Understanding How the Public Perceives and Values Pharmaceutical Quality

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February 3, 2020
Welcome & Overview
Opening Remarks from FDA
Introduction to Pharmaceutical Quality
The Importance of Pharmaceutical Quality

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Understanding How the Public Perceives and Values Pharmaceutical Quality
February 3, 2020
The Importance of Pharmaceutical Quality

• Pharmaceutical quality is what assures drugs on the market are safe and effective
• When quality goes wrong, everything can go wrong
• As we improve patient access to medicine, we cannot sacrifice quality
Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects.
CDER’s Tools for Regulating Quality

- Inspection
- Assessment
- Engagement
- Surveillance
- Outreach
- Enforcement
- Policy
- Testing
- Research

Improving Patient Access Without Sacrificing Quality
Improving Patient Access Without Sacrificing Quality

• Expect consistent quality regardless of where a drug or its ingredients are manufactured

• Maintain the integrity of the supply chain in an increasingly complex and globalized environment

• Simplify regulatory processes and strive for international convergence on quality standards
Quality is a Partnership With Many Stakeholders

- PAYERS
- PURCHASERS
- PROVIDERS
- STUDENTS
- COMPOUNDERS
- INT’L REGULATORS
- ENGINEERS
- PATIENTS
- CONSUMERS
- TEACHERS
- MANUFACTURERS
- PHARMACISTS
- HOSPITALS

YOU
Drug Quality and Shortages

Drug Shortages: Root Causes and Potential Solutions 2019

Quality Issues 62%

Natural Disaster 5%
Production Discontinuation 3%
Increase in Demand 12%
Unknown 18%

All Drugs Newly in Shortage

Biotech 3%
Unapproved 4%

All Drug Products in Shortage

NDA 30%
ANDA 63%

All Approved Generic Drug Applications

Actively Marketed 39%
Not Marketed 61%
Incentivizing Investment in Quality Management Maturity

Root causes for drug shortages:
• Lack of incentives for manufacturers to produce less profitable drugs
• Market does not recognize and reward manufacturers for “mature quality systems”
• Logistical and regulatory challenges make it difficult to recover from a supply disruption
Quality Management Maturity

- **Basic Quality Management Systems**
  - *Reactive*: focused on Current Good Manufacturing Practice (CGMP) compliance

- **Strong, mature Quality Management Systems**
  - *Proactive*: focus on performance, especially outcomes that affect the patient
Enduring solutions:

• Understanding the impact of drug shortages and the contributing contracting practices

• A ‘rating system’ to incentivize quality management maturity

• Sustainable private sector contracts for a reliable supply of medically important drugs
Investing in Quality at the FDA

Investing in IT Solutions

• Knowledge-aided Assessment and Structured Application (KASA)

Improving Inspections

• New Inspection Protocol Project (NIPP)
The KASA System

KASA – Knowledge-aided Assessment and Structured Application

Knowledge-aided Assessment

Pillar 1
Assessment of risk to quality by establishing rules and algorithms

Pillar 2
Control of risk to quality by assessing product design, understanding, and quality standards

Pillar 3
Control of risk to quality by assessing manufacturing & facility; when needed, performing preapproval inspection

The Knowledge Base
(Product, Manufacturing, and Facility)

FDA’s New Inspection Protocol Project (NIPP)

• Paradigm to better assess and record the state of quality in manufacturing facilities
  – Standardized electronic inspection protocols
  – Templated, semi-automated inspection reports
  – Quality maturity indicators
How can we make better decisions related to drug quality?

How can we help the public make better decisions related to drug quality?
Introduction to Pharmaceutical Quality
The Office Of Pharmaceutical Quality’s Role in Regulating Quality

Michael Kopcha, Ph. D., R.Ph.
Director - Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Understanding How the Public Perceives and Values Pharmaceutical Quality
February 3, 2020
Office of Pharmaceutical Quality

Across the lifecycle…
Across the globe…

Policy
Research
Assessment
Surveillance
Inspection

Development → Premarket → Postmarket

new drugs
biologics
generics
biosimilars
compounded
drugs
over-the-counter
drugs
International
Domestic
manufacturing
OPQ
Before Application Approval

• Assess how the applicant develops, manufactures, and tests the active ingredients and final drug products

• When needed, address whether the product is sterile (microbiology)

• When needed, address whether the drug has the appropriate rate and extent of absorption after administration to the human body (biopharmaceutics)

• Assess whether the proposed facilities are appropriate and prepared for commercial manufacturing
  – When needed, may include an onsite, product-specific facility inspection
How Does OPQ Regulate Quality?

