FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

The Boy Scout's Guide to FDA Inspections

(Hint: Be Prepared)

Presented to:
Los Angeles Section, ASQ

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August 9, 2017

Disclaimer

Neither the slides nor their contents have been endorsed by the
Government of the United States,
The Department of Health and Human Services or
The US Food & Drug Administration

The contents of these slides have been prepared by me, and comprise my opinion on the topics discussed

Motivation

The mission of the US Food & Drug Administration is:

To Protect and Advance the Public Health

And our primary goal is to achieve this by:

Voluntary Compliance

Education and dialogue can help get us there together to serve the American public.

About me…

- I have been privileged to serve as a Consumer Safety Officer / Investigator for the past 3.5 years, first as a Drug Specialist and subsequently as a member of Team Biologics, a national cadre of Investigators who specialize in biological drug products.
- I have performed inspections at Food, Drug, Medical Device, and Biologics manufacturing sites
- Prior to joining the Agency, I worked in a number of multi-national pharmaceutical firms, focused on internal and supplier auditing and site remediation.

Agenda

- Resources FDA makes available to the Public
  - How can I use them? And why should I?
- Administrative Preparations
  - Give them what they want so that I can get back to work and help feed / cure people / animals!
- Things to Try and Avoid
- Inspection / Post Inspection
  - OK, the Investigator is gone and I've [not] been issued an FDA 483 Inspectional Observations –what happens now?
- ORA Program Alignment (if there's time / interest)

The interwebs are your friend!

AVAILABLE PUBLIC RESOURCES

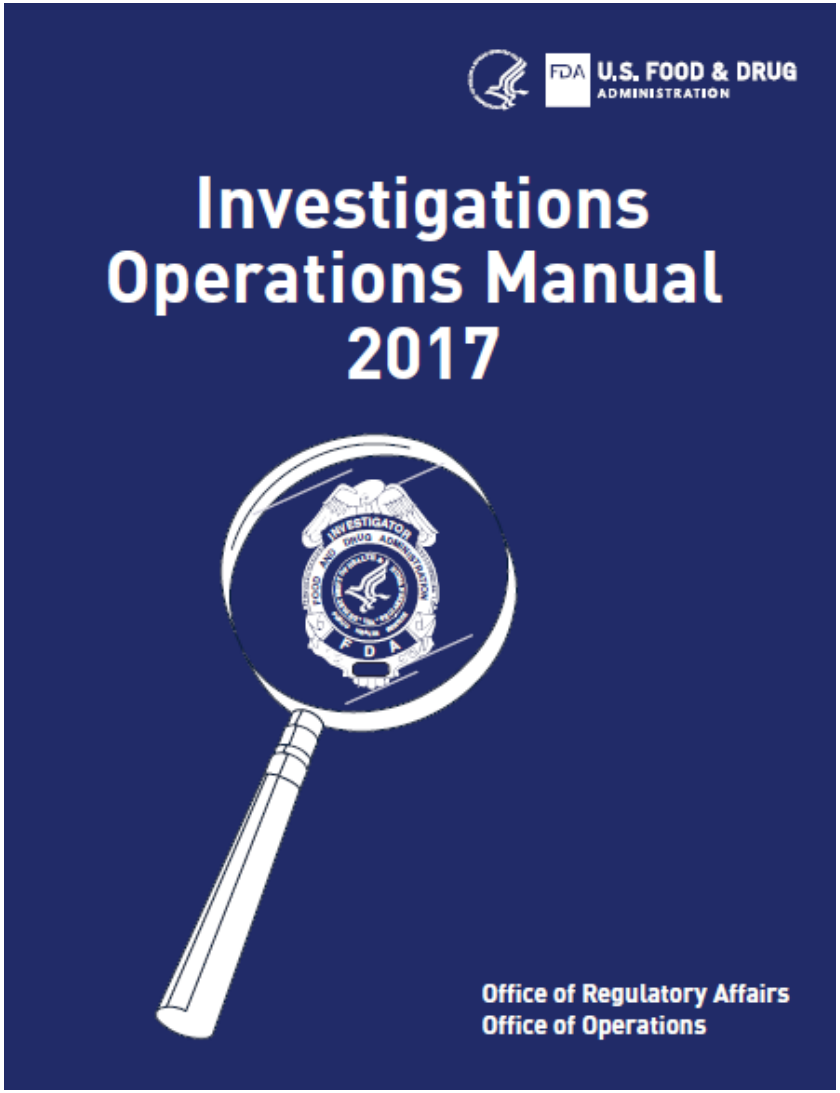
Introduction

- If you have a robust quality system and you're making good choices, congrats – you're prepared!
- So, what are the benefits of using FDA's resources?
  - Be on the same page as the Investigator!
  - Communicate in the same language
  - Avoid misunderstandings
  - Potential Quality System Improvements

Public Resources Available

Investigations Operations Manual

The IOM helps guide Investigators to do their job – it's like our Bible.



