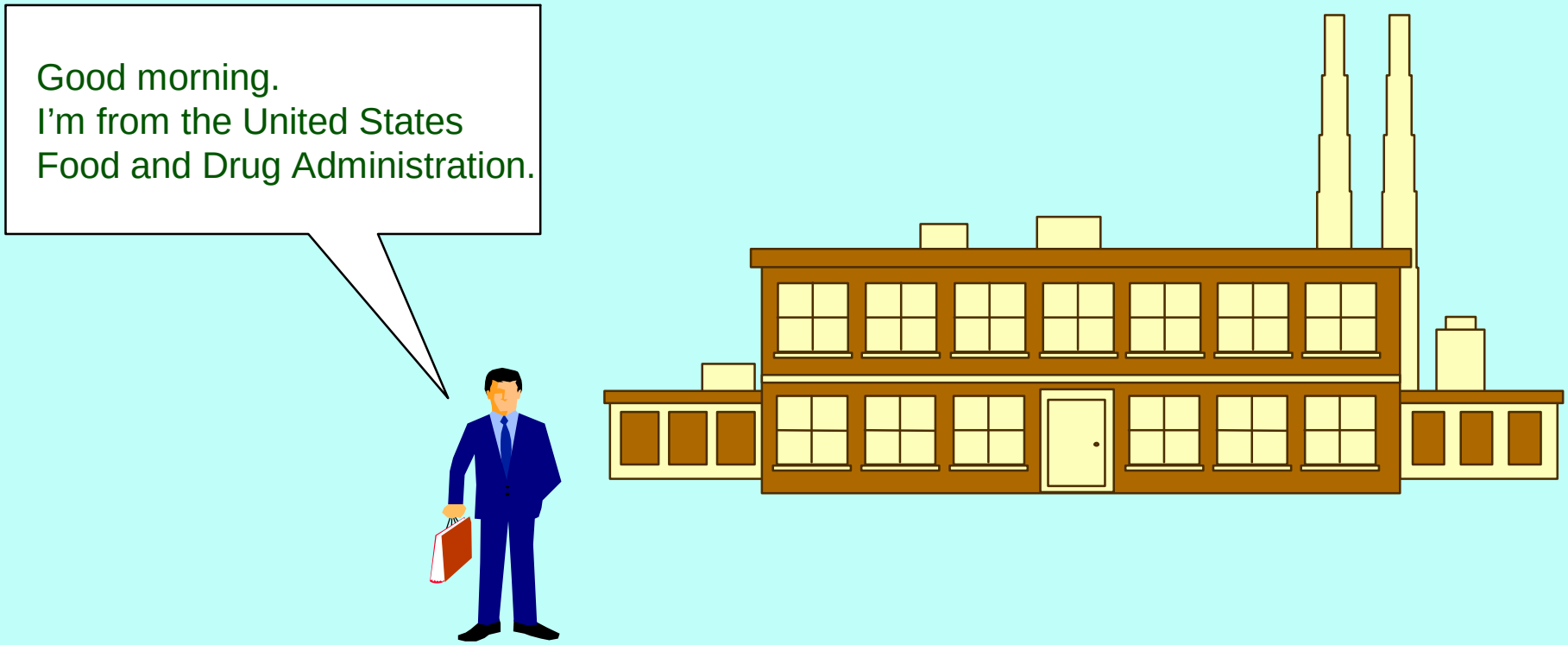
# Pre-Approval Inspection Training and Interfacing with FDA Investigators



# Purposes of this Training

- **Understand PAI Program Objectives**
- **Provide specific guidance on how to interface with the FDA Investigator(s)**
  - **“Do’s and Don’t’s”**
  - **Company policies**

# BACKGROUND INFORMATION

# FDA Terminology

- **FDA Forms**
  - **482-Notice of Inspection**
  - **484-Receipt for samples**
  - **483-Notice of Observations**
  - **EIR-Establishment Inspection Report**
- **Enforcement Activity (N/A in Europe)**
  - **Warrant**
  - **Warning letter**
  - **Consent Decree**
  - **Prosecution**

**For prescription drugs, Section 704 of the FD&C Act, the FDA Investigator has a right to inspect/enter our facilities at "Reasonable Times"**

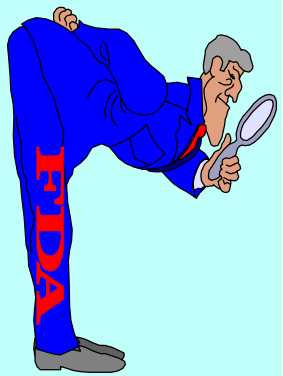
**Company policy is to conduct its business in compliance with all applicable regulatory mandates.**

