



Protecting Patients & Consumers from Drug Quality Risks

US FDA Center for Drug Evaluation and Research

Everyone deserves confidence
in their *next* dose of medicine.

Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.



Product Quality Risk

CDER uses complementary tools to keep product quality risks from becoming patient risks

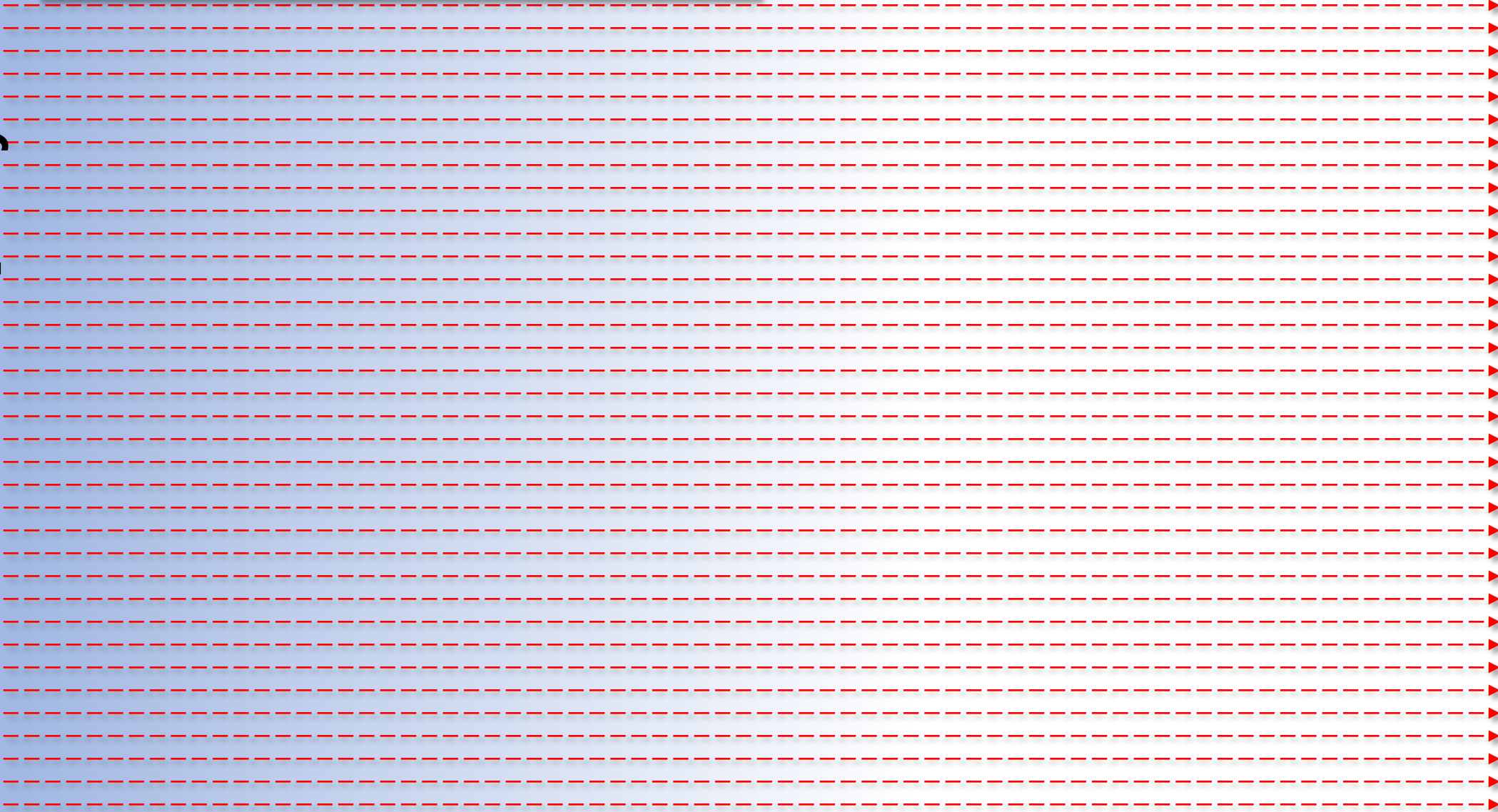
Patient Risk



A manufacturer identifies the critical attributes of their drug and develops a manufacturing process and controls needed to produce it