Investigations Operations Manual

Why bother though?

- Get insight into how we're trained
- Opens a window into what we experience and care about

Chapters of Interest:

- 5.2.3 Reports of Observations
- 5.2.5 Inspection Refusal
- 5.2.7 Discussions with Management
- 5.3.3 Exhibits

Investigations Operations Manual

Commodities discussed:

- 5.4 – Food
- 5.5 – Drugs
- 5.6 – Devices
- 5.7 – Biologics
- 5.8 – Tobacco Products
- 5.9 – Veterinary Medicine

Investigations Operations Manual

Last but not least:

- 5.10 Reporting (see also Field Management Directive FMD 145)
- Blue Pages

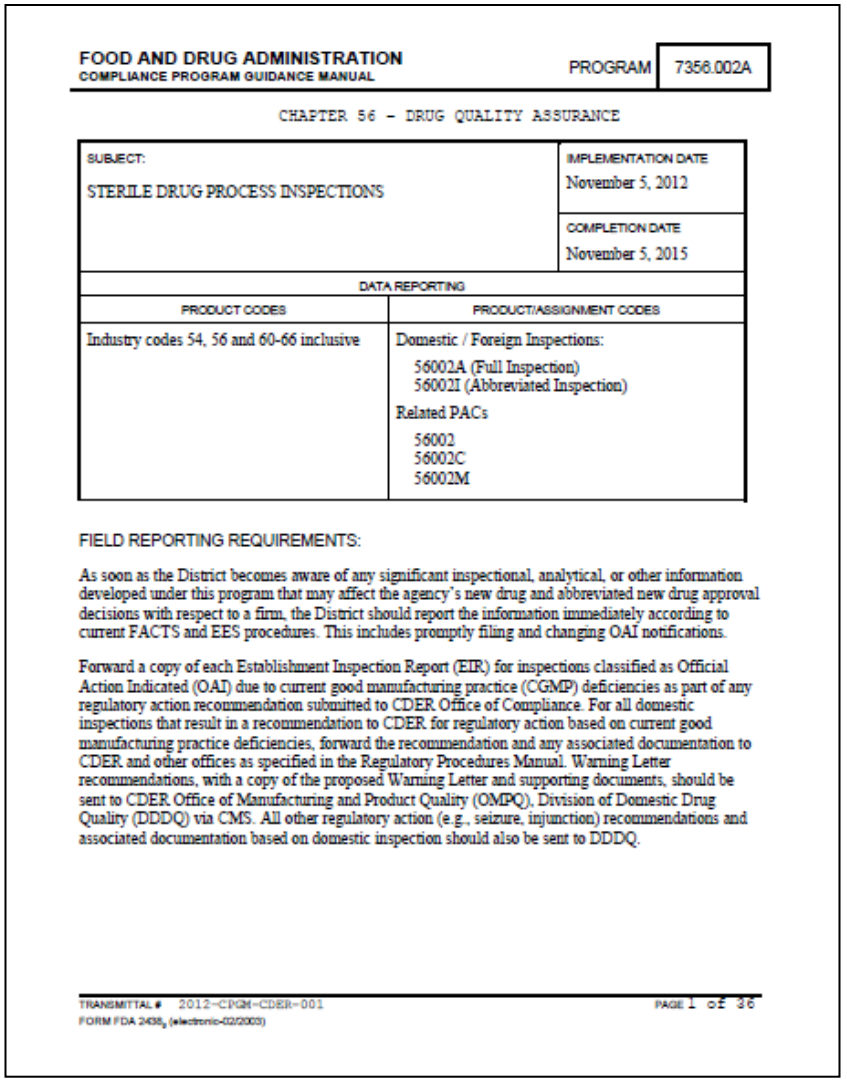
The 2017 edition of the IOM can be found at:

https://www.fda.gov/iceci/inspections/iom/default.htm (or just type IOM in the search box of the FDA internet site @ www.fda.gov)

Public Resources Available

Compliance Program Guidance Manuals

These documents have specific requirements for what we should be reviewing as part of our inspections. The manuals can help Investigators draw up a checklist.



FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL

PROGRAM 7356.002A

CHAPTER 56 – DRUG QUALITY ASSURANCE

SUBJECT:	IMPLEMENTATION DATE
STERILE DRUG PROCESS INSPECTIONS	November 5, 2012
	COMPLETION DATE: November 5, 2015

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry codes 54, 56 and 60-66 inclusive	Domestic / Foreign Inspections: 56002A (Full Inspection) 56002I (Abbreviated Inspection) Related PACs 56002 56002C 56002M

FIELD REPORTING REQUIREMENTS:

As soon as the District becomes aware of any significant inspectional, analytical, or other information developed under this program that may affect the agency's new drug and abbreviated new drug approval decisions with respect to a firm, the District should report the information immediately according to current FACTS and EES procedures. This includes promptly filing and changing OAI notifications.

Forward a copy of each Establishment Inspection Report (EIR) for inspections classified as Official Action Indicated (OAI) due to current good manufacturing practice (CGMP) deficiencies as part of any regulatory action recommendation submitted to CDER Office of Compliance. For all domestic inspections that result in a recommendation to CDER for regulatory action based on current good manufacturing practice deficiencies, forward the recommendation and any associated documentation to CDER and other offices as specified in the Regulatory Procedures Manual. Warning Letter recommendations, with a copy of the proposed Warning Letter and supporting documents, should be sent to CDER Office of Manufacturing and Product Quality (OMPQ), Division of Domestic Drug Quality (DDDQ) via CMS. All other regulatory action (e.g., seizure, injunction) recommendations and associated documentation based on domestic inspection should also be sent to DDDQ.

TRANSMITTAL # 2012-CPGM-CDER-001 PAGE 1 of 36
FORM FDA 2438, (electronic-02/2003)

Compliance Program Guidance Manuals

What's my ROI? / How can I use this document?

- If you look for what we look for, you're less likely to get an unpleasant surprise
- These documents can form the basis for your internal auditing program – someone has already done the heavy lifting for you!

Compliance Program Guidance Manuals

Normally at least six parts. Pay special attention to:

- Part III – Inspectional
- Part V – Regulatory (if things go sideways)
- Part VI - References
- Attachments – Can have specific information about particular commodities

Compliance Program Guidance Manuals

Note: Some commodities will utilize more than one CPGM

For example, a pre-license inspection for a monoclonal antibody (a sterile biological drug) could use:

7356.002 – Drug Inspections

7356.002A – Sterile Drug Inspections

7346.832 – Pre-Approval Inspections

7356.002M– Licensed Biological Therapeutic Drug Products

Compliance Program Guidance Manuals

Also note: Your site might be inspected for multiple commodities / regulatory aspects at once:

- Dietary Supplement / Drug Firms
- Combination Products
- Post Marketing Adverse Drug Events / Medical Device Reporting

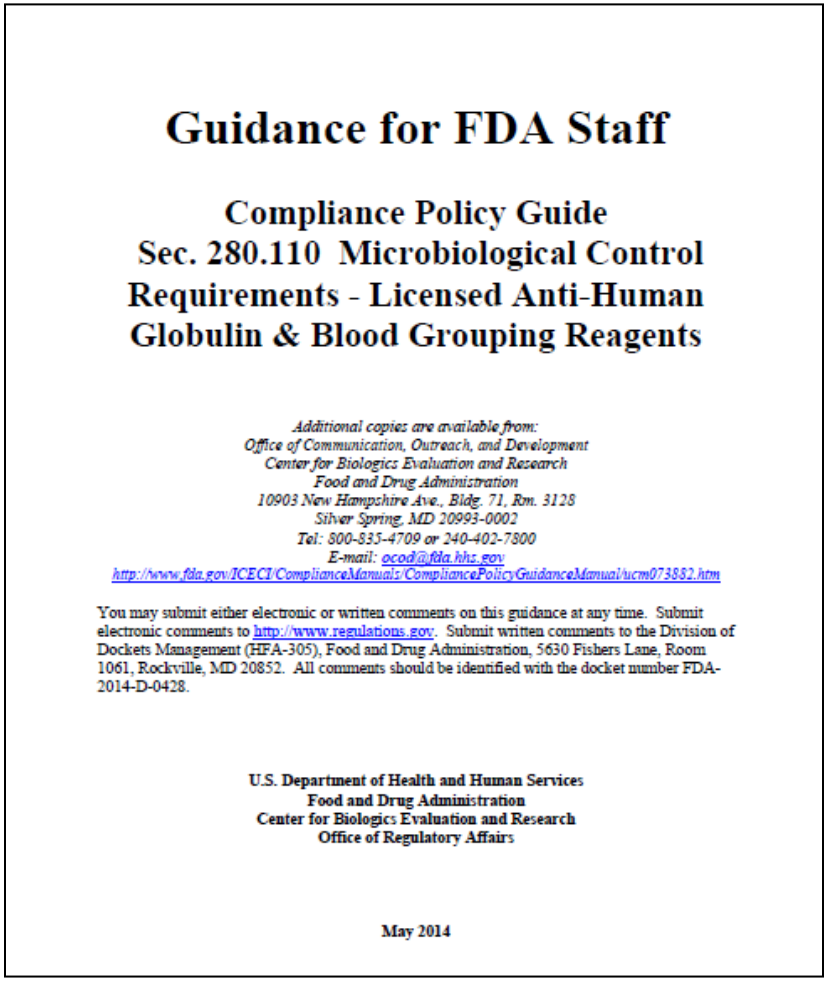
Compliance Program Guidance Manuals can be found on the FDA Internet at:

https://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograMManual/default.htm

