



U.S. –EU Harmonization

by

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Agenda

- ❑ Mutual Recognition Agreement
- ❑ Medical Device Single Audit Program (MDSAP)
- ❑ Quality Metrics
- ❑ Process Validation
- ❑ Data Integrity – Good Documentation Practices
- ❑ 2017 FDA Figures

<http://bec-global.com/links-and-downloads/>

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.

EU-U.S. MRA

FDA Reasons



- U.S. receives through 300 ports FDA-regulated materials from
 - 150 countries
 - 130.000 importers
 - 300,000 foreign sites
- Between 2011-2016,
 - 16% growth in registered sites from Europe
 - 55% from India and 63% from China
- During Fiscal Year 2016:
 - 16.000 domestic inspection
 - 3.500 international inspection (40% in EU countries)

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

- Agreement is between U.S and EU
- However, the FDA will assess each country regulatory authority individually
 - 28 countries, including UK
- November 1, 2017: Spain, Austria, Croatia, France, Italy, Malta, Sweden, and UK
- March 1, 2018: Czech Republic, Greece, Hungary, and Romania
- 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 vs. Post-approval



- Article 3: The provisions of this Annex apply to pharmaceutical inspections of manufacturing facilities carried out in the territory of a Party during the marketing of products (**post-approval inspections**) and, to the extent provided for in Article 11, before products are marketed (hereafter referred to as "pre-approval inspections").
- Article 11: Request for pre-approval or post-approval inspection.
- Article 20.3: No later than 15 July 2019, the Joint Sectoral Committee shall review experience gained in order to decide whether the provisions on pre-approval inspections provided in Article 11 shall be reviewed.

EU-U.S. MRA Scope

Pre-Approval Inspections (PAI)



- PAI is one step in the approval of a drug 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 Scope

Goals of the PAI



To assure that establishments involved in the manufacturing, testing, or other manipulation of new drug dosage forms and drug substances are evaluated for

- conformance with commitments in the application
- site cGMP compliance
- data authenticity, reliability and accuracy
- adequacy of analytical methodologies

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.

Medical Devices Singel 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) .

Quality Metrics Initiative: The Origin: FDASIA

- FDA's Quality Metric Initiative (QMI) began in 2012 with the passage of FDASIA

Regulatory Information

● Home ● Regulatory Information ● Laws Enforced by FDA ● Selected Amendments to the FD&C Act ● Food and Safety at (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

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.**

Quality Metrics Initiative: The Origin: FDASIA



- Section 704: requires FDA to maintain accurate electronic registration using a UFI (unique facility identifier).
- Section 705: requires FDA to replace biennial inspections with a risk-based inspection schedule for domestic and foreign manufacturers.
- Section 706: gives FDA authority to obtain certain records from a drug manufacturer in lieu of, or in advance of, an inspection.

Original Quality Metrics 2015 Draft Guidance



- FDA issued draft guidance on quality metrics in July 2015, requiring ten kinds of data to calculate:
 - Lot Acceptance Rate
 - Product Quality Complaint Rate
 - Invalidated Out-of-Specification (OOS) Rate
 - APR/PQR On Time Rate
- Optional Metrics suggested:
 - Senior management engagement in APR review
 - CAPA effectiveness related to training
 - Process capability performance

Original Quality Metrics: Data

- 1) The number of lots attempted of the product;
- 2) The number of specification-related rejected lots of the product, whether rejected during or after manufacturing;
- 3) The number of attempted lots pending disposition for more than 30 days;
- 4) The number of OOS results for the product, including stability testing;
- 5) The number of lot release and stability tests conducted for the product;
- 6) The number of OOS results for lot release and stability tests for the product that are invalidated because of a lab error;
- 7) The number of quality complaints received for the product;
- 8) The number of lots attempted that are released for distribution or for next stage of manufacturing;
- 9) Whether the associated annual product review or product quality review were completed within 30 days of their annual due date; and
- 10) The number of APRs or PQRs required for the product.

