Build trust with the USP Ingredient Verification Program

About USP

We believe in trust

We envision a world in which all have access to high-quality, safe, and beneficial medicines and foods they can trust.

Every day, with a sense of urgency and purpose, we aim to improve global health through public standards and related programs.

A history unmatched

200+

years building quality foundations for a healthier world

150+

countries utilizing USP standards with 50 countries recognizing them as law

Expertise from across the globe

More than **900**

experts in science, industry, healthcare, academia, and government liaisons from

31 countries

Impact

2 billion

people around the world have access to quality medicines, dietary supplements, and food as a result of our standards, advocacy, and education

Improving global health

9,000+

standards for medicines, dietary supplements, and food ingredients

What we do

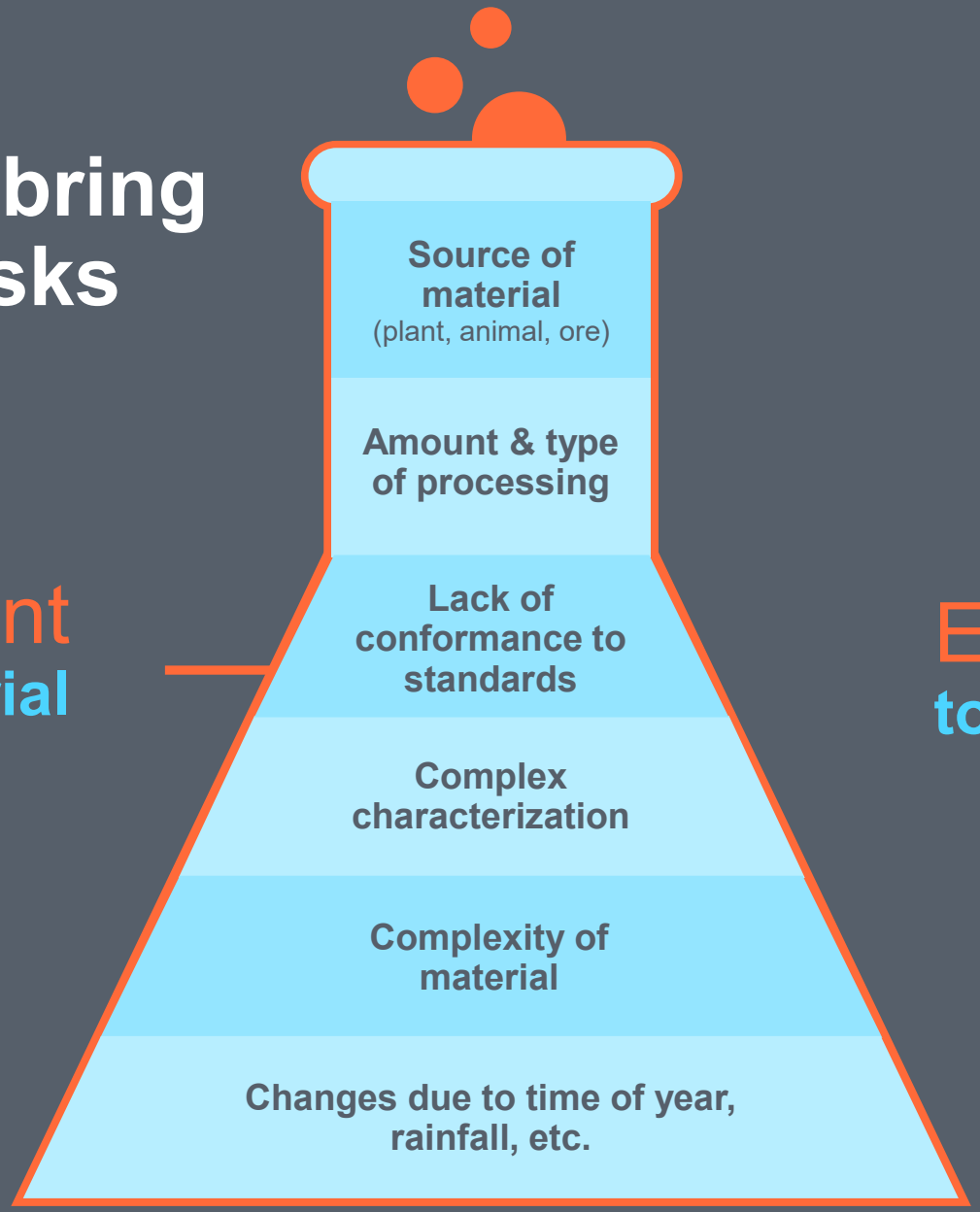
- Advancing the science of quality
- Building strong health systems
- Advocating for quality
- Exploring the future of quality

