U.S. FDA

Updated Trends

by

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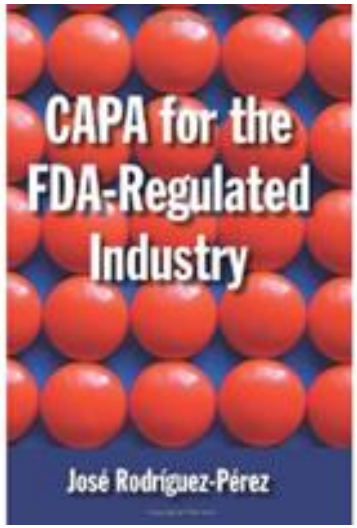

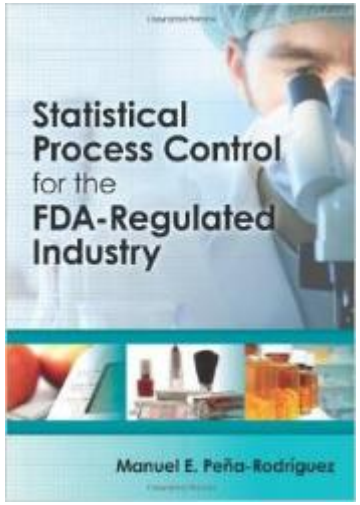

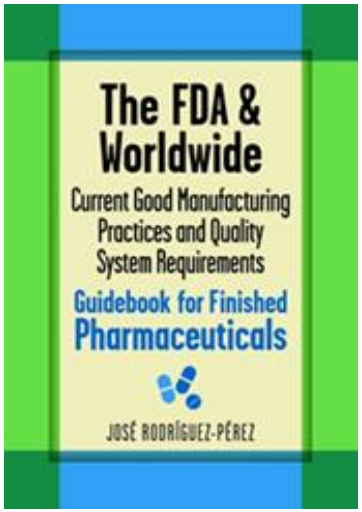

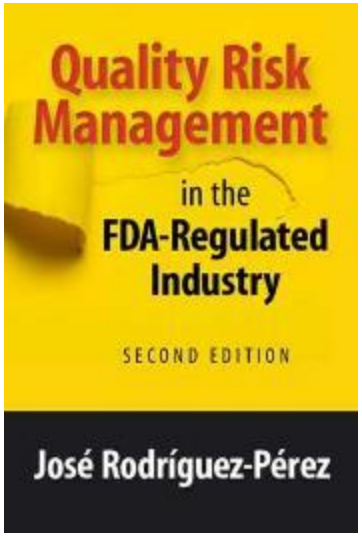

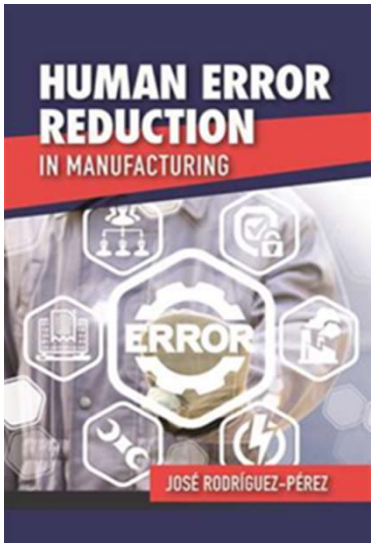

Agenda

Pharmaceutical

- Generals / Keys Concepts
- Generic Drugs Update
- Mutual Recognition Agreement
- U.S. Government Shutdown
- 2018 GMP Inspectional Trend
  - Examples

Medical Devices

- Medical Device Single Audit Program (MDSAP)
- 2018 GMP Inspectional Trend
  - Examples

FOOD AND DRUG ADMINISTRATION

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Approved by the FDA Reorganization Coordinator & Principal Delegation Control Officer 25 September 2017

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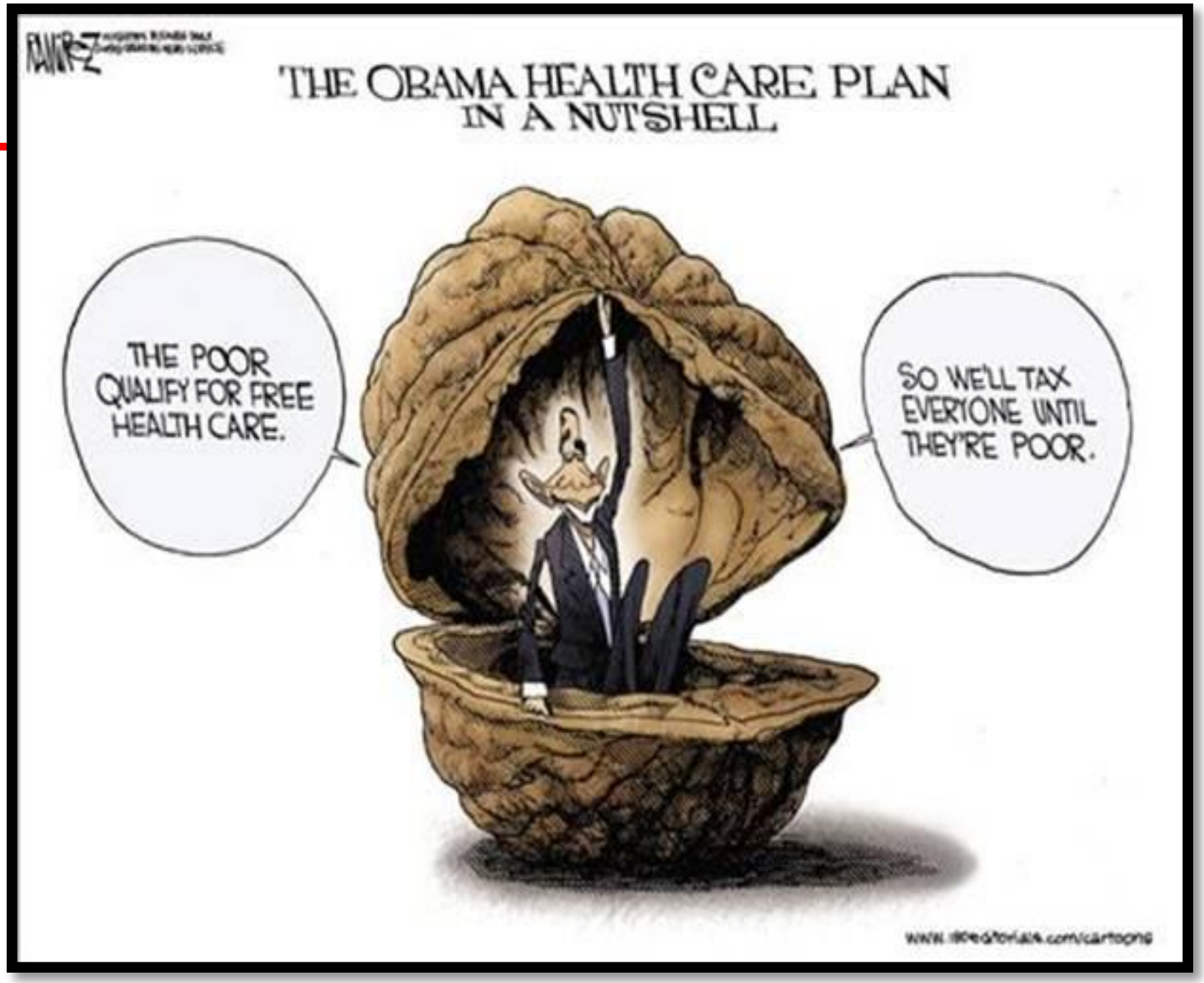
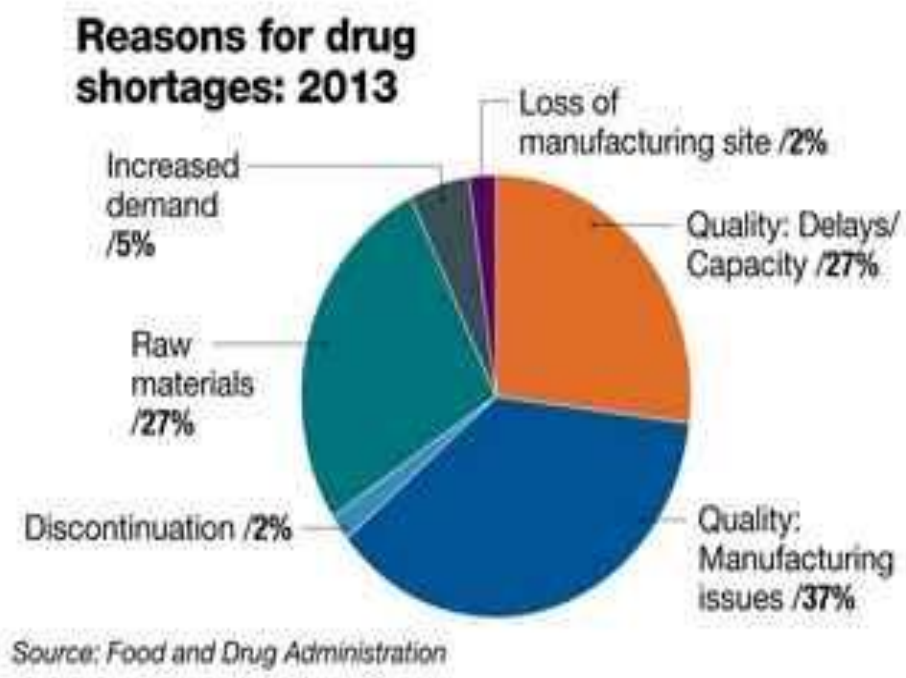
Legend:
- - - - Direct report to DHHS General Counsel
. . . . . Indirect reporting relationship to the Office of Chief Scientist