Original Four Quality Metrics



- ❑ **Lot Acceptance Rate** = $1 - x$ (x = the number of specification-related rejected lots in a timeframe divided by the number of lots attempted by the same establishment in the same timeframe).
- ❑ **Product Quality Complaint Rate** = the number of product quality complaints received for the product divided by the total number of lots of the product released in the same timeframe.
- ❑ **Invalidated Out-of-Specification (OOS) Rate** = the number of OOS test results for the finished product invalidated by the establishment divided by the total number of OOS test results divided by the total number of tests performed by the establishment in the same timeframe.
- ❑ **Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate** = the number of APRs or PQRs completed within 30 days of annual due date at the establishment divided by the number of products produced at the establishment.

Quality Metrics: Effects of Non-Reporting



- ❑ The failure to report requested quality data may elevate an establishment's predicted risk in FDA's prioritization of inspections and may lead to an earlier inspection.
- ❑ In addition, products associated with an establishment that does not report as required under section 704(a)(4)(A) may be deemed **adulterated** under section 501 and subject to enforcement action.

Revised Quality Metrics

2016 Draft Guidance



- ❑ **Lot Acceptance Rate (LAR)** as an indicator of manufacturing process performance.
 - LAR = the number of accepted lots in a timeframe divided by the number of lots started by the same covered establishment in the current reporting timeframe.
- ❑ **Product Quality Complaint Rate (PQCR)** as an indicator of patient or customer feedback.
 - PQCR = the number of product quality complaints received for the product divided by the total number of dosage units distributed in the current reporting timeframe.
- ❑ **Invalidated Out-of-Specification (OOS) Rate (IOOSR)** as an indicator of the operation of a laboratory.
 - IOOSR = the number of OOS test results for lot release and long-term stability testing invalidated by the covered establishment due to an aberration of the measurement process divided by the total number of lot release and long-term stability OOS test results in the current reporting timeframe.

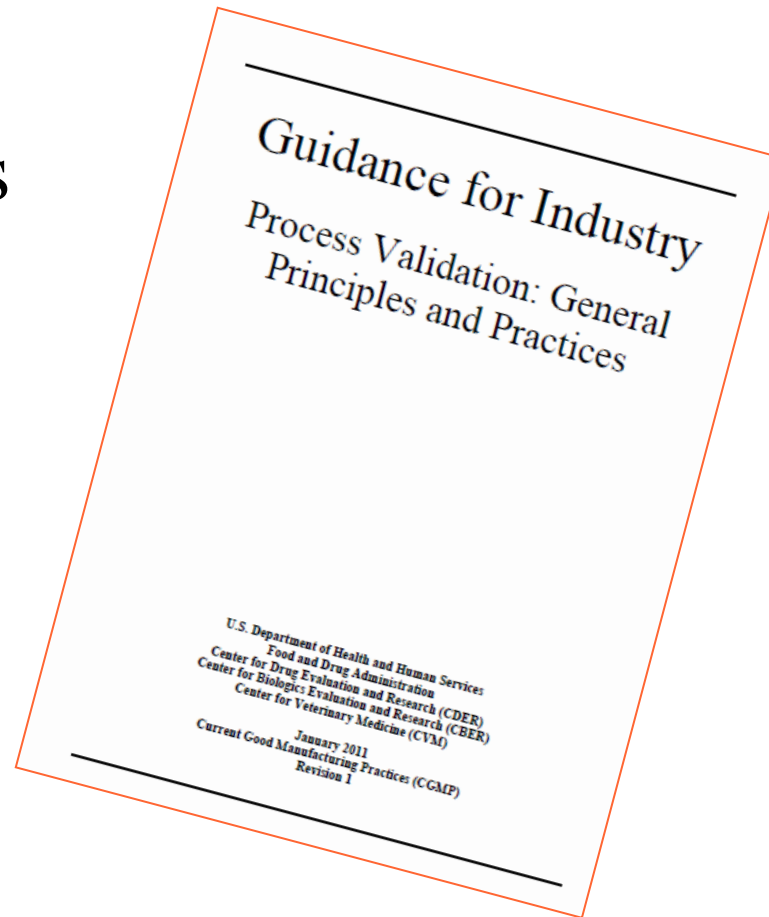
Revised Quality Metrics 2016 Draft Guidance