Product Quality Risk



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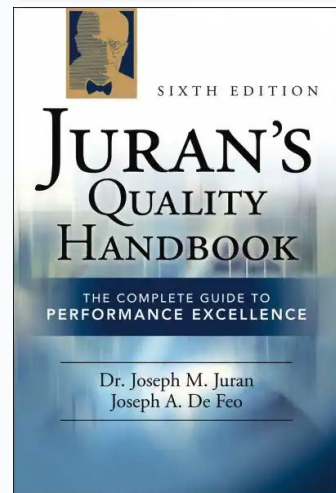
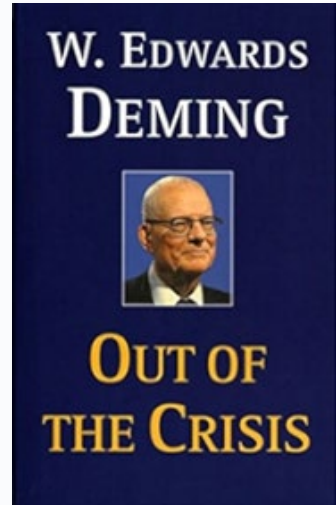
The guiding principle of modern quality management is that **quality must be designed into a product.**

Quality cannot be tested or inspected 'into' a product after it is made.

This is a globally accepted concept in *ICH Q8 Pharmaceutical Development*.

No amount of testing or inspection can overcome a poorly designed product or process.

This is why so much of CDER's application assessment focuses on the applicant's design of the product and the process they will use to make it.





Product Quality Risk

A manufacturer identifies the critical attributes of their drug and develops a manufacturing process and controls needed to produce it

A manufacturer establishes a specification listing the tests and criteria for releasing their drug to the market

Patient Risk



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All analytical methods must be shown **to meet their intended purpose.**

If a manufacturer uses their own in-house method, **it must be validated.**

If a manufacturer uses a USP monograph method, **it must be verified** (it has already been validated by USP).

For generic drug substances and products, many tests and criteria are defined in USP monographs.

Verified (easier) = show the procedure can be used for its intended purpose under the conditions of use for a specific drug substance or product

Validated (harder) = A large series of studies: Accuracy, Precision, Specificity, Detection Limit, Quantitation Limit, Linearity, Range, Robustness

It is not only the finished product that is tested. A manufacturer also tests all components used to manufacture the product, and certain intermediates formed during the manufacturing process.



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Patient Risk



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In an application, a manufacturer typically shows that they can make **batches of product that pass all tests in the specification**, for generic drugs **at 1/10th scale (at minimum)** of the proposed commercial process.

Before an application is approved, the manufacturer shows that the product **passes all proposed tests over a defined period and when stored appropriately over its shelf-life**.

If a product is approved before real-time shelf-life testing can be completed, then **manufacturer provides additional testing data after approval to confirm the full shelf-life**.

For generics there is less stability risk due to knowledge of the innovator drug's stability profile.



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Since the application batches are often made at smaller scale, **a manufacturer may need to scale up their process* after approval and validate it.**

Process validation was founded on the acknowledgment that **one-time testing of a final drug product is not enough** to assure patient safety.

Meaning: The process is **defined**. The process is **evaluated**. The process remains in a **state of control**.

*Continuous manufacturing processes are designed to scale up, so there is often little scale-up burden.

A manufacturer **tests every batch they make** based on the approved release specification. **Only passing batches can be released** to market.

Product testing can be destructive. A manufacturer samples from a batch using a sampling plan that provides appropriate confidence for assuring batch quality.



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A manufacturer must manage the ongoing release and stability testing and **ensure the completeness, consistency, and accuracy of data** for all regulatory records.

This includes **data related to the product and manufacturing process**.

Even after establishing an appropriate shelf-life with tests, a drug is approved with **a stability protocol that defines the ongoing stability testing** that will be conducted over its entire lifecycle.

The data generated by this testing is one **focus of FDA inspection**.

CDER releases guidance on product development and establishes quality standards (tests & criteria for release)

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Manufacturers do not typically make up all their own tests and criteria for drug development and release.

CDER releases guidance to address tests and criteria for release (ICH Q3 Impurity Guidelines) and the demonstration of generic drug equivalence (product-specific guidance).

CDER works with standard-setting organizations, most often USP, to establish tests and criteria in general chapters (applying to many/all drugs) and monographs (applying to one specific drug).



Patient Risk

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CDER assesses the application for product and process quality and conducts inspection if warranted based on risk

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Nothing is more important than showing that the product and process were designed to generate a quality product: *every dose safe & effective and free of contamination & defects.*

If a generic drug, thorough tests must show it is a **Therapeutic Equivalent** to innovator drug.