Public Resources Available

Compliance Policy Guides

- More specific information that may apply to your site
- We are trained to refer to them as part of the preparation process and they are referenced in the CPGMs
- Contents may answer questions not easily found elsewhere



Guidance for FDA Staff

Compliance Policy Guide
Sec. 280.110 Microbiological Control Requirements - Licensed Anti-Human Globulin & Blood Grouping Reagents

Additional copies are available from:
Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Rm. 3128
Silver Spring, MD 20993-0002
Tel: 800-835-4709 or 240-402-7800
E-mail: ocod@fda.hhs.gov
http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073882.htm

You may submit either electronic or written comments on this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2014-D-0428.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Regulatory Affairs

May 2014

Compliance Policy Guides

The Guides are divided into chapters by Commodity:

Chapter 1 – General

Chapter 2 – Biologics

Chapter 3 – Devices

Chapter 4 – Drugs

Chapter 5 – Food, Colors & Cosmetics

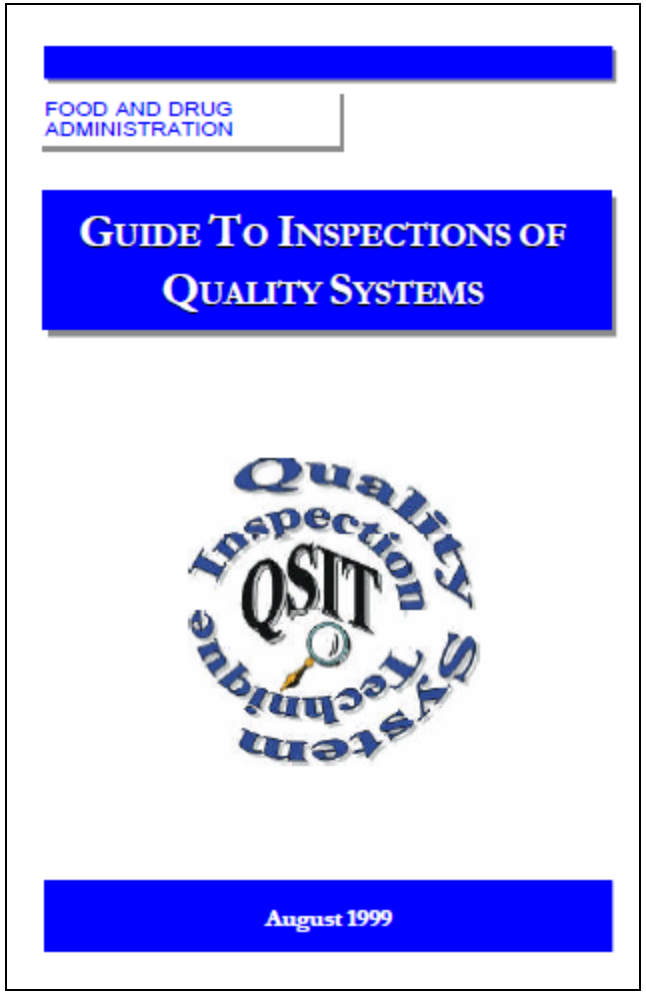
Chapter 6 – Veterinary Medicine

Listing of Compliance Policy Guides:
https://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm

Public Resources Available

Guidance Documents

- These documents reflect the Agency's current thinking, but are not enforceable. However…
- They typically make reference to sections of the regulations, so if you aren't applying an alternative approach that meets the regs, then you can be cited.



Guidance Documents

Lots and lots of guidances exist (4,140 are listed currently) and new ones are published all the time. So how do I keep on top of things?