- Voluntary phase during 2018
- Due date for mandatory reporting: ??
- Quality culture:
 - Mentioned 9 times in the 2015 version
 - Not mentioned at all in the 2016 version
- For the FDA this is the “beginning of a journey”

FDA Requirements: Process Validations

- Product Lifecycle concept
- Human and veterinary drugs
- Biotech products
- Finish products & APIs
- Drug constituent of a combination product
- EMA revised Annex 15 to align with FDA PV
Guidance for Industry 2011



Focus on alignment with 'product lifecycle'



Three-stage approach to process validation:

□ **Stage 1 – Process Design**

- Building and capturing process knowledge and understanding
- Establishing a strategy for process control

□ **Stage 2 – Process Qualification**

- Design a facility and qualification of utilities and equipment
- Process performance qualification
- PPQ protocol
- PPQ protocol execution and report

□ **Stage 3 – Continued Process Verification**

Data Integrity Guidances 2016



PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 041-1 (Draft 2)
10 August 2016

DRAFT PIC/S GUIDANCE

**GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED
GMP/GDP ENVIRONMENTS**

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Data Integrity and Compliance With CGMP Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. 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, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Karen Takahashi 301-796-3191; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CVM) Jonathan Bray 240-402-5623.

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

April 2016

US FDA Guidance for Industry– April 2016



- ❑ FDA has increasingly observed cGMP violations involving data integrity during cGMP inspections
- ❑ **75%** of warning letters have involved data integrity issues in drug manufacturing since 2015
- ❑ Ensuring data integrity is a critical component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health

What is “data integrity”?

Data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)

- **A**tttributable – data are identified with a specific subject and a specific observer and recorder
- **L**egible – data are readable and understandable by humans
- **C**ontemporaneous - data are recorded at the time they are generated or observed
- **O**riginal or true copy– data are recorded for the first time.
- **A**ccurate – data are correct

Data Integrity: Not a New Concept

Principles from the paper-and-ink era **still** apply:

- ❑ §211.68 requires that backup data are exact and complete, and secure from alteration, inadvertent erasures, or loss
- ❑ §212.110(b) requires that data be stored to prevent deterioration or loss
- ❑ §§211.100 and 211.160 require that certain activities be documented at the time of performance and that laboratory controls be scientifically sound
- ❑ §211.180 requires true copies or other accurate reproductions of the original records; and
- ❑ §§211.188, 211.194, and 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.

Can an internal tip regarding a quality issue, such as potential data falsification, be handled informally outside of the documented cGMP quality system?



- ❑ **No.** Suspected or known falsification or alteration of records required under parts 210 and 211 must be fully investigated under the cGMP quality system to
 - ❑ determine the effect of the event on patient safety, product quality, and data reliability;
 - ❑ to determine the root cause; and
 - ❑ to ensure the necessary corrective actions are taken (§ 211.22(a), § 211.125(c), § 211.192, § 211.198, and § 211.204)

- ❑ *FDA invites individuals to report suspected data integrity issues at DrugInfo@fda.hhs.gov. “cGMP data integrity” should be included in the subject line of the email.*

Should personnel be trained in detecting data integrity issues as part of a routine CGMP training program?

- ❑ **Yes.**
- ❑ Training personnel to detect data integrity issues is consistent with the personnel requirements under § 211.25, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.

How does FDA recommend data integrity problems identified during inspections, in warning letters, or in other regulatory actions be addressed?