THE OBAMA HEALTH CARE PLAN
IN A NUTSHELL
THE POOR QUALIFY FOR FREE HEALTH CARE.
SO WE'LL TAX EVERYONE UNTIL THEY'RE POOR.

SHORTAGES


Reasons for drug shortages: 2013
Loss of manufacturing site /2%
Increased demand /5%
Quality: Delays/ Capacity /27%
Raw materials /27%
Discontinuation /2%
Quality: Manufacturing issues /37%
Source: Food and Drug Administration

CONCEPTS

- **Approval**
- **Tentative Approval**
- **Complete Response**
- **Easy Correctable Deficiencies**

- **PAS** *(Prior Approval Supplement)*
- **CB** *(Change Being Effected)*
- **CB - 30** *(Change Being Effected)*
- **NDA 505 (b)(2)**
- **Product Hopping, Forced switching or Evergreening**

- **AB Rating** Same API, route, strentgh, biequivalent

FRAMEWORK

TYPE	REGULATION	DESCRIPTION	
NDA	505(b)(1) of the FD&C Act	Application that contains **full safety and efficacy reports**	Reports were conducted by or for the Applicant or for which the applicant has a right of reference or use.
NDA	505(b)(2) of the FD&C Act (also known has modified or hybrid submission)	Application that contains **full safety and efficacy reports**	One or more of these studies **was not conducted by the Applicant** and the Applicant **has not obtained the right to reference or use** these reports. (eg. Published literature, FDA´s finding of safety and effectiveness for an approved drug)
ANDA	505(j) of the FD&C Act	An application for a **duplicate of a previously approved drug product** that was submitted and approved (Reference Listed Drug). An ANDA relies on FDA's finding that the RLD is safe and effective. An ANDA generally must contain information to show that the proposed generic product is: 1. The **same as the RLD** with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) 2. **Bioequivalent** to the RLD	

DMF

Information	Description	
Who must file a DMF?	NOBODY!!! There is no legal or regulatory requirement to file a DMF. Information can be in an Application (ie. NDA, ANDA, etc.) or a DMF.	
Why file a DMF?	• Maintain confidentiality of proprietary information (e.g., Manufacturing procedure) for the holder • Permit review of information by reviewers at FDA to support applications submitted by one or more applicants (i.e. IND, NDA, BLA, ANDA, another DMF, etc.)	
Can a DMF be considered approved?	NO. It is not approved or disapproved. A DMF is reviewed to determine whether it is adequate to support the particular Application that references it.	
Regulatory framework	21 CFR 314.420 Drug Master Files Guidance documents: general website, completeness review	
Types of DMFs	Type II	Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
	Type III	Packaging Material
	Type IV	Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
	Type V	FDA Accepted Reference Information
Type II DMFs	Format	• CTD structure: Modules 1 (Admin), 2 (QOS) & 3 (DS & Regional (if applicable)) • Starting in May 2018, new DMFs submitted to the FDA must be in eCTD

DMF

Information	Description
DMF List	Every quarter, the FDA publishes a list of DMF received and for which acknowledgement letters were sent. See Q3 2017 list. Status: • "A" = Active. This means that the DMF was found acceptable for filing, administratively, and has not been closed. • "I" = Inactive. This means a DMF that has been closed, either by the holder or by the FDA.
Obligations of DMF Holders	➢ Submit all changes as amendments when they occur. (There are no reporting categories for DMFs. All changes must be reported as amendments). ➢ Notify authorized parties of changes. ➢ Submit Annual Report (AR): ➢ List of authorized parties ➢ List of all changes reported since last AR ➢ If no changes, include a statement to that effect ➢ Submit Letter of Authorization (LOA) for each item referenced for each customer.

ORANGE BOOK

- A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use.
- All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).
- The Orange book contains the following information.
  - Product with an effective approval has not been withdrawn for safety or efficacy reasons.
  - Application number
  - TE code: therapeutic equivalence status
  - Reference Listed Drug (RLD) and Reference Standard (RS) status
    - RLD: drug product upon which an applicant relies in seeking approval of its ANDA.
    - RS: drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an *in vivo* bioequivalence study required for approval.
    - Ordinarily, FDA will select the RLD as the RS. However, in some instances (e.g., where the RLD has been withdrawn from sale and an ANDA is selected as the RS), the RLD and the RS may be different.
  - Patents and exclusivities

PATENTS

Party	Action	Details		
Innovator (NDA)	List patents	➢ NDA sponsor must identify in NDA those patents reasonably related to drug product, drug substance, or method of using drug (ie. MOU) for which approval is sought. ➢ NDA sponsor must submit patents for listing **within 30 days** of NDA approval. ➢ FDA "lists" patents identified by NDA sponsors in "Orange Book" (OB).		
Generic (ANDA)	Certify patents	**Type**	**Certification**	**Impact**
		Paragraph I certification	Patent information has not been filed	FDA can approve ANDA when approval-ready
		Paragraph II certification	Patent has expired	FDA can approve ANDA when approval-ready
		Paragraph III certification	The date the patent will expire	FDA can approve ANDA when patent expires and ANDA is approval-ready
		Paragraph IV certification	The patent is invalid or not infringed by the drug product proposed in the ANDA	Complex approval landscape

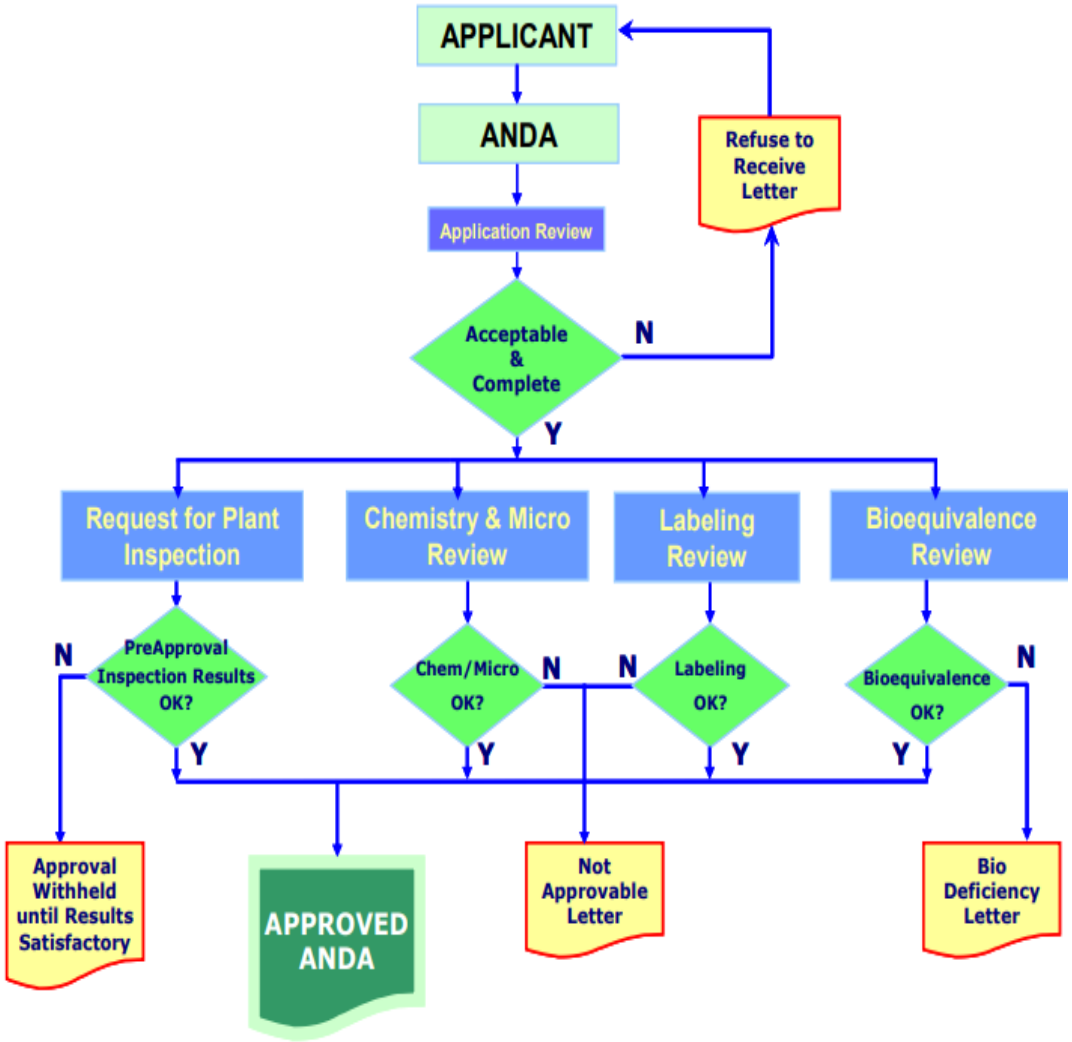
Generic Drug User Fee Amendments (GDUFA)