Beyond Application Approval

- Develop standards and policies based on science and benefit/risk
  - Also for over-the-counter drugs and certain compounded drug products
- Conduct research to support the development of science-based quality policies and standards
- Oversee quality throughout the lifecycle of a drug product by assessing changes proposed after application approval
- Monitor the state of quality for all regulated manufacturing sites and drug products
  - Develop a risk-ranking of all manufacturing sites to guide inspection planning
## Assessing New Drugs vs. Generics

<table>
<thead>
<tr>
<th>Brand-Name Drug Approval Requirements</th>
<th>Generic Drug Approval Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>Drug Substance</td>
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<tr>
<td>Drug Product</td>
<td>Drug Product</td>
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<tr>
<td>Manufacturing Process</td>
<td>Manufacturing Process</td>
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<tr>
<td>Manufacturing Facilities</td>
<td>Manufacturing Facilities</td>
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<tr>
<td>Microbiology</td>
<td>Microbiology</td>
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<tr>
<td>Biopharmaceutics</td>
<td>Biopharmaceutics</td>
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<tr>
<td>Labeling</td>
<td>Labeling</td>
</tr>
<tr>
<td>Animal Studies</td>
<td>Bioequivalence</td>
</tr>
<tr>
<td>Clinical Studies</td>
<td></td>
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</tbody>
</table>

**Quality elements are the same**

**Clinical elements are different**
The Pharmaceutical Quality Lifecycle

With a staff of ~1,300 OPQ’s quality assessments average in a given year:

• Around **20** biologics
• Around **200** new drugs
• Around **3,000** investigational new drugs
• Around **4,000** generics
• Around **7,000** supplements
The State of Pharmaceutical Quality

- OPQ continuously monitors the quality of all CDER-regulated drugs

- We now publish a yearly ‘snapshot’ of the industry’s ability to deliver quality pharmaceuticals

- This snapshot provides an objective assessment, using the quality indicators we can share with the public
  - Based on available FDA drug product-specific and manufacturing site-specific data
Stakeholder Input

• OPQ makes decisions in the name of patients and consumers not drug companies

• We need better understanding of physician and consumer knowledge and perception of drug quality

• We teamed up with WebMD to begin learning from U.S. consumers and physicians
The Shortage Issue

Root causes for drug shortages:
- Lack of incentives for manufacturers to produce less profitable drugs
- Market does not recognize and reward manufacturers for “mature quality systems”
- Logistical and regulatory challenges make it difficult to recover from a supply disruption

Enduring solutions:
- Understanding the impact of drug shortages and the contributing contracting practices
- A ‘rating system’ to incentivize quality management maturity
- Sustainable private sector contracts for a reliable supply of medically important drugs
Modernizing Pharmaceutical Manufacturing

- Consumers and patients deserve quality products with minimal risks of shortages or recalls
- Quality of manufacturing in pharma lags other industries (e.g., semiconductors >six sigma)
- CDER’s Emerging Technology Program encourages and supports the adoption of innovative technology in pharmaceutical development and manufacturing
What is Advanced Manufacturing?

- Innovative **manufacturing technology** or approach that can enhance drug quality, improve the reliability and robustness of the manufacturing process and supply chain, and increase timely access to quality medicines for the American public

- Novel **dosage forms** or delivery systems to improve drug delivery and targeting

- Novel **analytical tools** to improve product quality testing, process monitoring and/or control
Why is Advanced Manufacturing important for both FDA and pharmaceutical industry?

• **Addresses the underlying causes of drug shortages**
  - Helps mitigate or prevent future production problems

• **Facilitates new clinical modalities**
  - Precision and individualized medicines
  - A wider range of novel dosage forms and doses - without extensive alterations of the process
  - Convenient fixed-combination dosage forms

• **Improves manufacturing efficiency**
  - Increase process robustness
  - Lower manufacturing costs
  - Increase supply chain flexibility
CDER’s Tools for Regulating Quality

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- Research

Improving Patient Access Without Sacrificing Quality
One Quality Voice for Patients

We Are Patients, Too.
Introduction to Pharmaceutical Quality
The State of Pharmaceutical Quality
Report on the State of Pharmaceutical Quality

Cindy Buhse
Director, Office of Quality Surveillance
FDA/CDER/Office of Pharmaceutical Quality
Understanding How the Public Perceives and Values Pharmaceutical Quality
February 3, 2020
U.S. Drug Distribution & Reimbursement System Is Complex, Private Contracts Are Opaque

Wall Street Journal
**Vision:** The Office of Quality Surveillance continuously monitors and provides the state of quality for all regulated sites and products.