Quality ingredients matter

The global drug supply chain is complex and vulnerable

to disruptions, as many intermediaries play a role in a drug product's production, distribution, and delivery.

Disruptions bring increased risks



Inherent
to the material

External
to the material

- Country of origin
- Complexity of supply chain
- Value of material (economic motivation for adulteration/substitution)
- Reputation of manufacturer/distributor(s)
- Historical experience w/ manufacturer/distributor(s)
- Changes in management or ownership

Quality risks can lead to product recalls

*The US FDA reported the recall of **53,000+** pharmaceutical products between 2004-2011*

http://ipimediaworld.com/wp-content/uploads/2014/03/Pharmaceutical-product%E2%80%A6pdf.pdf

Major contributors to product recalls:

Microbiological quality issues

- Lack of sterility assurance and microbial contamination

Problems with product compositions

- Undeclared/mis-declared ingredients, impurities, and sub/over-amount of a chemical entity

Packaging defects

- Mislabeling, misinformation, mix up, incorrectly marked or damaged primary packaging material, out-of-order packaging, un-updated leaflet instructions, dosage forms mixing, inadequate blister pack seal, leakages, and missing batch number along with expiry date information

https://meridian.allenpress.com/innovationsjournals-JQSH/article/2/2/34/434833/Drug-Recall-Monitoring-and-Trend-Analysis-A

Case in point: NDMA recalls

Quality issue: assay

In the past few years, N-nitrosodimethylamine (NDMA) has been found above the acceptable daily limit in multiple drug products. As of November 4, 2020, there have been

254 recalled metformin products,

a drug used by people living with diabetes to control high blood sugar, due to NDMA contamination.

Public health impact

In the United States alone,

34.2 million

adults have diabetes

10.5%

of the population

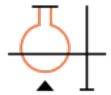
Metformin has been prescribed to more than