- Sign up for Guidance Document email updates
- Search for guidances of interest: https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Public Resources Available

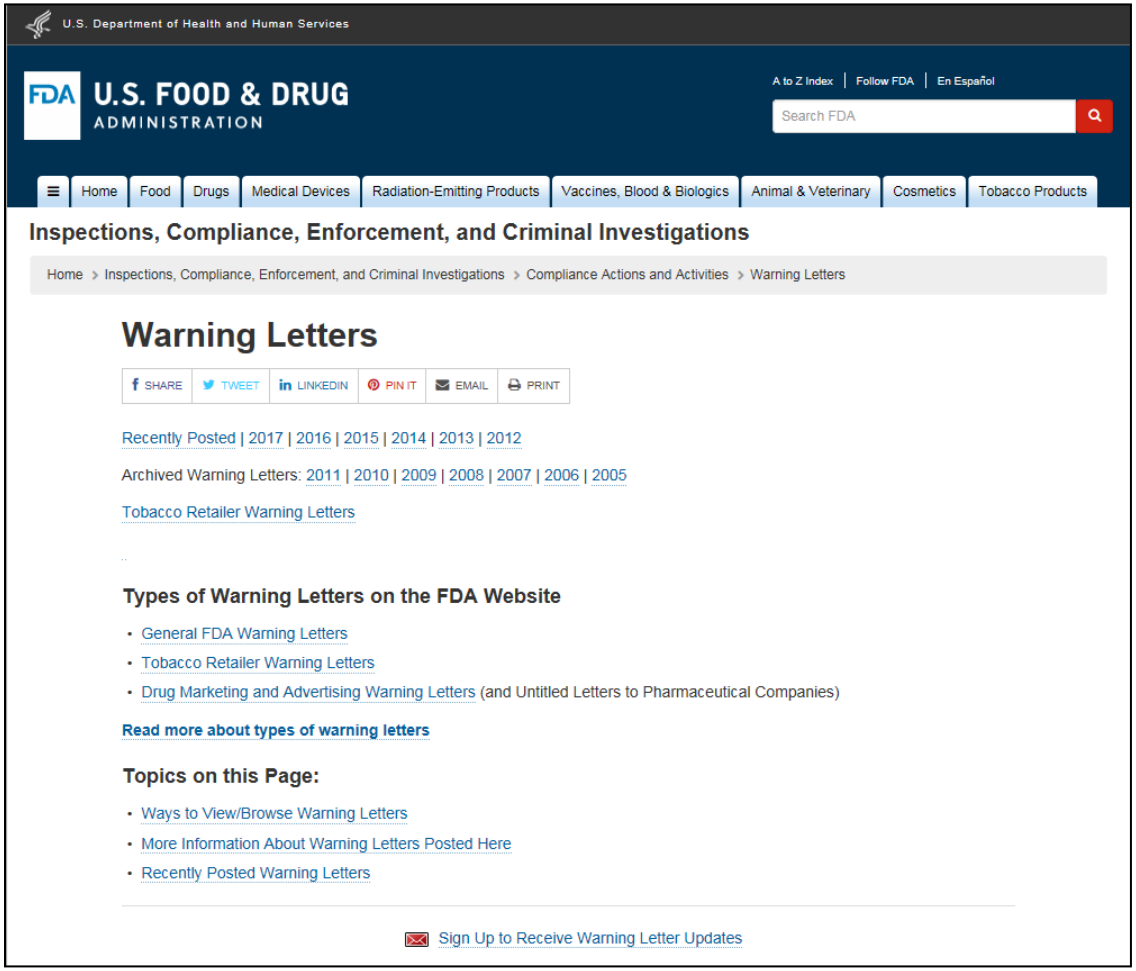
Pursuant to the **Freedom of Information Act**, you have access to government work product FDA has a interest in being transparent and shares:

- Warning Letters
- Selected FDA 483 Inspectional Observation Reports for Drug Manufacturers

You do not have access to trade secrets or any non-government work product.

FOIA Reading Rooms

These documents form the baseline expectations for **current** GMP requirements



FOIA Reading Rooms

All Warning Letters can be found at:
https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

Selected Drug FDA 483 Inspectional Observation Reports can be found at:
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/CDERFOIAElectronicReadingRoom/ucm515118.htm

Other regulatory documents can be found at:
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/default.htm

Public Resources Available

Training – **FDA Basics** include general trainings / webinars and guidance. There are also specific resources available for specific commodities

- These trainings are available 24/7 and free of charge
- FDA Fundamentals is a good place to start to get some basic familiarity of what the Agency does