**Mission:** The Office of Quality Surveillance assures that quality medicines are available through signal detection, data analysis, review of the state of quality, and proactive stakeholder engagement.
Sources of Information for Quality Surveillance

- Facility and Inspection Data
- Quality Defect Reports
  - MedWatch Reports
  - Recalls
  - Consumer Complaints
  - Industry quality report submissions
- Drug Quality Sampling and Testing Results
- Application data
- External data
  - Foreign regulatory authority information
  - Public information – social media, consumer reviews (e.g., drugs.com), blogs, news outlets, etc.

www.fda.gov
General Overview of Surveillance Activities

• Characterize the population of CDER-regulated sites and the products they manufacture
• Monitor and assess the state of quality
• Proactively identify potential quality signals and trends before serious quality problems occur
Surveillance vs Enforcement

Need for Firm Engagement

Severity of Adverse Signals

Surveillance and Risk Analysis

Enforcement – Office of Compliance

www.fda.gov
Human Drug Inventory by Approximate Numbers

Facilities:
• ~6,000 human drug manufacturing sites
  – ~2,000 Medical Gas (MG) manufacturers (nearly all in U.S.)
  – ~4,000 Non-Medical Gas manufacturers
    • 44% domestic
    • 56% foreign

Products:
• 120,000 unique finished dose
• 35,000 unique Active Pharmaceutical Ingredients

Note: Based on July 2019 Surveillance Catalogs and current eDRLS listings.
Drug Manufacturing Facilities

- Excluding medical gas, 4060 sites are in the catalog as of July 2019. Facilities enter and leave the market daily (registrations, deregistrations, application approvals).
  - Domestic: 1782 sites
  - Foreign: 2278 sites
    - China: 347 sites
    - India: 476 sites
    - Rest of the World: 1455 sites

* The hierarchy for this analysis tags a site that makes both FDF and API as FDF facilities and a facility that makes both application and non application products as an application site.
Facilities by Drug Product Types

- Facilities* are also categorized through a hierarchy of industry sectors:
  - 20% of all facilities are listed in new and biotech drug applications only
  - 14% of all facilities are listed in generic drug applications only
  - 26% of all facilities are listed in both generic and new drug applications
  - The remaining 60% of facilities are not listed in any applications (non-application sites including some over-the-counter and homeopathic products)

- 60% of all facilities are listed in application products
- 40% of all facilities manufacture non-application products

* Medical Gas not included
% of Manufacturing Facilities with Acceptable Final Outcome, as of August 2019

- European Union: 98%
- Rest of World: 94%
- United States: 93%
- China: 90%
- India: 83%
Surveillance Testing

252 Immediate Release Samples:
17 Active Ingredients
> 40 firms
5 regions
brand and generic

Colors represent different USP market standard criteria for dissolution.
Lines represent USP market standard criteria for dissolution and dosage unit uniformity
Public Information with FDA Access Links

- Inspections Classification Database
  [https://www.accessdata.fda.gov/scripts/inspsearch/](https://www.accessdata.fda.gov/scripts/inspsearch/)

- Drug Shortages

- Drug Recalls

- Drug Quality Sampling and Testing Programs

- FDA Social Media

[www.fda.gov](http://www.fda.gov)
U.S. Drug Distribution & Reimbursement System Is Complex, Private Contracts Are Opaque

Wall Street Journal
Take Aways

• OQS continually explores innovative ways to inform risk-based decisions.

• Some quality information is publicly available; however, there is a lack of transparency between facilities and products.

• OQS continues to engage stakeholders and support related academic research. Our goal is to keep all sites in compliance and all products available for the patient.

• OQS monitors the state of quality for sites and products so every dose is safe and effective, free of contamination and defects and patients can be confident in their next dose.
The State of Pharmaceutical Quality
Patient and Provider Perceptions of Pharmaceutical Quality

Adam Fisher, Ph.D.
Office of Pharmaceutical Quality
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U.S. Food and Drug Administration
February 3, 2020
One Quality Voice for Patients

We Are Patients, Too.
Consumer Knowledge of Drug Quality

FDABAA-16-00122
HHSF223201710128C

Physician Knowledge of Drug Quality

FDABAA-16-00122
HHSF223201710128C
Respondents

Consumers

• 3,037 WebMD site visitors
  – Desktop & Mobile
• 62% Age <50 Years
• 12.5% Hispanic
• 14.4% Black

Physicians

• 650 Physicians from Email Invite
  – Age >26, 5 years post-residency, >40% direct patient care, etc.
  – $25-50 Amazon Gift Card
• 61.5% Primary Care Physicians
• 55% >15 Years in Practice
• 7.7% Each:
  • Cardiologists
  • Dermatologists
  • Endocrinologists
  • Orthopedics
  • Rheumatologists
Overall Perceptions of Drug Quality

The overall quality of [...] drugs... is very good/excellent

- Physician ratings for drug quality were higher compared to consumers
- Physicians had more tendency to associate brand-name drugs with superior quality than generics
Age & Perceptions of Drug Quality

Consumers:
The overall quality of [...] drugs... is very good/excellent

- Consumers age 50 or over are more likely to rate drug quality as very good or excellent as compared to those <50
- The younger cohort was more likely to give a good or fair rating
Perceptions of Drug Manufacturing

Do you believe drugs manufactured outside the U.S. and sold in the U.S. adhere to strict manufacturing standards and regulations required by the FDA?