It must be, among other things, a **Pharmaceutical Equivalent** and **Bioequivalent**

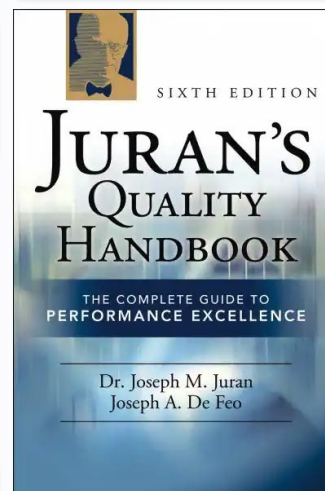
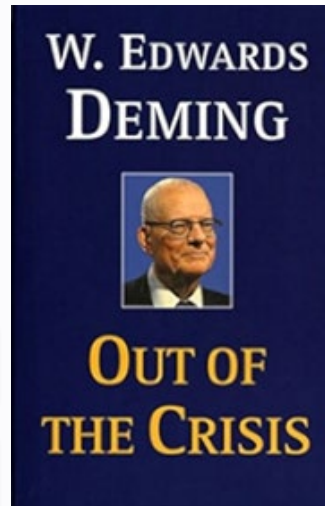
Pharmaceutical Equivalent = same amount of the same active ingredient, dosage form, route of administration, etc.

Bioequivalent = performs in same manner as innovator

A preapproval inspection may be conducted, if warranted based on risk/history, to in part confirm the data (including testing data) submitted in an application.

Important: For post-approval changes, manufacturers also test product and demonstrate it continues to meet specification criteria before implementing the change.

Remember:





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CDER uses surveillance inspections and remote regulatory assessments

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CDER uses surveillance inspections and remote regulatory assessments

After a product has been approved, **surveillance inspections are one way that CDER monitors the manufacturing process and quality of products** on the market.

All manufacturing sites are subject to routine surveillance activities.

CDER's Site Selection Model prioritizes sites for surveillance inspection based on risk.

A surveillance inspection or remote regulatory assessment covers data integrity and manufacturing practices for all products and processes at a site.



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CDER conducts data-driven market surveillance

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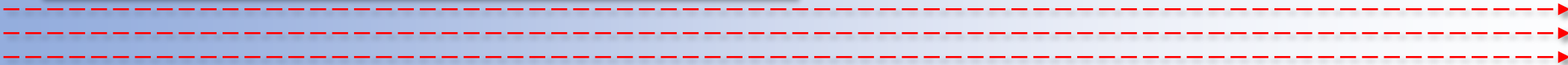
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Product Quality Risk



CDER conducts data-driven market surveillance

To find potential quality signals, CDER's surveillance program **uses analytics and quality data sources**, such as post-market quality reports, inspection reports, and application data.

Informs the **Site Selection Model** that prioritizes surveillance inspections

Informs **product sampling and testing** strategy

CDER developed and deployed a **Risk-Based Statistical Signal Detection Algorithm** to inform sampling assignments.

Prioritizes drug products and targets the types of tests that could uncover quality issues

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CDER conducts risk-based product sampling & testing

Patient Risk



Residual risk cannot go to **zero**, but it can be minimized.



CDER conducts risk-based product sampling & testing

Expertise-based approach + **Analytics-based** approach identifies problems that warrant testing

Experts in the quality assessment, surveillance, compliance, and inspection disciplines are **solicited for their recommendations.**

In some situations, a **suspected public health hazard can be resolved faster with another FDA action** (such as requesting recalls or issuing warning letters).

Sampling and testing can be assigned at any point in the year, so it can be responsive to risk, workload, and developing issues.

There is not typically unbiased or randomized testing.

This has not proven to be a good use of testing resources in the past. Typically, a product is tested if it has been signaled by experts or algorithms for surveillance testing.

CDER conducts risk-based product sampling & testing

The amount of product to sample is dependent on the type of test, number of tests needed, the size of the lot or batch under investigation, and the amount available.

Important: No single test can be used for all quality attributes, so tests typically focus on attributes with suspected risks.

Very Important: The amount of product sampled for testing should not significantly impact the amount of product available to patients and consumers.

Enough sample is needed to: verify or validate the method, perform the testing, perform confirmatory testing, and retain, if results are contested.

No sampling strategy can be representative of the entire market (> 140,000 drug products).

CDER can use statistical sampling to make inferences about a population of interest (for example, hand sanitizer manufacturers) while quantifying the uncertainty due to sampling.

Testing product for the market is **best done by a manufacturer running a process designed with appropriate controls**, including release testing with an appropriate sampling plan.

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CDER releases guidance on product development and establishes quality

A Look Forward

Additional info, not necessarily from additional product testing, but rather from **Quality Management Maturity** assessments and **Quality Metrics** can further reduce supply chain risk.

- **Quality Management Maturity** assessments will be voluntary and conducted at points in time to encourage manufacturers to implement robust quality management practices.
- **Quality Metrics** Quality Metrics can help monitor a manufacturer's sustained performance between points in time and help identify opportunities for improving the manufacturing process.

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