120 million people worldwide

https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-metformin-products

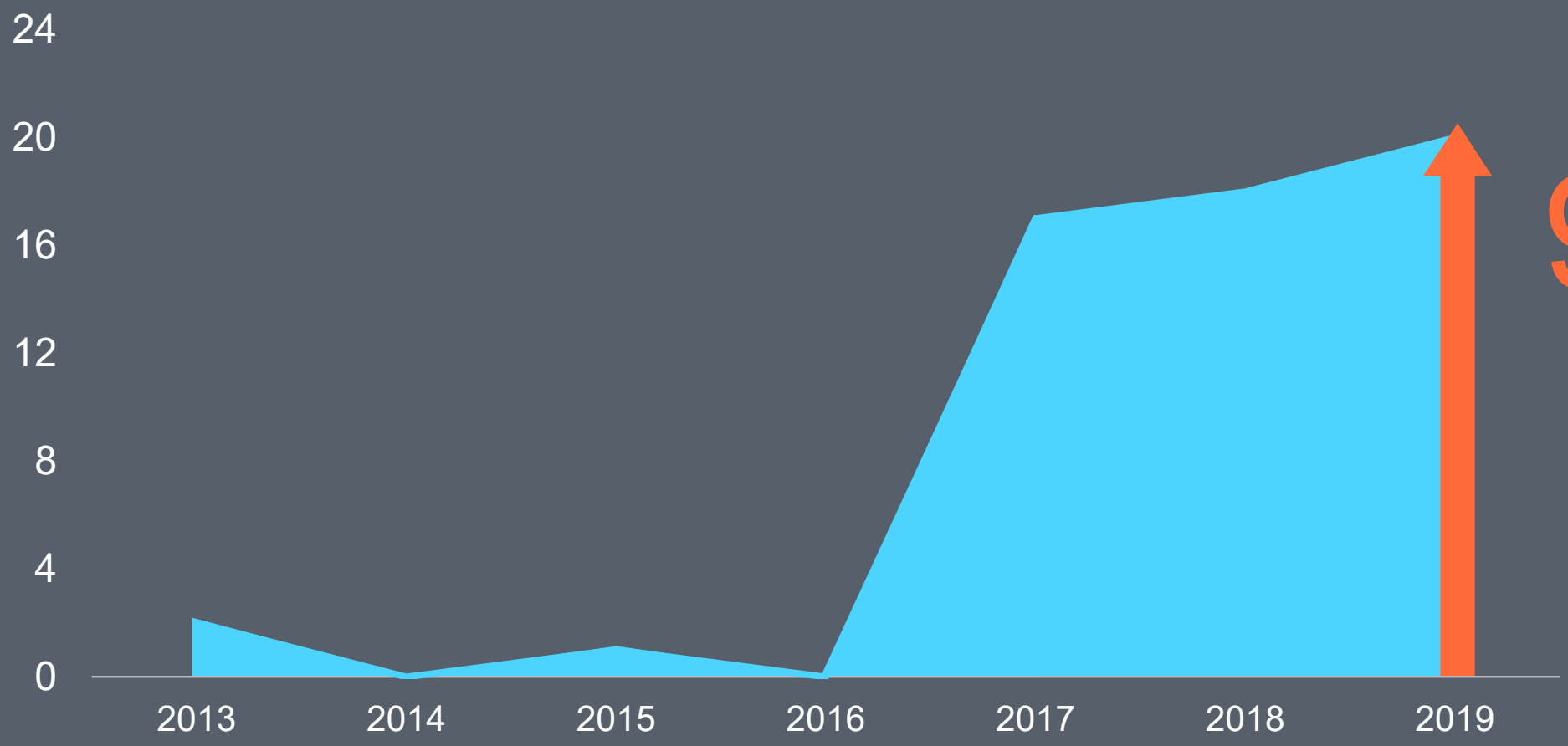
FDA Warning Letters include citations related to quality issues

Top 10 reasons for US FDA citations for pharmaceutical products in 2019:

1.  Validated production and process controls
2.  Investigations of discrepancies and OOS results
3.  Inadequate stability testing
4.  Responsibilities of quality unit
5.  Failure to test finished products
6.  Components tested for identity and conformity with specifications
7.  Responsibilities of quality unit; written procedures
8.  Equipment cleaning and maintenance
9.  Lack of established lab controls
10.  Laboratory records are incomplete

https://www.pharmaceuticalonline.com/doc/comparing-the-top-pharma-inspection-findings-from-fda-mhra-russia-s-ministry-of-health-0001

Sharp increase in FDA warning letters citing excipient testing issues



900%

increase over the last 6 years

Source: According to an analysis by the US Pharmacopeia (USP) of FDA warning letters issued between 2013 and 2019: https://www.e-digitaleditions.com/i/1173734-tc1019/11?

Case in point: glycol contamination

Quality issue: purity

The FDA has taken recent contamination risks seriously and sent warning letters to facilities for:

- Not ensuring adequate cleaning procedures, records, and documentation to prevent contamination
- Failing to assess the risk that impurities would find their way into solvent

Public health impact

Poor quality controls:

ColdBest-PC cough syrups' excipient propylene glycol was contaminated with the chemical diethylene glycol, a chemical similar to antifreeze.