FDA encourages you to demonstrate that you have effectively remedied your problems by:

- ❑ hiring a third party auditor
- ❑ determining the scope of the problem
- ❑ implementing a **global** corrective action plan
- ❑ **removing at all levels individuals responsible for problems from cGMP positions.**
- ❑ FDA may conduct an inspection to decide whether cGMP violations involving data integrity have been remedied

Clear Accountability for Data Integrity

- ❑ Consider implementing an enhanced ethics program focused on data integrity awareness
- ❑ Data integrity problems are not always intentional: sometimes they result from poorly controlled systems
 - ❑ In correspondence with the agency, you indicate that no malicious data integrity patterns and practices were found. Also, you state that no intentional activity to disguise, misrepresent or replace failing data with passing data was identified and no evidence of file deletion or manipulation was found. Your response and comments focus primarily on the issue of intent, and do not adequately address the seriousness of the CGMP violations found during the inspection.” Warning Letter January 2015

A Tale of Two Firms

Firm 1: DI event transpires (bonus: reported through company hotline!).

- ❑ Investigation, CAPA, and assessment of effects on product quality/risks to patients are well defined and understood. Self-audit and CAPA. FDA learns about the events and CAPAs during a scheduled inspection.

Firm 2: Adverse event triggers FDA inspection. During inspection of the lab, we observe:

- ❑ Results have been deleted or replaced; some results not recorded or reported as part of complete records.
- ❑ Many analyses were performed without use of audit trails; many analysts shared passwords and permissions.
- ❑ 483 Response: This is an isolated event! We will retest the relevant lots and fire the people responsible!

FDA's Annual Product Review vs. EU's Product Quality Review



Objectives	FDA's APR	EMA's PQR
Determine appropriateness of, and/or need to change product specifications	Required	Required
Appropriateness of starting material specifications	Not specified	Required
Determine the need to change manufacturing procedures	Required	Not specified
Determine if need to change manufacturing control procedures	Required	Not specified
Verify consistence of the existing process	Not required	Required

FDA's Annual Product Review vs. EU's Product Quality Review



Objectives	FDA's APR	EMA's PQR
Determine the need to revalidate the production process	Not specified (required by 2011 PV Guidance)	Required (also specified in Annex 15)
Highlight trends	Expected but not specified	Required
Identify product and process improvements	Not specified	Required
Identify corrective actions	Expected but not specified	Required

Other Themes

- Good Distribution Practices (EU/WHO)
- Quality Agreements (U.S.)
- Dedicated facilities/Toxicology

Third-Party Certification Body Accreditation for Food Safety Audits: Model Accreditation Standards: Guidance for Industry and FDA Staff

*Additional copies are available from:
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740
(Tel) 240-402-1700
<http://www.fda.gov/FoodGuidances>*

You may submit either electronic or written comments regarding 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, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

**U.S. Department of Health and Human Services
Food and Drug Administration
Office of Foods and Veterinary Medicine**

December 2016

2017 U.D. FDA Drug Highlights



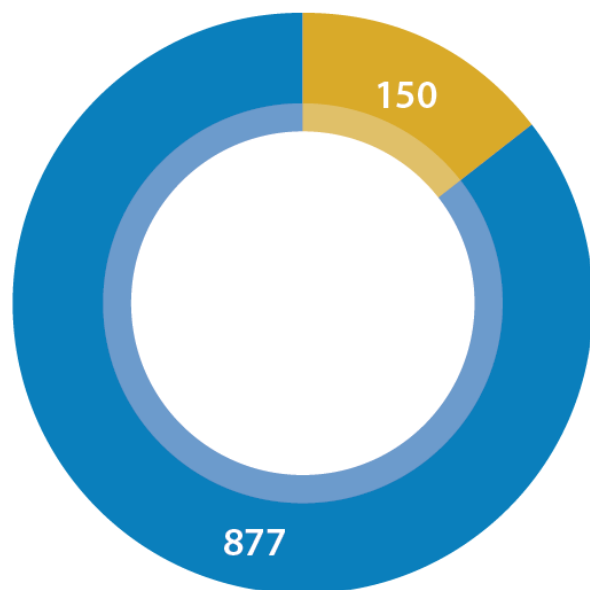
- Approval or tentative approval of:
 - 132 new drug applications, including 13 breakthrough therapies
 - 1,027 generic drug applications, including 150 priority first generics
 - 21 biologics applications, including 7 breakthrough therapies and 5 biosimilars