- User fee program paid by the industry to the FDA.
- Program is based on a 5-year period:
  - GDUFA I: 2012-2017
  - GDUFA II: 2018-2022
- In August of each year, the FDA publishes the fee structure for the following calendar year. (It should be noted that the FDA´S fiscal period is October to September).
- Important: GDUFA requires that the FDA and the industry must meet certain requirements and commitments.
  - FDA: performance goals, refuse-to-receive standards, etc.
  - Applicants: high-quality submissions that can be accepted for filing.

Generic Drug User Fee Amendments (GDUFA)

Fee type	Details	GDUFA I (2012-2017) Year 2017	GDUFA II (2018-2022) Year 2018
ANDA	One-time fee, ANDA-specific	$70,480	$171,823
Program	Annual fee for application holders - Large: ≥20 approved ANDAs - Med: 6-19 approved ANDAs - Small: ≤5 approved ANDAs	-	Large: $1,590,792
		-	Medium: $636,317
		-	Small: $159,079
DMF	One-time fee, DMF-specific	$51,140	$47,829
Facility	Annual fee due on October 1 of each fiscal year	Fee incurred for being referenced in **pending ANDAs**	Fee incurred for being referenced in **approved ANDAs**
	- Domestic API	$44,234	$45,367
	- Foreign API	$59,234	$60,367
	- Domestic FDF	$258,646	$211,087
	- Foreign FDF	$273,646	$226,087
	- Domestic CMO	-	$70,362
	- Foreign CMO	-	$85,362
PAS	One-time fee, change-specific	$35,240	0

ANDA REVIEW PROCESS



Filing review: the FDA usually takes 30-45 days for the filing review.

- **No filing deficiencies:**
  - FDA issues Acceptance Letter.
  - The original submission date is taken to calculate the GDUFA goal date.
- **<10 minor filing deficiencies:**
  - FDA issues Filing Review Comments.
  - ANDA Applicant has 7 days to respond.
  - If response is accepted, FDA issues Acceptance Letter.
  - The original submission date is taken to calculate the GDUFA goal date.
- **1 major deficiency or 10 minor deficiencies:**
  - FDA issues Refuse-to-Receive letter.
  - Applicant loses 25% of the ANDA GDUFA submission fee (e.g. 2018: $43,000)

Information source: "Refuse-to-receive standards" guidance document

Generic Drugs Update

In 2018, FDA

- Approved or tentatively approved 1021 ANDAs
- Approved or tentatively approved 894 Pre-Approval Supplements (PAS)
- Communicated with industry through 1180 information requests and 2648 complete response letters
- Responded to a record of 2919 controlled correspondence letters

Major GDUFA II Performance Goals and Commitments

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Generic Drug User Fee Amendments Reauthorization (GDUFA II)

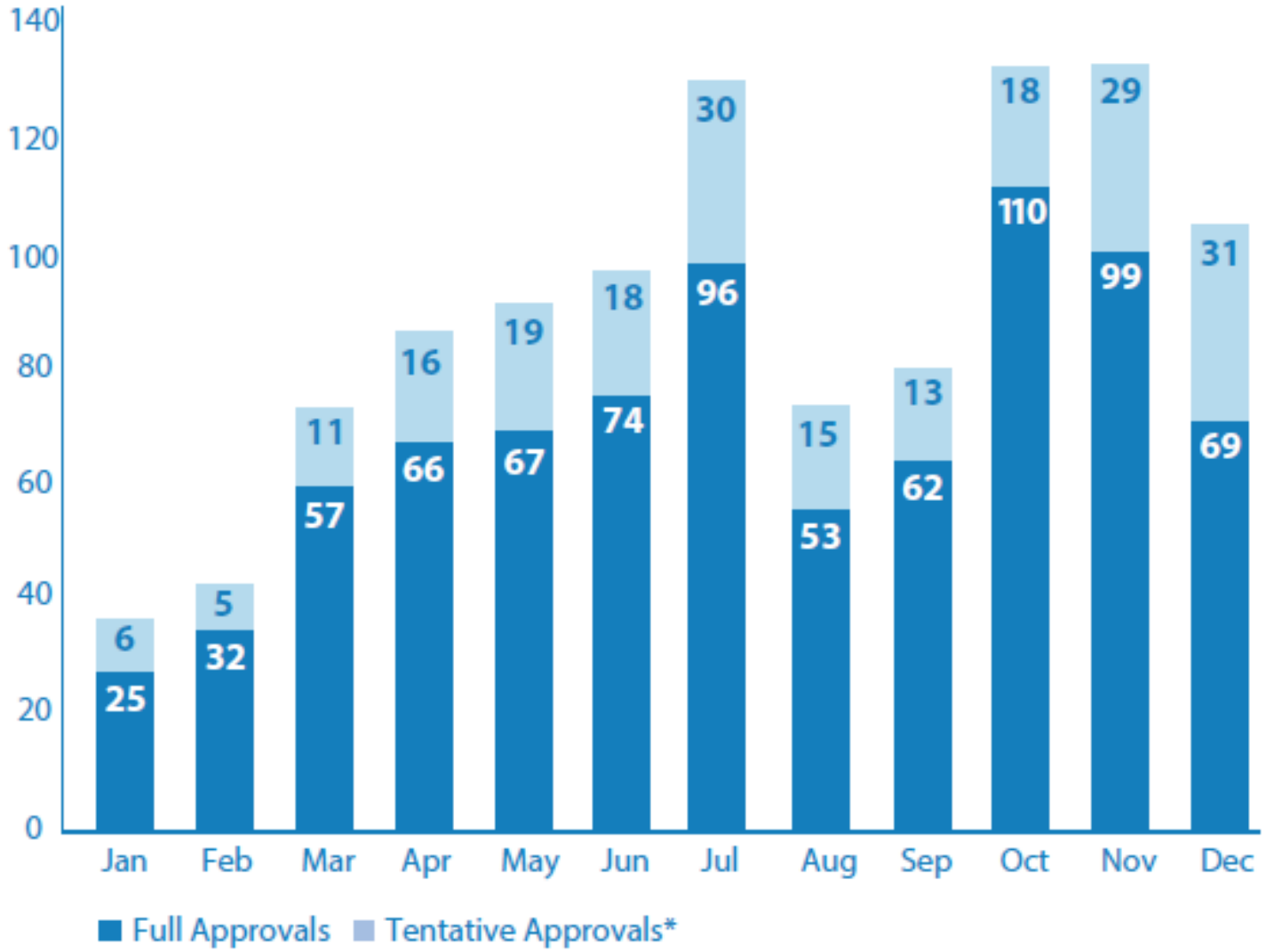
Submission Type	GDUFA II Goal
Standard Original ANDAs	90% within 10 months
Priority Original ANDAs	90% within 8 months with successful Pre-Submission Facility Correspondence (PFC) 90% within 10 months without successful PFC
Standard Major ANDA Amendments	90% within 8 months if preapproval inspection not required 90% within 10 months if preapproval inspection required
Priority Major ANDA Amendments	90% within 6 months if preapproval inspection not required 90% within 8 months if preapproval inspection required with successful PFC 90% within 10 months if preapproval inspection required without successful PFC
Standard Original PAS	90% within 6 months if preapproval inspection not required 90% within 10 months if preapproval inspection required
Priority Original PAS	90% within 4 months if preapproval inspection not required 90% within 8 months if preapproval inspection required with successful PFC 90% within 10 months if preapproval inspection required without successful PFC
Standard Major PAS Amendments	90% within 6 months if preapproval inspection not required 90% within 10 months if preapproval inspection required
Priority Major PAS Amendments	90% within 4 months if preapproval inspection not required 90% within 8 months if preapproval inspection required with successful PFC 90% within 10 months if preapproval inspection required without successful PFC
Standard Controlled Correspondence	90% within 60 days
Complex Controlled Correspondence*	90% within 120 days