This caused the death of

9 children

https://economictimes.indiatimes.com/news/politics-and-nation/death-of-jammu-children-test-confirms-syrup-was-adulterated/articleshow/74492777.cms

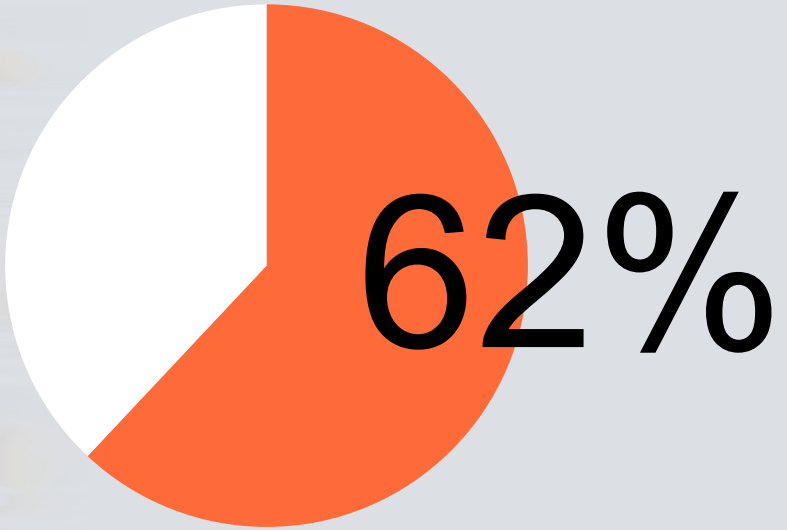
Quality risks can lead to patient harm

High demand for certain ingredients and drug products can cause shortages, and consequential surges, in production.

Surges are as worrisome as shortages, because they likely mean that drug-product manufacturers are quickly sourcing materials from new ingredient suppliers.

FDA examined a sample of **163 drugs**

for which shortages first occurred between 2013 and 2017. They found:



62%

of the shortages arose after supply distributions related to product quality or manufacturing problems occurred.

https://www.fda.gov/media/131130/ o

Case in point: hand sanitizer shortages & surges

Ingredient Quality Issues

Between June 2020 – June 2021, there have been more than

250 **hand sanitizer products listed on the FDA's Do Not Use List**

Public health impact

During May and June 2020,

15 **people in Arizona and New Mexico were hospitalized**

after ingesting hand sanitizer containing methanol.

3 **people were left with visual impairments**

4 **people died as a result**

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use (as of June 21, 2021)
https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e1.htm

Basics of conformance

What are CGMPs?

Current Good Manufacturing Practices

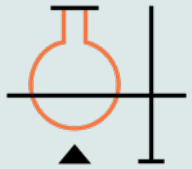
CGMPs help create systems that ensure proper design, monitoring, and control of manufacturing processes and facilities.

If adequately put into practice, CGMPs help prevent instances of contamination, mix-ups, deviations, failures, and errors.

Adherence to CGMP regulations ensures the identity, strength, quality, and purity of drug products and ingredients to adequately control manufacturing operations.

https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps#:~:text=What%20are%20CGMPs%3F,of%20manufacturing%20processes%20and%20facilities

CGMPs are established to be flexible



Allows each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures.

Allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement.

https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps#:~:text=What%20are%20CGMPs%3F,of%20manufacturing%20processes%20and%20facilities

If an ingredient manufacturer is not following CGMPs, are the ingredients safe for use?

If a company is not complying with CGMP regulations, any ingredient/drug it makes is considered “adulterated” under the law.

- Adulteration in this context means that the ingredient/drug was not manufactured under conditions that comply with CGMP.
- It does not necessarily mean that there is something wrong with the ingredient/drug.

https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps

What is ICH?

International Council for Harmonization
of Technical Requirements for Pharmaceuticals for Human Use

Organization and now includes 17 Members and 32 Observers

It brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines.

Its mission is to achieve greater worldwide harmonization to ensure that safe, effective, and high-quality medicines are developed and maintained in the most resource-efficient manner, while also meeting high standards.

What is ICH Q7?