2017 U.D. FDA Drug Highlights

ANDA Approvals & Tentative Approvals

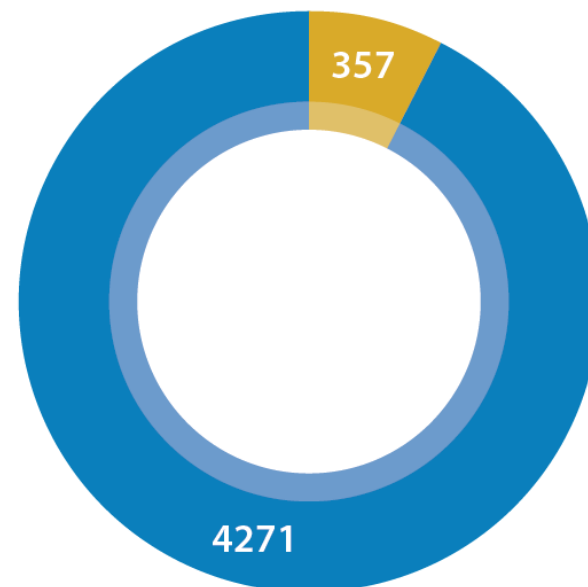


ANDAs



- Originals
- Priority 1st Generics

ANDA Supplements



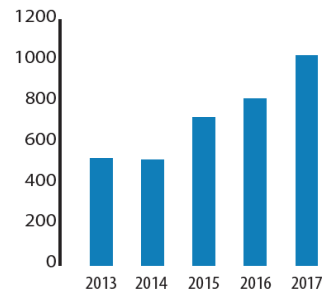
- CBE Supplements
- Prior Approval Supplements

2017 U.D. FDA Drugs Highlights



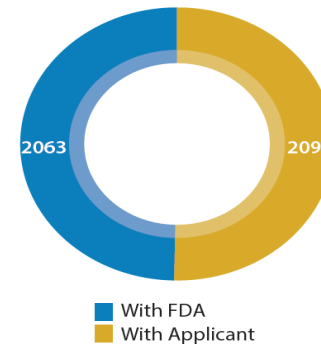
There was a record number of ANDA approval actions (approvals and tentative approvals) in 2017

ANDA Approval Actions by Year



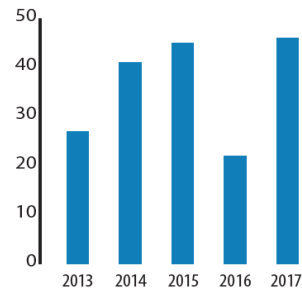
At the end of 2017, for the first time, more ANDAs were pending response from industry than FDA assessment

ANDAs



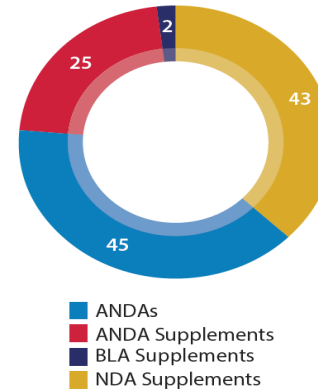
Novel drug approvals rebounded in 2017

Novel Drug Approvals by Year



In 2017 OPQ expedited many quality assessments due to potential drug shortage considerations

Expedited Submissions Due to Shortage Considerations



The active ingredient or ingredients in a **novel drug** have never before been approved in the United States. Novel drugs, are often among the more innovative products in the marketplace, and/or help advance clinical care by providing therapies never before marketed in the United States. Note that while many new drug approvals are not novel drugs, they still offer important medical value to patients in need.

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Muchas Gracias