Generic Drugs Update

- **Product Specific Guidances (PSGs)**
  - 128 new and 117 revised
  - As of December 31, 2018 = 1660 PSGs
- **Guidances for Industry**
  - 4 revised guidances
  - 3 new guidances
  - Good ANDA Submission Practices
  - ANDA Submissions – Amendments to ANDAs under GDUFA

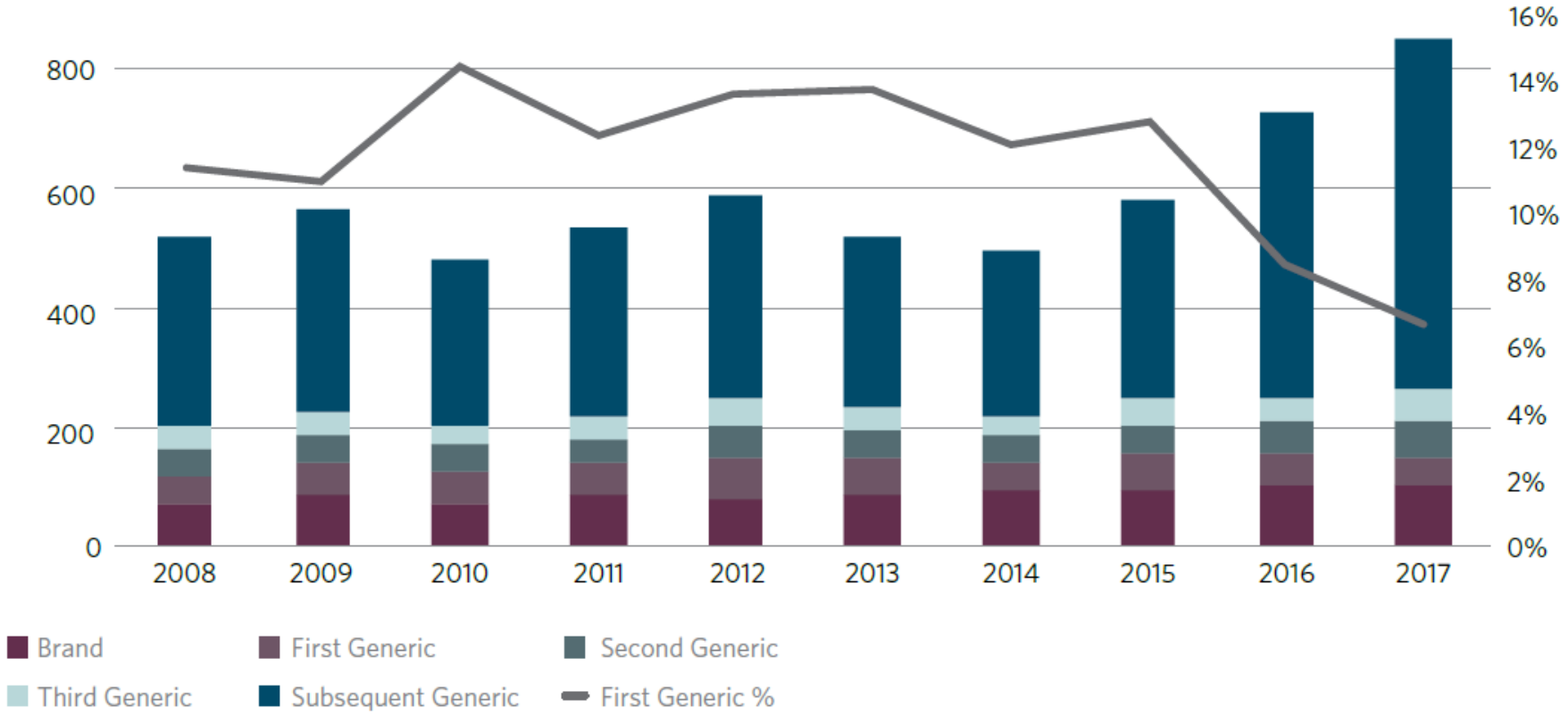
2018 Generic Drugs Approved

843 Full Approvals/211 Tentative Approvals



Drug Approvals by FY 2008-17

754 ANDAs



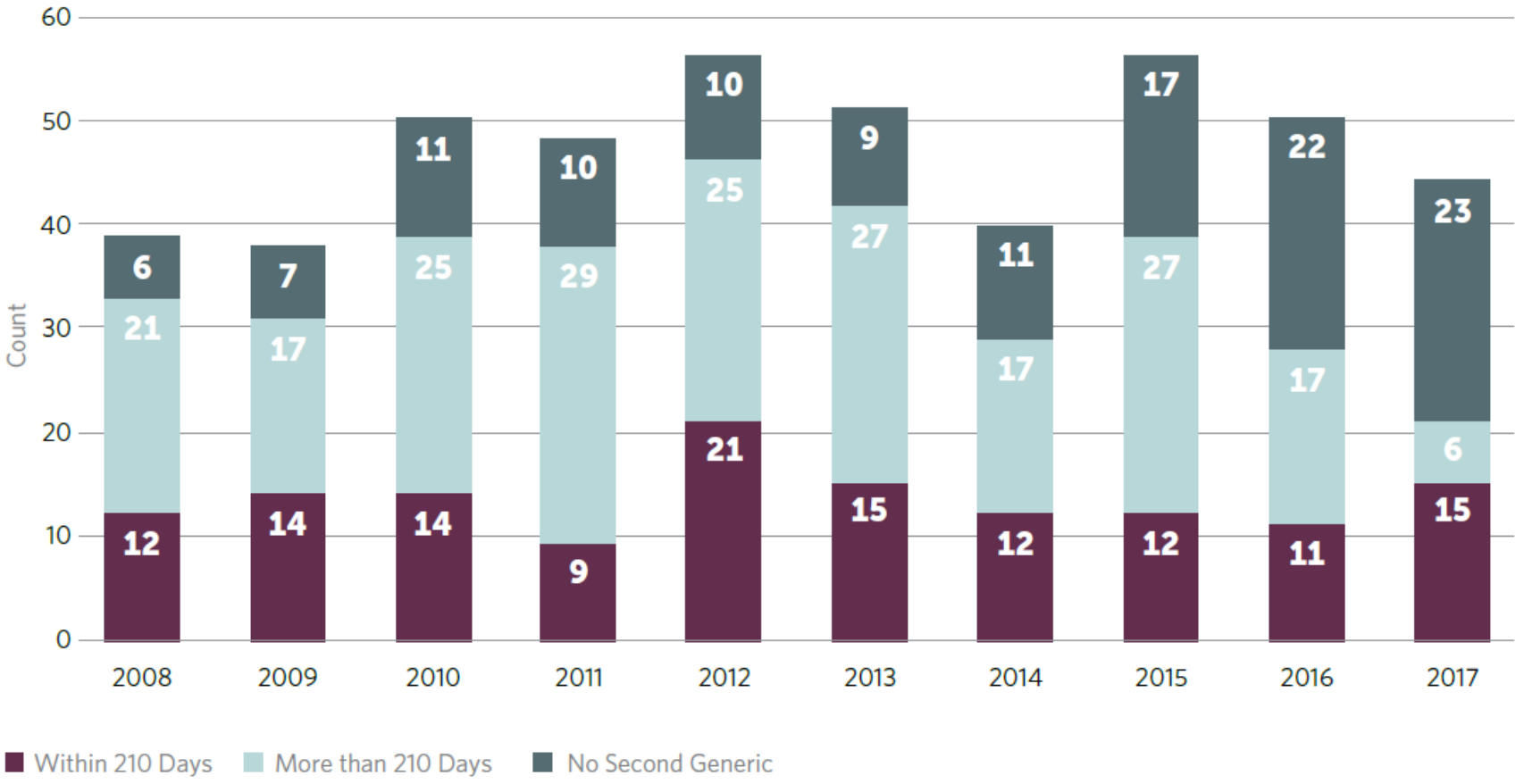
Source: Analysis by The Pew Charitable Trusts