A guideline concerning the Good Manufacturing Practice (GMP) for the manufacturing of Active Pharmaceutical Ingredients (APIs)

Applies to the manufacture of APIs for use in human drug (medicinal) products

Purpose:

- Harmonize expectations during inspections
- Remove ambiguities and uncertainties

Includes a Q&A document to addresses technical issues regarding GMP of APIs

Supplier qualification

Key outcomes and considerations

Paper audit

- Confirms they have a Quality Management System (QMS)

  …But not how well it is implemented

  …Also, is information trustworthy?

On-site audit

- Shows implementation of QMS
- Quality of facility, general maintenance, and procedures

  …But it is only a periodic snapshot in time

USP Ingredient Verification Program

Disruptions to your supply chain do not have to mean compromising quality.

The USP Ingredient Verification Program helps you ensure the quality of ingredients, in addition to supporting the qualification of suppliers.

Active Pharmaceutical Ingredient

Excipient

Why USP Verification?

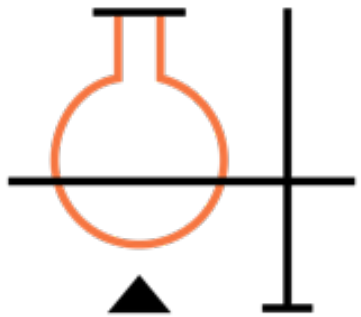
Helps demonstrate conformance with applicable Current Good Manufacturing Practice (CGMP) requirements

Verify conformance to appropriate specifications for identity, strength, purity, and quality

Helps ensure conformance with acceptable limits for impurities and contaminants

Helps ensure ingredient consistency from batch to batch

Why USP Verification?

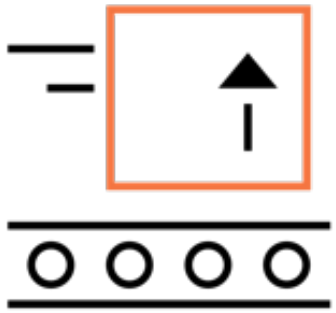


To ingredient suppliers:

USP Verification makes the quality of your products visible

- Demonstrates quality of ingredients to customers
- Helps differentiate ingredients from others in the market
- Strengthens confidence that GMP and product quality standards have been met for continual improvement

Why USP Verification?