- Nearly three quarters of consumers AND physicians do not believe or are not sure.
Frequency of writing “DAW” for prescription brand-name drugs when a prescription generic is available

- Nearly half always/often/sometimes write DAW
- Significantly more specialists (21%) write DAW compared to PCPs (14%)
  - Highest among cardiologists (26%) and endocrinologists (28%)

Base: Total respondents - Physicians
Reasons for Dispense as Written

**Primary reasons for writing “DAW”**

- Patients specifically request prescription brand-name drugs: 73%
- I am not always aware of what generic versions are available: 28%
- I do not trust prescription generic drugs: 16%
- Generic drugs may interact with other drugs a patient is taking: 15%
- I do it out of habit: 7%

Nearly three-quarters say it’s because their patients specifically request brand-name drugs.

Base: Physicians Respondents who always/often/sometimes write DAW
Factors Indicative of Drug Quality

Percentage Somewhat/Strongly Agree […] Is an Indicator of Drug Quality

- Nearly **one-quarter of physicians** and nearly **one-third of consumers** think advertising is an indicator of drug quality

Base: Total respondents
**Physicians:**
Which, if any, of the following are functions of the FDA in terms of regulating drug quality?

<table>
<thead>
<tr>
<th>Function</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Remove a drug from market if unexpected risks are detected</td>
<td>78%</td>
</tr>
<tr>
<td>Evaluate and approve new drugs before they can be sold</td>
<td>77%</td>
</tr>
<tr>
<td>Make certain all drugs marketed in US are safe and effective</td>
<td>73%</td>
</tr>
<tr>
<td>Monitor use of marketed drugs for unexpected health risks</td>
<td>72%</td>
</tr>
<tr>
<td>Monitor truth in advertising for Rx drugs</td>
<td>62%</td>
</tr>
<tr>
<td>Prevent unapproved drugs from being imported to the US</td>
<td>58%</td>
</tr>
<tr>
<td>Oversee research, dev, manufacture, and marketing of drugs in US</td>
<td>56%</td>
</tr>
<tr>
<td>Work with other orgs, such as USP, to set quality standards for drugs</td>
<td>53%</td>
</tr>
<tr>
<td>Test drugs</td>
<td>40%</td>
</tr>
<tr>
<td>Set prices for drugs</td>
<td>10%</td>
</tr>
<tr>
<td>Manufacture drugs</td>
<td>9%</td>
</tr>
<tr>
<td>None of the above</td>
<td></td>
</tr>
<tr>
<td>Not sure</td>
<td></td>
</tr>
</tbody>
</table>

1 in 10 believes the FDA manufactures or sets prices for drugs (similar for consumers)
Drug Shortages

Consumers:

Have you experienced any difficulty in filling your prescription(s) due to drug shortage?

- Over one-third of consumers may have experienced difficulty in filling their prescription(s) due to drug shortage.

Consumers who experienced a drug shortage were more likely to have used an Rx generic drug in the past 3 years (88% vs. 68% Rx Brand).

Consumers who experienced drug shortages tended to rate Rx generic drug quality lower (64% vs. 73% very good/excellent).

Base: Total respondents - Consumers
Constant Availability vs. Quality

There are times when the FDA may take steps to maintain safety and quality standards for a drug, which can cause a supply shortage.

Use the scale below to indicate where you feel that the FDA should stand on this tradeoff.
Key Takeaways

 Consumers
• Three-quarters are uncertain that drugs manufactured abroad adhere to FDA’s quality standards
• Most, but not all, knew the FDA neither manufactures drugs nor sets drug prices
• Experiences with shortages influence perceptions of quality

 Physicians
• Half believe drugs manufactured abroad are of lower quality
• One-quarter believe a drug advertisement is an indicator of a quality
• Half sometimes or often write DAW
• Three-quarters do this because patients request them to
Key Takeaways

To maintain confidence in medicine, there is an opportunity for FDA to better understand stakeholder sentiments and to help facilitate conversations between physicians and patients about the quality of their drugs.
The State of Pharmaceutical Quality
Closing Remarks
Adjournment
Thank You!

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