Median Review Times from ANDA Receipt to Approval

	2010*	2011*	2012*	2013†	2014‡	2015§	2016‖	2017#
Median review time from ANDA receipt to approval (months)	27.85	29.52	31.75	36	42	42	39.42	37.26

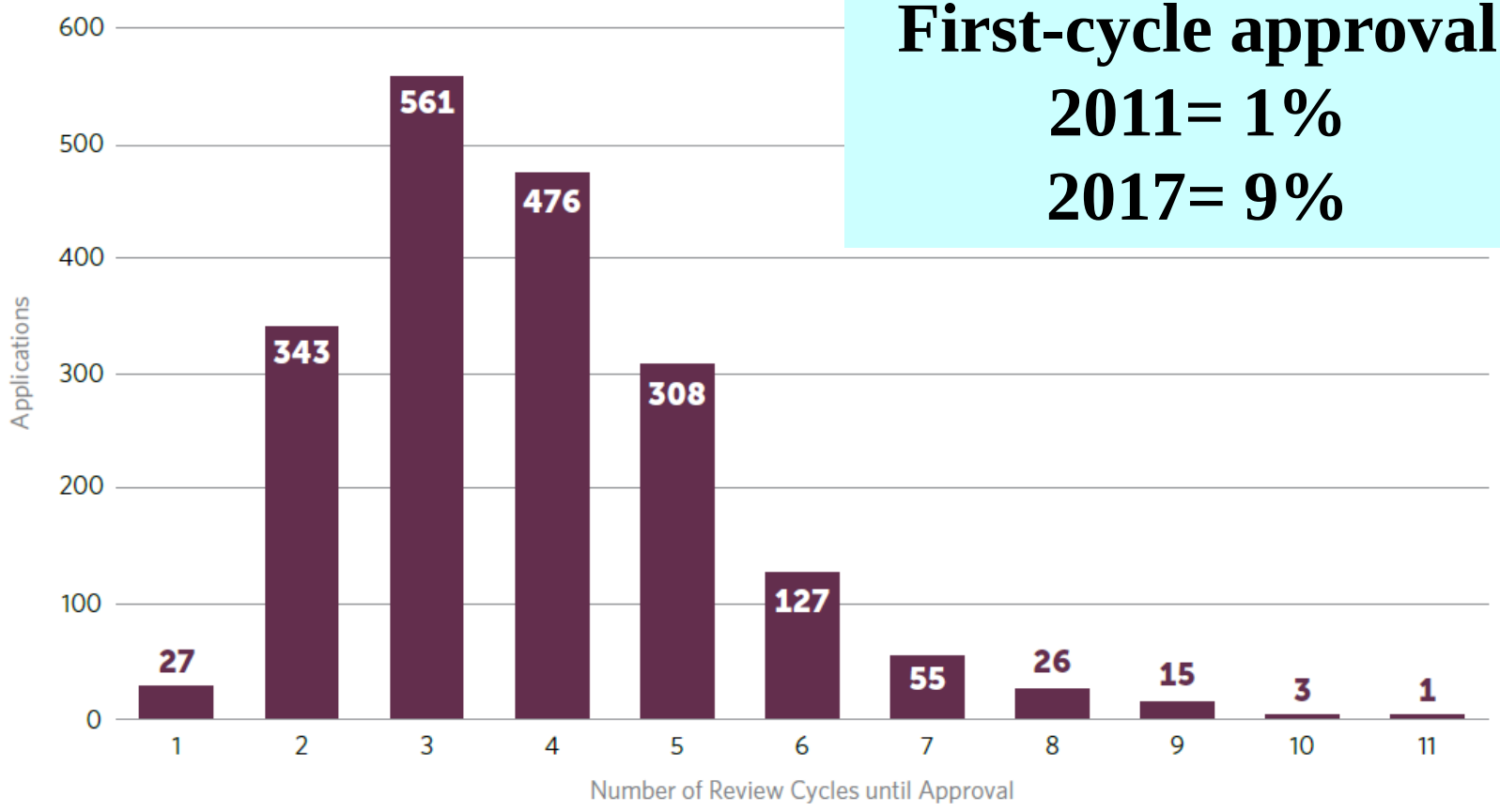
Note: Includes all approved applications (backlog and Generic Drug User Fee Amendments cohort abbreviated new drug applications).

Time to Second Generic by FY 2008-17



Source: Analysis by The Pew Charitable Trusts

Number of Review Cycles to ANDA Approval (2009-July 2014)



First-cycle approval
2011= 1%
2017= 9%

Note: The average number of review cycles before abbreviated new drug application approval is 3.8.

GDUFA Review Goals and Outcomes

	Review goal	Outcome
Backlog (before Oct. 1, 2012)	Review and act on 90% of backlogged ANDAs by end of GDUFA Program (end of FY 2017)	As of oct. 1, 2017, FDA had taken action on 98% of backlogged ANDAs
FY 2015	Review and act on 60% of ANDA submissions within 15 months of submission	Reviewed and acted on **97%** of ANDA within 10 months of receipt
FY 2016	Review and act on 75% of ANDA submissions within 15 months of submission	Reviewed and acted on **100%** of ANDA within 15 months of receipt
FY 2017	Review and act on 90% of ANDA submissions within 15 months of submission	Reviewed and acted on **99%** of ANDA within 10 months of receipt

Summary of GDUFA Program

- Over the five years of the first GDUFA program, from FY 2013 - 2017, FDA approved 2,700 new generic drugs, compared with 2,309 from FY 2008 - 2012, an increase of 16.9 percent. However, the median approval time did not significantly decline.

- The increase in approved drugs was largely driven by approvals of the fourth, fifth, sixth and even later versions of generics. Costs generally decline most significantly once second and third generics enter the market, but versions after the third generic usually reduce prices less effectively.

Summary of GDUFA Program cont.

- Approval times are slowed when drug applications go through multiple review cycles, which are triggered when FDA finds deficiencies in the drug application.

- Despite the increased approvals of generics overall, more than 500 brand drugs still lack competition, even though there are no patent protections or periods of exclusivity that would prevent the approval of competing generic versions. These “sole source” products are most at risk for price spikes.

FDA New Regulatory Pathway for Generic Drugs

- FDA has announced new, efficient guidelines for the use of a novel pathway that provides incentives for developing generic versions of drugs that currently face little or no competition.

- Designation of a drug as a Competitive Generic Therapy (CGT) can be granted to a company submitting an application for their generic drug when there's inadequate generic competition for that drug (meaning there is not more than one approved drug in the active section of the Orange Book.) Companies may submit requests to designate a drug as a CGT at the time of submitting an ANDA or at any time before the original ANDA submission.

Mutual Recognition Agreement (MRA) for Pharmaceutical Inspections

- In 1998, the U.S. and the EU signed the Agreement on Mutual Recognition which included a Pharmaceutical Annex providing for recognition of each other's GMP inspections.
  - However, this Annex was never fully implemented

- The 2017 amended Sectoral Annex to the 1998 U.S.-EU MRA allows the FDA and the EU inspectorates to use inspection reports to help determine whether a facility is manufacturing high quality drugs.

Mutual Recognition Agreement (MRA) for Pharmaceutical Inspections

- Companies that had never been inspected by the FDA had a violation rate of 25% (Official Action Indicated, OAI)
- Companies routinely inspected by FDA had a violation rate of 5%
- Between 2011-17, the number of registered drug facilities
  - Increased by 75% in China
  - Increased by 65% in India

EU-U.S. MRA Scope

Included

- Finished pharmaceutical including
  - Medical gases
  - Radiopharmaceutical or radioactive biological products
  - Herbal (botanical) products
  - Homeopathic products
- Biological products
  - Therapeutic derived biotech products
  - Allergenic products
- In-process/intermediates
- APIs
- Investigational product (clinical trial materials)

Not Included

- Human blood
- Human plasma
- Human tissue and organs
- Veterinary immunological
- Vaccines and plasma-derived product will be re-evaluated no later than July 15, 2022
- Veterinary product will be considered for inclusion no later than July 15, 2019

EU-U.S. MRA Scope

- November 2017: Spain, Austria, Croatia, France, Italy, Malta, Sweden, and UK
- March 2018: Czech Republic, Greece, Hungary, and Romania
- June 2018: Ireland and Lithuania
- September 2018: Portugal
- November 2018: Belgium, Denmark, Finland, Latvia, and Estonia
- February 2019: Poland and Slovenia
- Rest of countries: no later than July 15, 2019

Does this MRA mean that FDA will never inspect in the EU?

- NO, both the FDA and the EU reserve the right to inspect at any time and in any country.