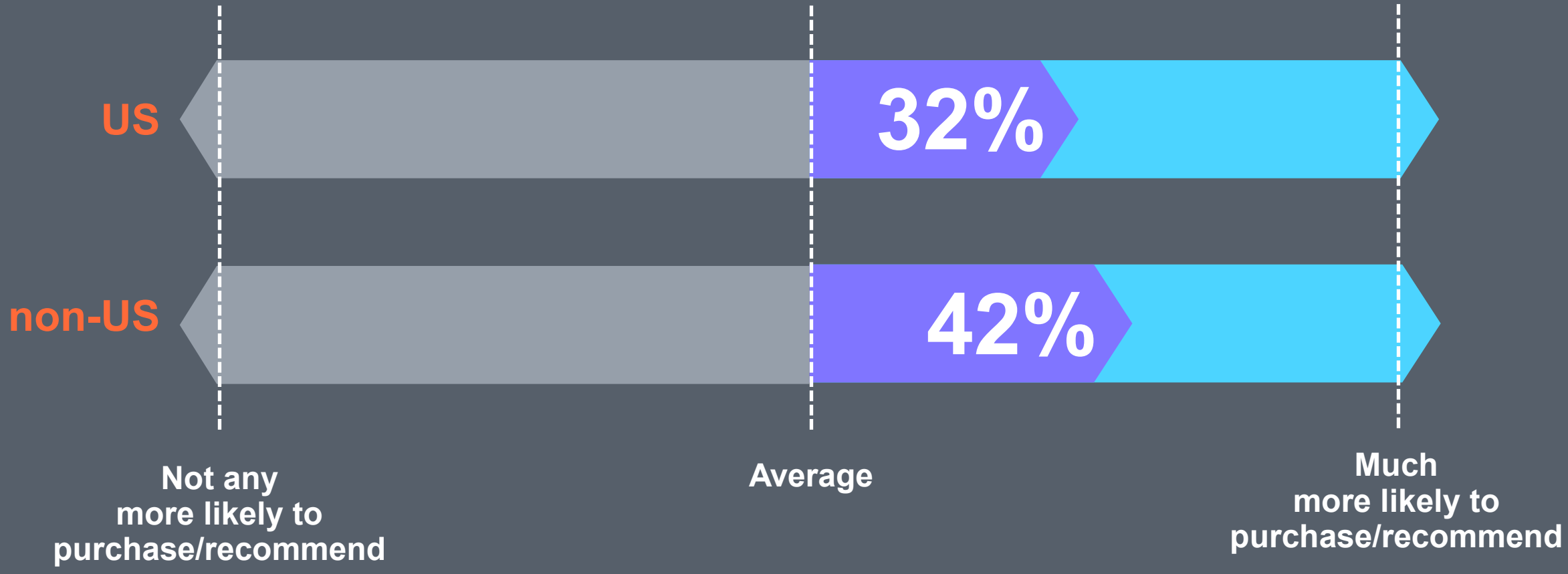


To drug-product manufacturers:

Independent third-party helps mitigate risk to your supply chain

- Helps to qualify suppliers
- Helps reduces inspection costs
- Builds confidence in ingredient quality
- Reduces risk of inconsistent, substandard quality ingredients

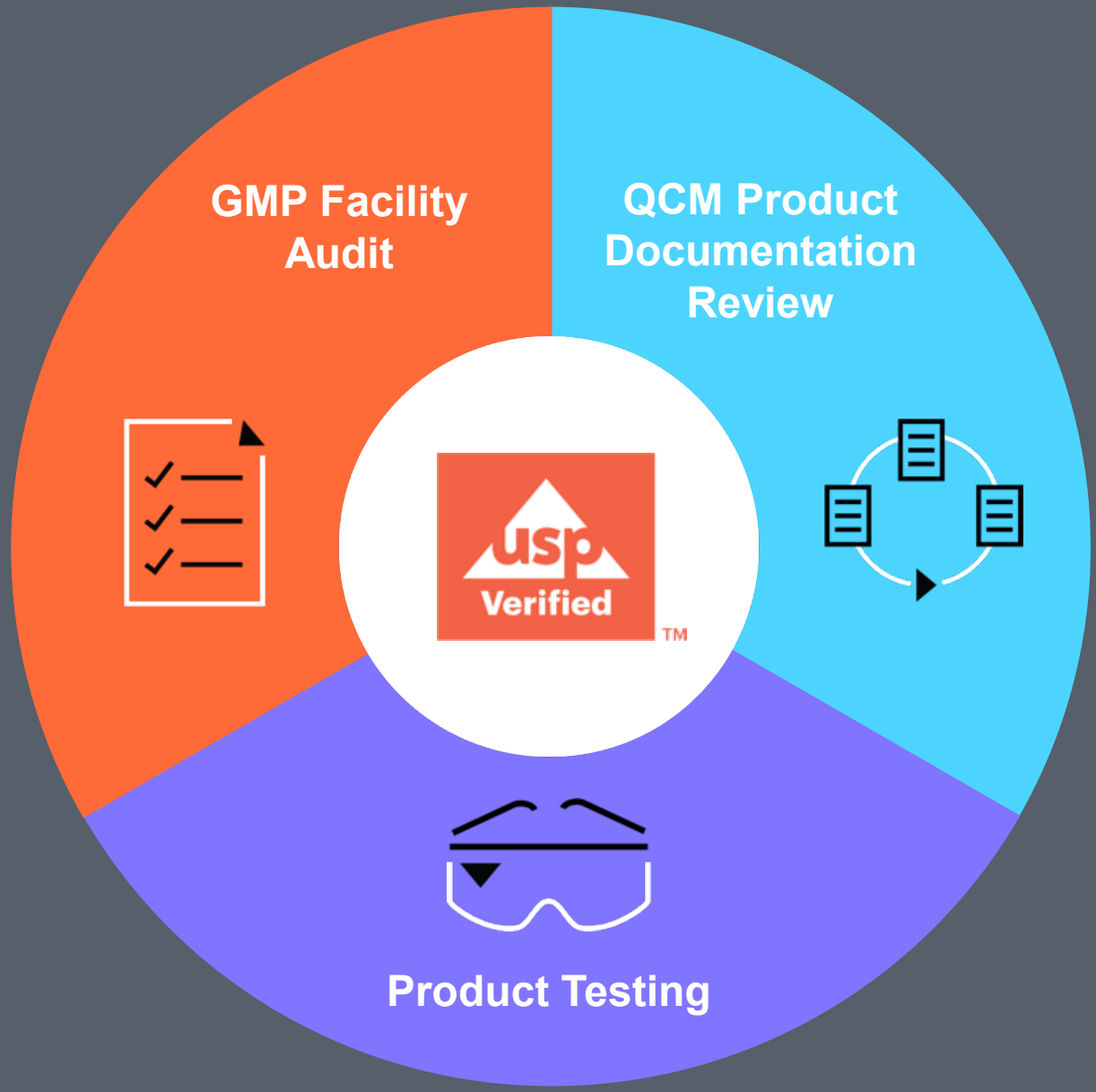
Globally, manufacturers are 37% much more likely to purchase/recommend excipients that have been USP verified