# When FDA Representatives Visit Us

**They visit**

- **Our Manufacturing Facilities, (make, pack, test)**
- **Research & Development Laboratories,**
- **Regulatory/Medical offices and**
- **Distribution sites**

**for one or more of the following reasons:**




# Why FDA Inspectors Visit

- **General inspection of Manufacturing facilities**
  - **usually every two years (Section 704 of FD&C Act)**
- **Good Clinical Practices Inspection**
  - **usually every two years**
- **General inspection of Non-clinical Research Laboratories**
  - **usually every two years**


**Routine Sample Collections**

# Why FDA Inspectors Visit, not Routine Visits

- **Product Recalls**
- **Special FDA Compliance Programs Related to a Specific Drug or Class of Drugs**
- **Adverse Event investigations**
- **Customer Complaints**

# Pre-NDA Approval Inspections (PAI)

- **Approval of a new or supplemental NDA is predicated upon an acceptable outcome from inspections of:**
  - **Manufacturing/Packaging/Testing Facilities (GMP)**
  - **Product Development (GMP)**
  - **Contractors (GMP)**
  - **Bulk Drug Substance Supplier (GMP)**
- **Potentially extend to:**
  - **Non clinical (GLP) Facilities**
  - **Clinical Study Sites (GCP)**

# PAI Program Objectives
## (Compliance Program 7346.832)

- **Assure all establishments involved in manufacturing, testing, or other manipulations of new drug dosage forms and new drug substances are investigated:**

- **through on-site inspections for compliance with cGMPs**

  - **for conformance with application commitments**

  - **to assure data is authentic and accurate**

  - **laboratory testing of products, including evaluations of the adequacy of analytical methodology.**

# Pre-Approval Inspection Objectives

- **Evaluation of establishments compliance with cGMPs, including coverage of specific batches upon which the application is based.**
- **Evaluation as to whether the establishment has adequate facilities, equipment, procedures and controls to manufacture in conformance with application commitments.**
- **Audit of the completeness and accuracy of preapproval batch manufacturing and testing submitted with the application.**
- **Sample Collection**
  - **Forensic samples of the biobatch from the bioequivalence test laboratory and the applicant**
  - **Analytical method validation verification samples**

# FDA District Office Will Recommend Withholding Approval For The Following Reasons:

- **Significant deviations from GMP regulations**
- **Necessary facilities/equipment not in place**
- **Significant deviations in application data or commitments**

**Examples**

- **Application misrepresents data or conditions relating to pre-approval batches**
- **Inconsistencies/discrepancies raising significant questions about validity of records**
- **Pre-approval batches not made in accordance with GMPs**
- **Failure to report adverse findings or test data without adequate justification**

# Post-Approval Inspection Objectives

- **District office is responsible for program to ensure validation data in place prior to shipment of newly approved drugs**
- **Focus on process validation**

# DOs and DON'Ts DURING an INVESTIGATION


QA

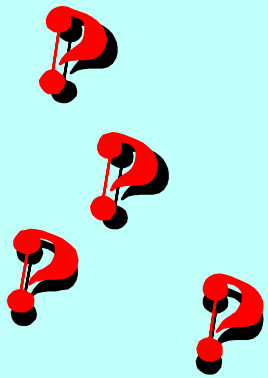
- **It is the Company's policy to cooperate with the FDA Investigator(s)**
  - **and to provide them with reasonable assistance in carrying out their responsibilities.**
- **We do not consider ourselves to be an adversary of the FDA.**
- **Rather, we have the same basic objective -**
  - **to see to it that the Drug (s) we develop and manufacture are safe, pure and effective.**

# During an Investigation

- **During the inspection, it is important to treat the FDA Investigator in a cordial, respectful manner.**

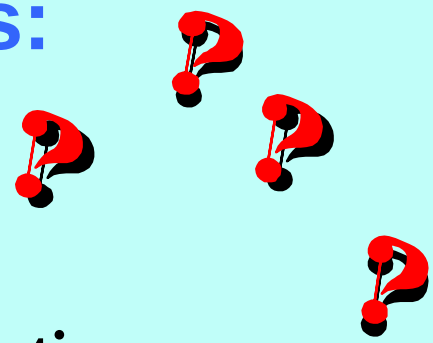
- **Because information supplied to the FDA becomes public knowledge, or may be used later in possible prosecution, care needs to be exercised in revealing information.**

# When answering questions:



- Be sure you understand the question. Ask for clarification, if needed.
- Answer only the question asked.
- Answer the question accurately and honestly.
- Allow a slight pause between the investigators question and your answer to allow the host or hostess to intervene,
- if necessary.
- Don’t guess, if you are not sure, Say “I don’t know”, refer question to others.
- Don’t volunteer any additional data/information. (beware of the "pregnant pause")
- No "off the record" statements.