- It is however expected to be the exception rather than the rule since, following positive capability assessments, the FDA will recognize the EU inspectorates as capable and thus recognize their drug manufacturing facility inspections

MRA Article 8.2
No Recognition of Inspections

- A Party may in specific circumstances opt not to accept an official GMPs document issued by a recognized authority of the other Party for manufacturing facilities located in the territory of the issuing authority.

- Examples of such circumstances include the indication of material inconsistencies or inadequacies in an inspection report, quality defects identified in the post-market surveillance or other specific evidence of serious concern in relation to product quality or consumer safety.

EU-U.S. MRA Scope
Pre-Approval Inspections (PAI)

- PAI is one step in the approval of a drugs by FDA
  - Evaluation of the Dossier (NDA, ANDA, BLA, Biosimilar, etc)
  - Evaluation of manufacturing site
  - In a NDA review there are 12 steps, PAI is the 11th

- FDA charges companies for the PAI

EU-U.S. MRA
Qualified Person

- The qualified person will be relieved of responsibility for carrying out the controls laid down in Article 51 paragraph 1 of Directive 2001/83/EC and in Article 55 paragraph 1 of Directive 2001/82/EC provided that:
  - these controls have been carried out in the U.S.
  - the product was manufactured in the United States
  - each batch/lot is accompanied by a batch certificate issued by the manufacturer certifying that the product complies with requirements of the marketing authorization and signed by the person responsible for releasing the batch/lot.

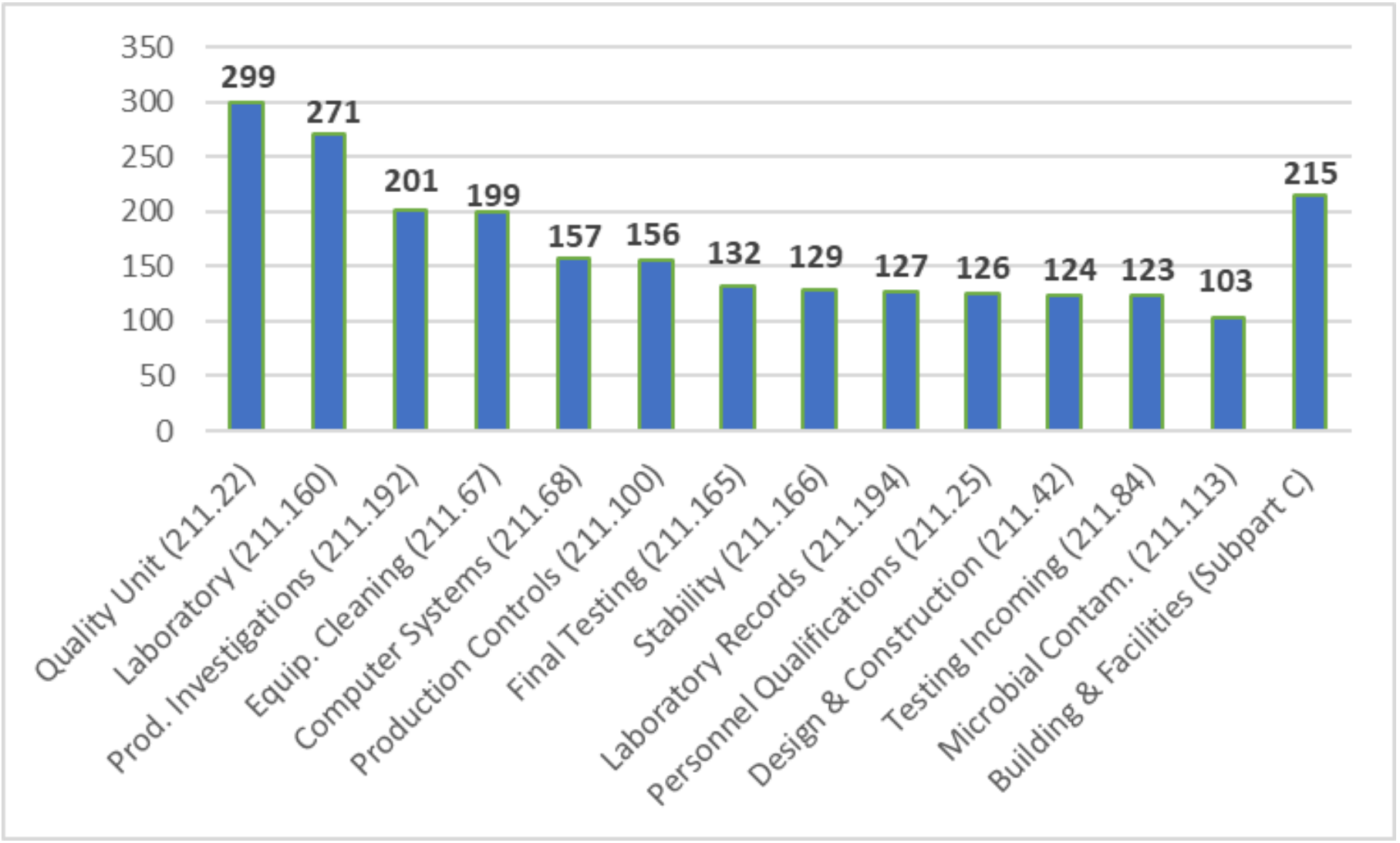
U.S. Government Shutdown

- 35-day lapse
- Focused on the high risk establishment
  - Injectable, Vaccines, Blood
  - Pre-approval reviewers moved to post-marketing surveillance evaluation
  - Stopped routine food safety inspections
- 2019 Inspectional work= 10% reduction

Top Observations U.S. FDA Drug Inspections FY 2018 (716 Forms 483s, 3080 observations)

Reference Number	Short Description	Frequency
21 CFR 211.22(d)	Procedures not in writing, fully followed	208
21 CFR 211.160(b)	Scientifically sound laboratory controls	127
21 CFR 211.192	Investigations of discrepancies, failures	107
21 CFR 211.100(a)	Absence of Written Procedures	86
21 CFR 211.67(a)	Cleaning / Sanitizing / Maintenance	81
21 CFR 211.68(b)	Computer control of master formula records	71
21 CFR 211.67(b)	Written procedures not established/followed	64
21 CFR 211.110(a)	Control procedures to monitor and validate performance	64
21 CFR 211.68(a)	Calibration/Inspection/Checking not done	60
21 CFR 211.165(a)	Testing and release for distribution	56

Top Observations U.S. FDA Drug Inspections FY 2018 (716 Forms 483s, 3080 observations)



Examples of FDA Citations

Stability Program

- You have not defined time zero for your stability study program and you have not specified the maximum allowable time between the end of manufacturing and the time the stability study sample should be place in the stability chamber.

- There is no maximum time between release of the product and the stability time point T=0

Examples of FDA Citations

Stability Program

- You did not follow the testing time points of your stability program, which included stability testing at three months, six months, one year, and two years.

Specifically, for one lot of your **(b)(4)**, you performed three-month stability testing on the same day the lot was packaged and you performed six-month stability testing nine months after the initial stability testing.

Examples of FDA Citations

Final testing

- You released over-the-counter (OTC) drug products without testing for identity and strength. Our investigator documented that you only test your finished drug products for specific gravity, pH, refraction value, and microbiological tests.

- In your response, you indicated you will request that your contract laboratory perform identity and strength tests on drug products manufactured in the future. Your response is inadequate because you provided no timeline for this action and did not include a plan to test retain samples of drug products within expiry that have been distributed to the U.S. market.

Examples of FDA Citations

Data Integrity

- Your batch production and control records do not include complete information.

- Our inspector reviewed several batch records and found use of white-out correction liquid, unintelligible data, and/or missing information such as density test results and the date of approval of the batch. Several entries were over written and crossed out with no signature, date, or explanation.

- In addition, laboratory test results (e.g., viscosity, density, appearance, and odor) lacked initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

Examples of FDA Citations

Investigations

- In the last year, your firm reported numerous (>50) microbiology laboratory investigations due to in-process bioburden our of limits

- You have not been able to identify the cause through an appropriate investigation to determine why the bioburden limit levels are continuing to be reached

Examples of FDA Citations

Investigations

- Investigation report evaluated lacked adequate and through scientific justification to invalidate OOS results

- Investigation report was initiated due to OOS results obtained during the assay by titration. The root cause and conclusion attributed the OOS results to analyst error (blank contaminated with sample pipette). However it is not scientifically possible to obtain this type of OOS in this scenario

Examples of FDA Citations

Investigations

- Your firm invalidated out-of-specification (OOS) results without adequate investigation and scientific justification. Examples include:

- In January, 2017, you obtained OOS results for the **(b)(4)** impurity during stability testing of **(b)(4)** injection batches **(b)(4)**. Your OOS investigation reports stated that the postulated cause was "poor column efficiency" although no chromatographic abnormalities were noted and system suitability criteria were met. During the inspection, your lab management indicated that retention times, theoretical plates, and tailing factor appeared appropriate and no specific root cause had been demonstrated. You repeated the analyses, obtained passing results, and invalidated the OOS results.

