherence to CGMP requirements.
- We acknowledge your July 2009 response that indicates the **(b)(4)** in the completion of your APRs and your commitment to **(b)(4)** to complete APRs.
  - X Please provide timeframes for the completion of the **(b)(4)**. In addition,
  - X please provide corrective actions to prevent similar deviations regarding your failure to follow your APR procedure.
  - X Note that failure to have an adequate number of qualified personnel is not justification to circumvent your adherence to CGMP requirements.

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Gibson Laboratories

- Your firm rejected 14 lots of product in 2008 due to contamination and the corrective action was to retrain employees on aseptic technique.
  - X This corrective action was not effective. In 2009, your film received 23 complaints on contaminated product and rejected 13 lots of product due to contamination.
  - X Additionally, your firm's failure investigations into nonconforming products do not include reviewing the results of environmental testing of the fill room for the days in which contaminated product has been produced.
  - **X You have failed to conduct a failure investigation that identifies the root cause of contamination**
  - **X You have not taken a corrective action that reduces the trend of contaminated product.**

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Washington Homeopathic Products, Inc.

- Broken glass was identified in filled 15 cc glass bottles of T-Gone Remedies Type 4 (lot **(b)(4)**) on January 20, 2009, during product filling operations. This lot was rejected and destroyed on January 29, 2009. "Deviation Report," dated January 22, 2009, stated: "Broken glass was in the prepackaged and sealed bottles from the distributor. No risks were involved. Product was pulled and destroyed on January 29,2009. The broken glass inside the bottles accrued at the distributor's operation. The drug product with the broken glass was destroyed and all other products that were used with that component was rechecked and all were all were clear."
  - X **The investigation failed to identify other related products and lots manufactured with the implicated glass vials to assure no additional broken glass was present.**
  - X **Finally, the specific lot number of the problematic glass bottles (components) used to fill T-Gone Remedies Type 4 (lot (b)(4)) on January 20, 2009 was not documented in the investigation.**

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Dr. Cook Warning Letter

- We acknowledge your July 2009 response and commitment to complete stability testing, **(b)(4)** to ensure adherence to the stability procedure.
  - X However, we believe your response does not provide adequate preventive actions because **(b)(4)** do not address the failure of the QCD to ensure your procedures are followed and training is effective. Please provide corrective action to prevent recurrence of similar deviations. For example, you may develop a contingency plan to send your stability samples for testing to a qualified contract laboratory, or you may reduce your product line to reduce the laboratory workload.

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483 Response

Ensure safety of this product/lot # identified. Determine disposition

Evaluate status of product collected and remaining in establishment quarantine/released inventory

Evaluate status of product (same type and/or lot #) that has been release and may be in (hospital) inventory

Ensure future products are problem free

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483 Response Approach

- Root Cause Analysis ⇨Exact Cause
- Prevent reoccurrence through application of quality systems. E.G.:
  - design control
  - quality control
  - quality review (trending, etc.)
  - early detection of problems (through audit)

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Lessons Learned

- A good relationship with headquarters does not impact the inspection process
  - the inspectors are from “the field”
- Cellular Therapy area is new for FDA
  - Not always very familiar with processes or application of regulations
- Every inspection is unique:
  - Focus varies
  - Adverse findings will vary and/or conflicts with previous inspections
- Respond to 483 promptly and appropriately

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Questions

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