# When answering questions:



- **Don’t answer what if or hypothetical questions**
  - © **Answer, We have never had a situation such as this type occur since I have been in this job or**
  - © **We do not anticipate a problem of this nature considering our operating procedures**
- **Do not argue with the investigator, rather:**
- **Ask for clarification, and search for understanding**
- **Don’t say “impossible” or “couldn’t happen here”**
  - © **(this is a red flag to the investigator)**

# EMPLOYEE'S INTERVIEWS


- **The investigator has the right to interview any employee**

- **Prior to allowing an interview the host should:**
  - **Determine the specific needs of the investigator**

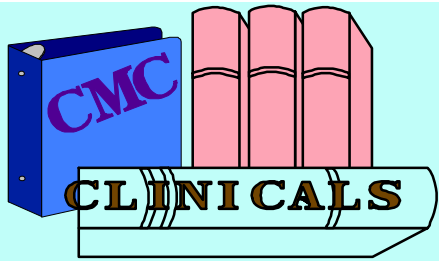
# EMPLOYEE'S INTERVIEWS


- **If the host feels it is in the best interest of the company, the following agreements are made:**
  - **A statement is written allowing an interview because the investigator deems it to be a requirement of law**
  - **Gain an understanding with the investigator that the Host will be present**
  - **Gain an understanding that the Host has the right to intervene in any response which might wander outside the knowledge/job responsibilities of the employee.**
  - **Move to a conference room for the interview**

# When Supplying Data

- **Make two copies, one for our files, if a copy is requested.**
- **Where possible, remove the document from books or files.**
- **Stamp the first page with “Exact Copy” initial & date. If confidential, stamp each page “Confidential”**

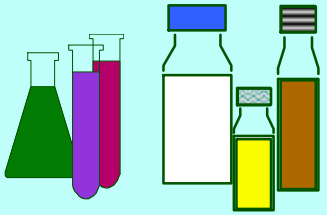
# When Supplying Data,




- **Do not share the following**
  - **Financial data**
  - **Sales Data (other than shipment data)**
  - **Pricing data**
  - **Personnel data (other than data as qualifications to perform duties)**
  - **Internal Audit Data**

- **Respectfully decline to read, sign or verbally affirm or deny information in an Affidavit.**
  - **If investigator prepares one, send to Legal**

# When Supplying Samples



- **Take duplicate samples,**
  - **usually enough to repeat testing twice**
- **Company policy is to not charge.**
  - **However, obtain a receipt.**

# Recording Equipment

- **Recording Equipment is not allowed**

- **Cameras are not allowed, except under extreme conditions or during pre-approval.**
  - **Contact Legal first.**

- **Investigators must always be escorted by P&G personnel while in a P&G facility**

# During the Inspection

- **All information provided is given to the Host /Coordinator first, for review**
- **Have one person take detailed notes**
- **If deviations are noted during inspection, take immediate corrective action where possible/appropriate.**
  - **Ask to have such action noted in inspection report.**

# During the Inspection

- If a 483 is presented
  - make no comments, unless observation is inaccurate or to ensure understanding.
  - respond to the FDA 483
    - within 10 days
- If the investigator prepares an affidavit regarding various details of the inspection, respectfully decline to read, sign or verbally affirm the details
- Send to Legal
- Do not offer to buy lunch or to cover any other expenses accrued by the inspector. Exception is if it will be cumbersome to have investigator pay for lunch.

# HOSTING PROCEDURE

- Greet the investigator in the lobby
- Expect to receive Inspection Form 482 (in US only).
- Ask for and inspect credentials.
- Escort investigator to the pre-assigned conference room
- Ask for purpose of visit.  Try to set up a rough agenda.
- At this point co-host should alert the appropriate people
  - based on reason for visit.
- Escort investigator at all times
- Furnish one record at a time

# HOSTING PROCEDURE

- **If a tour is requested ask the inspector to leave any cameras or recording devices with the receptionist**
  - **for safe keeping.**
- **Ensure a notetaker is available.**
- **Provide documents as requested per P&G policy.**
- **Determine needs of the investigator for the next day**
- **Call appropriate people that the investigator has left and review results/findings**

# Inspection Strategies for Risedronate and Azimilide PAIs

- **“Expert/Back-up” list**
- **Risk assessment tool**
  - **includes issues and strategies**
- **Consultant or internal “mock” audit**
  - **practice**
  - **further refine strategies**
- **Combined pre and post-approval inspections**
  - **focus on successful process validation**

# Expert/Backup Responsibilities

- **Review documents to be presented. Be familiar with all potential issues and strategies to address them.**
- **Know GMP's as they pertain to your area.**
- **Know your area**
  - **Product**
  - **Process**
  - **Equipment**
  - **Systems/controls**
  - **SOPs**
- **Present/answer questions in a confident and professional manner. Focus on the positive.**
- **Use**