Based on Top-3-Box (T3B) rating on an 11-point scale

Significantly higher/ lower than opposing region – 95% confidence. Non-US sub-regions compared to Non-US total

USP's Ingredient Verification Program Services



Good Manufacturing Practices facility audit

The facility audit helps ensure manufacturing sites comply with GMPs based on regulatory and industry best practice:

1. Quality Management System
2. Facilities and Equipment System
3. Material System
4. Production System
5. Packaging and Labeling System
6. Laboratory Control System

- ***ICH Q7*** *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* ***APIs***
- **USP General Chapter ⟨1078⟩** *Good Manufacturing Practices for Bulk Pharmaceutical* ***Excipients***
- **ANSI 363** *Good Manufacturing Practices (GMP) for Pharmaceutical* ***Excipients***

Good Manufacturing Practices facility audit (cont.)

Auditor qualifications & training:

1 Program Certification

- ✓ ISO 17020

2 Qualifications

- ✓ ASQ CQA certification
- ✓ Relevant industry experience
- ✓ Relevant audit experience
- ✓ Thorough understanding with the specific regulations or guidelines

3 Training Provided

- ✓ USP specific training
- ✓ USP program training

Quality control and manufacturing process evaluation

Documentation review can uncover quality issues not discovered during GMP facility audits

During the Quality Control and Manufacturing (QCM) Process Evaluation, USP reviews:

- General information
- Manufacturing Process
- Control of raw materials, intermediates, and finished form
- Reference standards or materials
- Container closure system and labeling
- Stability ICH Q1, USP <1150>

Product testing

The USP Ingredient Verification Program tests ingredients for four key quality attributes:

- Identity
- Purity
- Assay
- Specific test for quality

Becoming USP Verified

Key: USP | Company | Both

Good Manufacturing Practice (GMP) Facility Audit

- Conduct Audit and Issue Report
- Respond to Audit Observations
- Assess and Address Audit Observations
- Everything Addressed and Reviewed?

Quality Control & Manufacturing (QCM) Process Evaluation

- Provide QCM Documentation
- Evaluate Documentation and Issue Report
- Respond to Evaluation Observations
- Assess and Address Evaluation Observations
- Everything Addressed and Reviewed?

Ingredient Testing

- Provide Ingredient Samples, Analytical Methods, and Supporting Information
- Assess Methods, Perform Testing, and Issue Report

→ USP Verified™ Excipient → **Continued surveillance**

Questions?

Paul Heslin

Senior Market Development Manager

Phone: 312-231-5038

Paul.heslin@usp.org