FDA Basics

You can find FDA Basics on the internet at:

https://www.fda.gov/AboutFDA/Transparency/Basics/default.htm

Public Resources Available

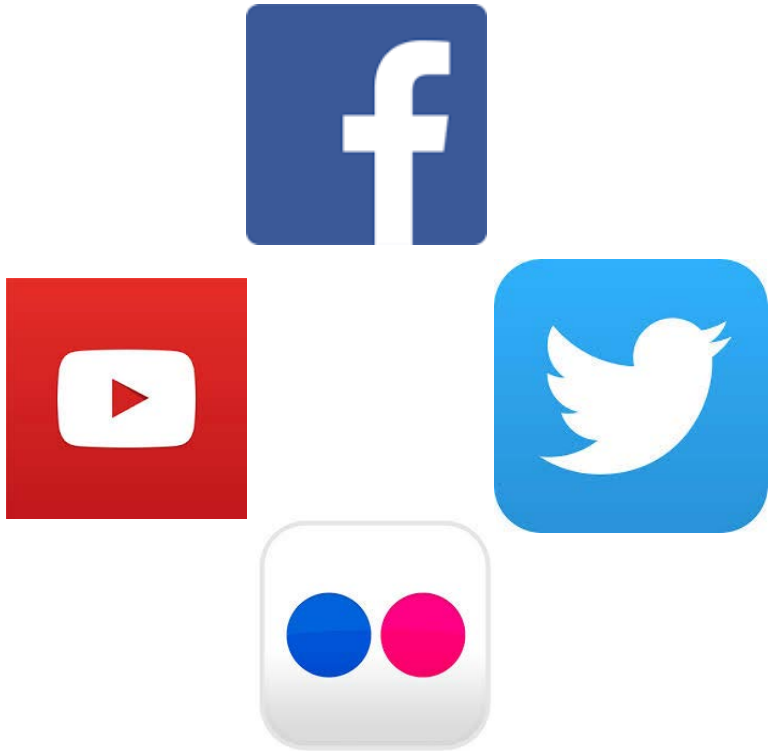
Many many many more resources are out there:

- Staff Manual Guides
- Field Management Directives
- Open FDA
- Phone Numbers / Emails

Public Resources Available

Social Media:

- Facebook
- Twitter
- YouTube
- Flickr



RSS Newsfeeds / Podcasts

Public Resources Available

Free advice (is worth…):

- Google, the Search Bar on www.fda.gov and Favorites are your friends!
- Don’t get frustrated if you encounter a broken link – or if you can’t figure out how to go back to where you found a gold nugget. The width and depth of information available makes managing / finding stuff on the website a gargantuan task.
- If you’re in compliance / quality – spend a day on the website to figure out what resources will benefit you most.

Get [us] in, get [us] out, get on with your life…

ADMINISTRATIVE PREPARATION

Administrative Preparation

FDA will normally visit a regulated site on regular basis; the periodicity of inspections is mandated by law – for example:

- Medical Devices: Biennially
- Drugs: Based on Risk

So, the question is not –
will I hear a knock at the door
but rather… when?

Administrative Preparation

So, what can you do to help your friendly neighborhood Investigator get their job done and happily on their way back to the office?

Anticipate what we want – keep the items up to date, and have everything ready for when we come for a visit.

Administrative Preparation

If you're going to prepare an opening presentation, consider including the following:

- Org Charts
- Changes to corporate structure / key personnel
- Legal structure / affiliates
- Hours of Operation

Number of Employees

- Batch numbering system
- Detailed floor plans
- Manufacturing flow diagrams

Administrative Preparation

Key Procedures:

- Management Controls
- Complaint / Required Report Handling
- Deviations and Investigations
- Corrective / Preventive Actions
- Change Control
- Trending
- Risk Management
- Training
- Validation Master Plan
- Equipment Qualification / Calibration
- Equipment / Facility Cleaning / Maintenance
- Pest Control
- Supplier Qualification and Management
- Material Release / Disposition
- Hygiene / Gowning Procedures
- Master Batch Records
- Line Clearance
- OOS Investigations
- Environmental Monitoring
- Annual Product Review

Administrative Preparation

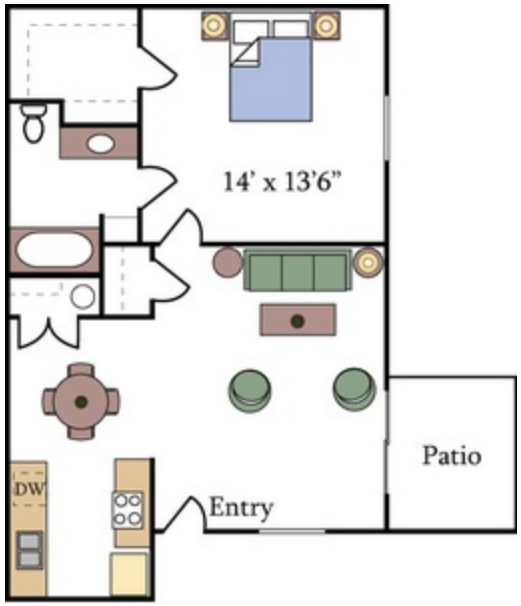
Lists of the following:

- Regulated Products Manufactured on site
- Procedures / Test Methods
- Equipment
- Deviations and Investigations
- CAPAs
- OOS Investigations
- Suppliers
- Changes - Process / Facilities / Equipment
- Validations
- Risk Assessments
- Computer Systems

Administrative Preparation

Drawing / Pictures of the following:

- Detailed Floor Plans
- P&IDs for Water System
- HVAC Layouts



Administrative Preparation

Other commonly requested documents:

- Site Master File / Quality Manual
- Responses to last FDA 483 and related evidence
- Evidence showing that discussion items or other issues documented in the previous EIR have been addressed

Free advice: Record the documents you provide us during the inspection; keep this list to prepare for our next visit

Administrative Preparation

FDA proudly [finally?] welcomes the 21st Century!

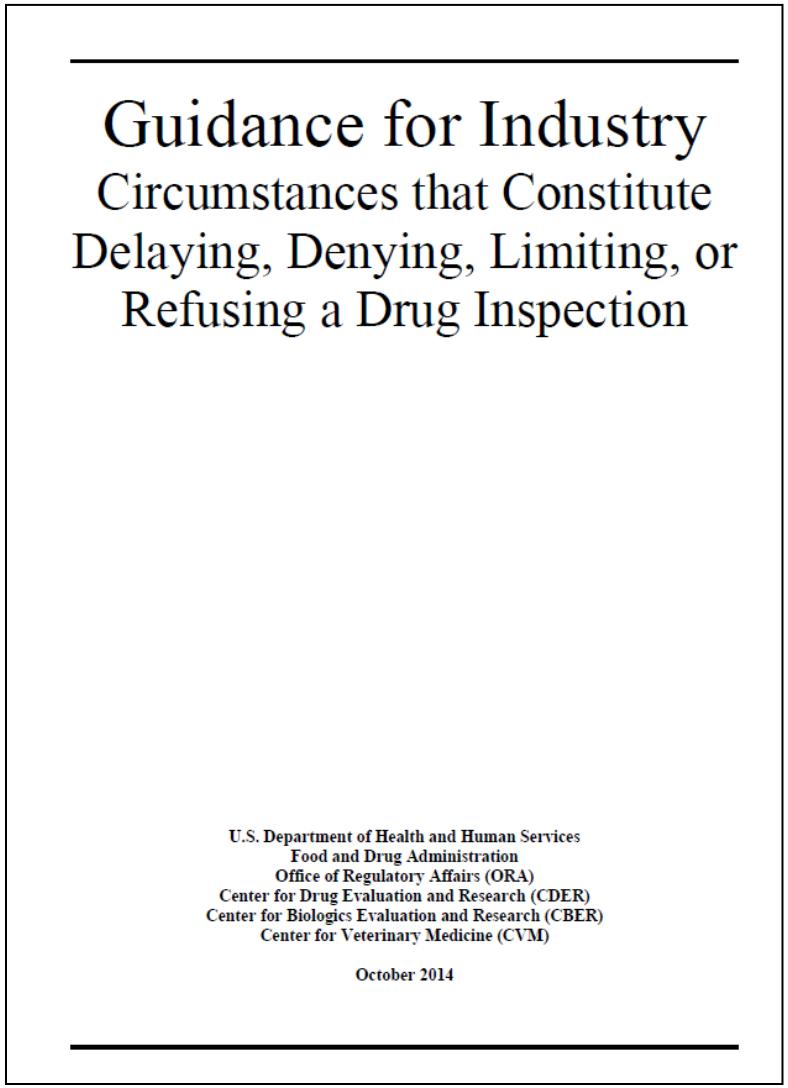
The facts ma’am, just the facts…

THINGS TO TRY AND AVOID

Behaviors to Avoid

Per FDASIA (Food & Drug Administration Safety and Innovation Act):

A drug can be considered **adulterated** if the responsible person "**delays, denies, or limits an inspection, or refuses to permit entry or inspection**"



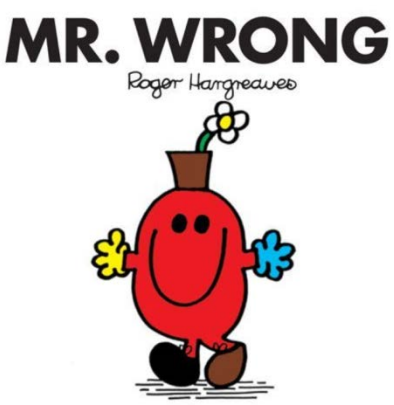
Guidance for Industry

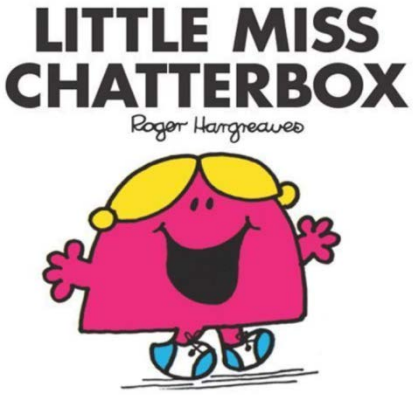
Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection

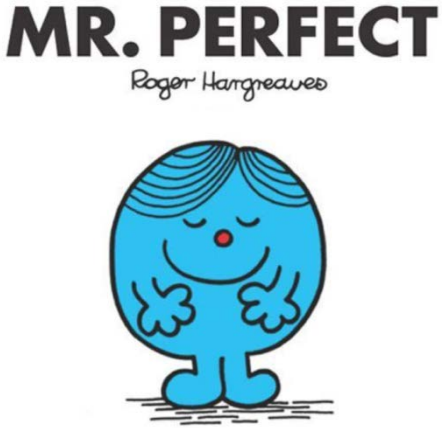
U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs (ORA)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

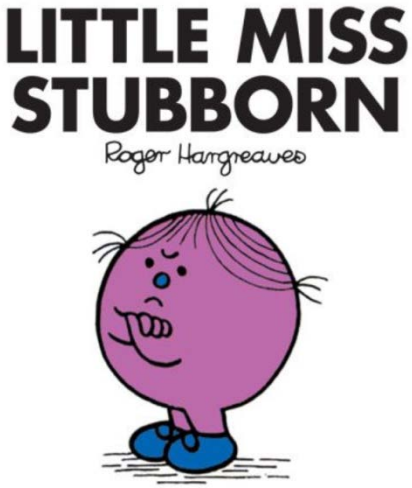
October 2014

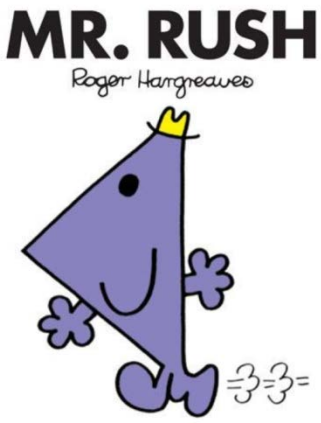
Behaviors to Avoid











Sadly, the investigator left. (Said no one. Ever.) Now what?

POST INSPECTION

Post Inspection

Everyone plays a unique role:

ORA Investigators

- Perform inspections
- Report on inspections
- Make initial recommendation
  - No Action Indicated
  - Voluntary Action Indicated
  - Official Action Indicated
  - Approve
  - Withhold

Post Inspection

ORA Compliance Officers

- Review reports, evidence, and **responses**
- Agree / disagree with inspection recommendation and document their determination
- Write Warning Letters (Direct Reference Cases)
- Interface with Centers on other violative cases

Post Inspection

Center Compliance Officers

- Handle violative cases, review all documentation, including Division Investigator / Compliance recommendations
- Write up Warning Letters
- Assign follow up / for cause inspections

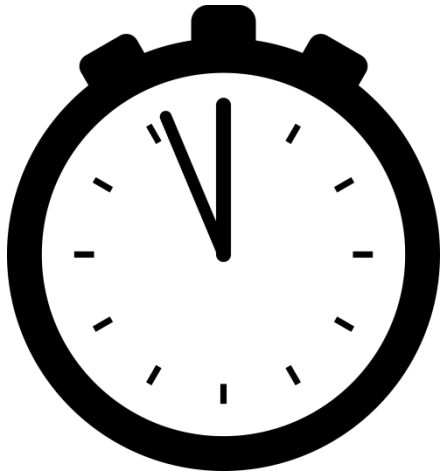
Center Review Divisions

- Final approve / withhold decision

Post Inspection

Free advice:

- Respond to the FDA 483 within 15 business days if you get one – responses are taken into account when making a final disposition decision – and why shouldn't the decision makers hear your voice?



ORA Ombudsman

Jessica Zeller, JD, MA
Ombudsman

- Informally and impartially addresses concerns, complaints, and disputes between ORA and external parties:
  - Industry
  - Federal, state, territory, and tribal government entities
  - Public
- Contact:
  - 513-679-2777 or 240-535-6021
  - ORAOmbudsman@fda.hhs.gov

PUBLIC HEALTH PARTNERSHIPS:

Enhancing ORA operations by serving as an objective, neutral resource to improve communication channels, resolve disputes, and foster positive relationships with internal and external stakeholders.

Questions are guaranteed in life, answers, not so much…

QUESTIONS?

FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

Thank You!

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