Examples of FDA Citations

Production and Process Controls

- Each component is not added to a batch by one person and verified by a second person.

- Specifically, the Master Manufacturing Batch Record for XXX does not provide instructions to perform, or space to sign, for the verification of the addition of any of the ingredients used during the production process. My review to the batch record of lot xxx evidence that the second person verification for the addition of the ingredients is not performed.

Examples of FDA Citations

- You have also recently informed us that HPLC units and PCs were removed from the facility for the duration of the inspection to conceal data manipulations. This action, which apparently also occurred in association with past inspections, is very worrisome to us and should be explained in your response to this letter.

- An employee was observed attempting to hide manufacturing related records in his pocket from the FDA Investigator.

- During the inspection your firm also repeatedly delayed, denied, limited or refused to provide information to the FDA investigators. Please be reminded that the Food and Drug Administration Safety and Innovation Act (FDASIA) § 707, also deems a product to be adulterated if drugs have been manufactured, processed, packed or held in an establishment by an owner or operator who has delayed, denied, or **limited** an inspection.

Food and Drug Administration Safety and Innovation Act (FDASIA)

Regulatory Information

Home › Regulatory Information › Laws Enforced by FDA › Selected Amendments to the FD&C Act › Food and Drug Administration Safety and Innovation Act (FDASIA)

Laws Enforced by FDA

- Selected Amendments to the FD&C Act
- **Food and Drug Administration Safety and Innovation Act (FDASIA)**
- FDASIA Title VII Drug Supply Chain Provisions
- FDASIA Title VII Overview
- FDASIA Section 907: Inclusion of Demographic Subgroups in Clinical Trials

Resources for You

- Full Text of the FDASIA Law
- FDASIA Implementation Tracking Chart (FDASIA-TRACK)
- Background on FDASIA

Food and Drug Administration Safety and Innovation Act (FDASIA)

The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, expands the FDA's authorities and strengthens the agency's ability to safeguard and advance public health by:

- **Giving the authority to collect user fees** from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products;
- **Promoting innovation** to speed patient access to safe and effective products;
- **Increasing stakeholder involvement** in FDA processes; and
- **Enhancing the safety of the drug supply chain**.

To help the public keep track of the agency's progress on these and other provisions, we've established a 3-year implementation plan, which is planned to be updated on a monthly basis.

Below are just some of the accomplishments FDA has achieved since the law was passed in 2012.

User Fees


A to Z Index | Follow FDA | En Español
Search FDA
U.S. FOOD & DRUG ADMINISTRATION
FDA
Tobacco Products
Cosmetics
Animal & Veterinary
Vaccines, Blood & Biologics
Radiation-Emitting Products
Medical Devices
Drugs
Food
Home
Medical Devices
Home › Medical Devices
Spotlight
Webinars
Public Meetings
CDRH Strategic Priorities and Updates
Collaborative Communities
Statement from FDA Commissioner Scott Gottlieb, M.D. and Jeff Shuren, M.D., Director of the Center for Devices and Radiological Health, on FDA's updates to Medical Device Safety Action Plan to enhance post-market safety
FDA Safety Communication
FDA Warns that the safety and effectiveness of using robotically-assisted surgical devices in mastectomy procedures or in the prevention or treatment of cancer has not been established.
1
2
3
4

2018 was a "Record" Year for FDA's Center for Device and Radiological Health

- 106 new medical devices approved (class III)
- The development of a new 510(k) pathway, known as the Safety and Performance Based Pathway, that relies on performance criteria rather than predicate devices to demonstrate safety and effectiveness.
- The finalization of the FDA's Breakthrough Devices Program, which provides extra support and a potentially smoother path to premarket clearance for devices receiving that designation.
- A framework to streamline 510(k) reviews of certain lower-risk medical devices.
- Improvements to the De Novo pathway.

FDA News Release

FDA approves new DNA-based test to determine blood compatibility

Test is first approved to report genotypes as final results

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release October 11, 2018

- The U.S. FDA today approved ID CORE XT, a molecular-based assay used in blood transfusion medicine to help determine blood compatibility. The assay can be used to determine blood donor and patient non-ABO red blood cell (RBC) types. ID CORE XT is the second molecular assay approved for use in transfusion medicine, and the first to report genotypes as final results.

FDA Approves Grifols ID CORE XT Test For Molecular Red Blood Cell Typing

Test Offers Shortest Time to Reportable Results For US Hospitals, Reference Labs and Blood Centers

- Efficient system analyzes 37 antigens of 10 blood group systems
- Helps minimize allo-immunization risk in blood transfusions
- Effective tool to generate "rare donor" database and expedite antibody identification in complex workups

FDA Transition to ISO 13485

- FDA intends to harmonize and modernize the Quality System regulation for medical devices
- The revisions will supplant the existing requirements with the specifications of an international consensus standard for medical device manufacture, ISO 13485:2016
- The revisions are intended to reduce compliance and recordkeeping burdens on device manufacturers by harmonizing domestic and international requirements
- The revisions will also modernize the regulation.

Why FDA will adopt ISO 13485?

- ISO 13485:2016 is already used by Reg. Authorities in other countries as a basis for their QMS requirements; therefore, one globally harmonized system will allow for opportunities
  - To work closer with foreign regulatory authorities and facilitate regulatory convergence on QMS
  - For medical device manufacturers to have a more globally harmonized QMS

- Differences between the 21 CFR 820 and ISO 13485:2016 are minor
  - Gain more than we lose
  - More robust QMS principles in many areas
  - Stronger ties to risk management principles and ISO 14971

Current Status

- FDA currently is currently working on the proposed rule which will be issued in 2019
  - A panel committee meeting will be held after issuance of the proposed rule

- Development of an AAMI Technical Information Report (TIR) which outlines the comparative analysis between ISO 13485: 2016 and the QS regulation and viceversa.
  - Developed jointly by FDA and Industry
  - Will be completed in early-mid 2019

Medical Devices Single Audit Program (MDSAP)

- Coalition of international medical device regulatory authorities including:


USA: U.S. Food and Drug Administration (FDA)


Canada: Health Canada/Santé Canada


Brazil: Agência Nacional de Vigilância Sanitária (ANVISA)


Australia: Therapeutics Goods Administration (TGA)


Japan: Ministry of Health, Labor and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA)

  - WHO and EU are Official Observers

Medical Devices Singel Audit Program (MDSAP)

- To allow a single regulatory audit of a medical device manufacturer's quality management system (QMS) to satisfy the needs of the participating regulatory jurisdictions.

- Enables medical device manufacturers to contract with an authorized **third-party Auditing Organization** to conduct a single audit of the medical device manufacturer that will satisfy the relevant regulatory requirements of the participating medical device regulatory authorities including the U.S. FDA

- Pilot ran from 2014 to 2016

MDSAP Covering

- The MDSAP audit process was designed and developed to ensure a single audit will provide efficient yet thorough coverage of:
  - The requirements of Medical devices - Quality management systems- Requirements for regulatory purposes (ISO 13485:2016)
  - Brazilian Good Manufacturing Practices (ROC ANVISA 16/2013)
  - Japan Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and In Vitro Diagnostic Reagents (MHLW Ministerial Ordinance No. 169)
  - FDA's Quality System Regulation (21 CFR Part 820), 21 CFR 803, 806, 807, and 821.

MDSAP Covering

- At the conclusion of an MDSAP audit, a standardized MDSAP Audit Report is generated.
- The standardized MDSAP Audit Report template was developed to assure the reporting requirements of all participating regulatory authorities (including the U.S. FDA) are effectively documented .
- The U.S . FDA recognizes MDSAP audit reports as a substitute for FDA Establishment Inspection Reports (EIRs) .

FDA Inspection Program for MDSAP Participating Firms

- MDSAP participating firms are not subject to FDA's routine surveillance inspections, however all other situations listed under the FDA's Compliance Program Guidance Manual (CPGM) 7382.845, Inspection of Medical Device Manufacturers, still apply.

Situations that can lead to an FDA inspection

- For Cause (with various scenarios)
- Risk Based Work Plan
- Pre/post-approval inspections
- Bioresearch Monitoring (BIMO)
- Compliance Follow Up inspections
- Electronic Product Radiation Control (EPRC)
- Inspections from other Centers

For Cause

- For Cause inspections are carried out in response to specific information that raises questions, concerns, or problems associated with a FDA regulated firm or commodity. This information could come to the attention of FDA from any source and including, but not limited to, the following:

  - Results of a sample analysis
  - Observations made during prior inspections
  - Recall or market withdrawal
  - Consumer or employee allegation
  - Adverse reaction report
  - Suspicion of fraud

Risk-Based Work Plan

- The risk based work plan inspection program was developed to focus limited resources on key public health needs.

- It reflects the broader goals of the FDA to utilize science-based risk management in the selection and prioritization of sites for inspection. This provides the most health promotion and protection to the public at the least cost by focusing on medical devices and firms which pose the greatest risk.

- Data collected throughout the total product life cycle (e.g. premarket submissions, recalls, adverse event reports) is analyzed to detect risks posed by medical devices. The beneficial public health impact of the devices and the potential risks of device failure are also considered.

Pre/Post Approval Inspections

- In making the determination of the firm's ability to design, manufacture or process the device, CDRH may issue an inspection assignment to the appropriate FDA Division. The inspection assignment will be issued when CDRH has determined that the manufacturer has demonstrated in the PMA submission that the design and manufacturing process meets the QS regulation requirements and the facility is ready for inspection.

- Postapproval inspections are conducted within eight to twelve months of approval of the PMA submission. The inspection will primarily focus on any changes that may have been made in the device design, manufacturing process, or quality systems.

Bioresearch Monitoring (BIMO)

- BIMO inspections involve evaluation of the clinical investigator's or sponsor-investigator's practices and procedures to determine compliance with applicable regulations.
  - PMA or PMA Supplement
  - IDE
  - 510(k)

Compliance Follow Up

- Compliance follow up inspections are necessary after a firm is found to have Situation I conditions during a previous QS inspection which was classified Official Action Indicated (OAI).

Inspection from other Centers

- Center for Biologics Evaluation and Research (CBER)
  - Devices Regulated by CBER
    - » The medical devices regulated by CBER are associated with blood collection and processing procedures as well as the cellular therapies regulated by CBER. CBER has developed specific expertise in blood, blood products and cellular therapies and the integral association of certain medical devices with those biological products supports the regulation of those devices by CBER.
  - Part 4, Combination products

- Center for Drug Evaluation and Research (CDER)
  - Part 4, Combination products

Top Observations U.S. FDA Devices Inspections
FY 2018 (966 Forms 483s, 3497 observations)

Reference Number	Short Description	Frequency
21 CFR 820.100(a)	Lack of or inadequate procedures	354
21 CFR 820.198(a)	Lack of or inadequate complaint procedures	229
21 CFR 820.50	Purchasing controls, Lack of or inadequate procedures	142
21 CFR 803.17	Lack of Written MDR Procedures	139
21 CFR 820.75(a)	Lack of or inadequate process validation	138
21 CFR 820.90(a)	Nonconforming product, Lack of or inadequate procedures	119
21 CFR 820.100(b)	Documentation	86
21 CFR 820.22	Quality audits - Lack of or inadequate procedures	78
21 CFR 820.30(i)	Design changes - Lack of or Inadequate Procedures	76
21 CFR 820.181	DMR - not or inadequately maintained	63

Examples of FDA Citations

- Failure to establish and maintain procedures for implementing corrective and preventive action (CAPA), as required by 21 CFR 820.100(a). Specifically, your firm's procedure "CORRECTIVE ACTIONS FOR QMS PROCEDURE did not include the following requirements:

  - Verification of effectiveness of corrective actions. For example, a review of the following CAPAs revealed your firm has not performed CAPA effectiveness verification.

Examples of FDA Citations

Failure to maintain complaint files and establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198(a).

- Customer concerns outside of your firm's warranty period of one year are not being documented as complaints, and are instead being handled through your firm's return system.

- Complaint numbers **(b)(4)**(noise noticed by customer) and **(b)(4)**, (device not working) were initiated on October 24, 2016, and May 3, 2017, respectively. Your firm has not evaluated these complaint to determine if they represent events that should be reported to the FDA per Medical Device Reporting requirements (21 CFR 803.)

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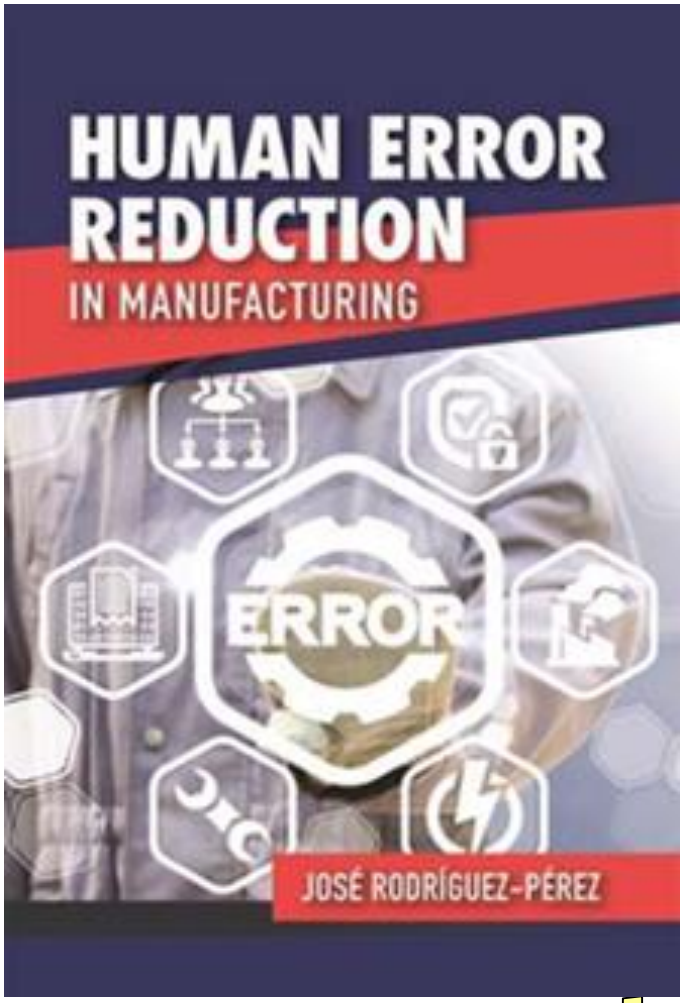

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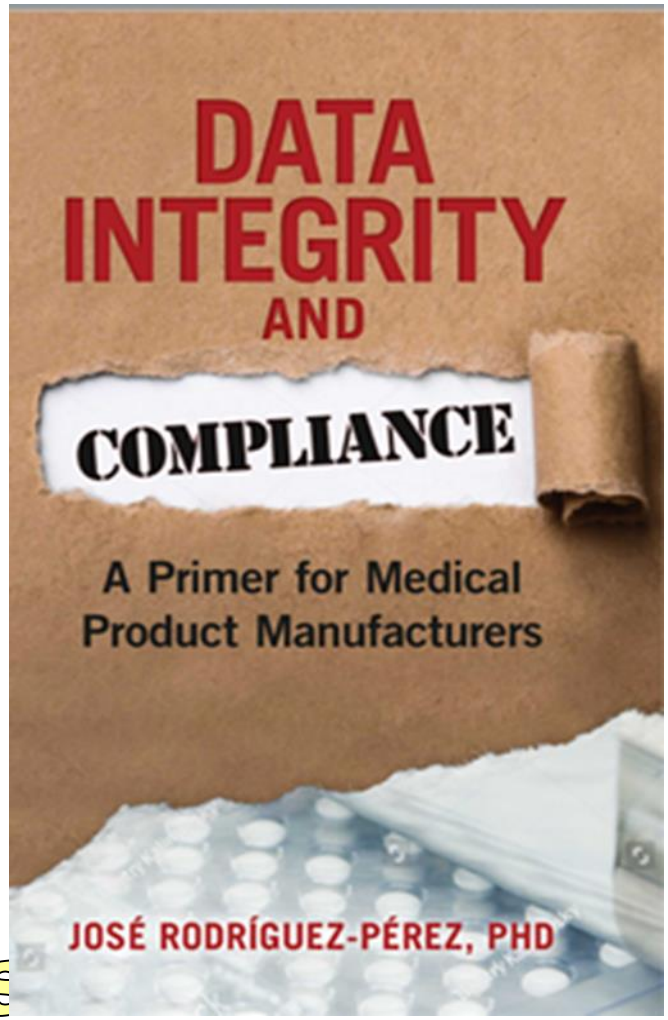

Muchas Gracias

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