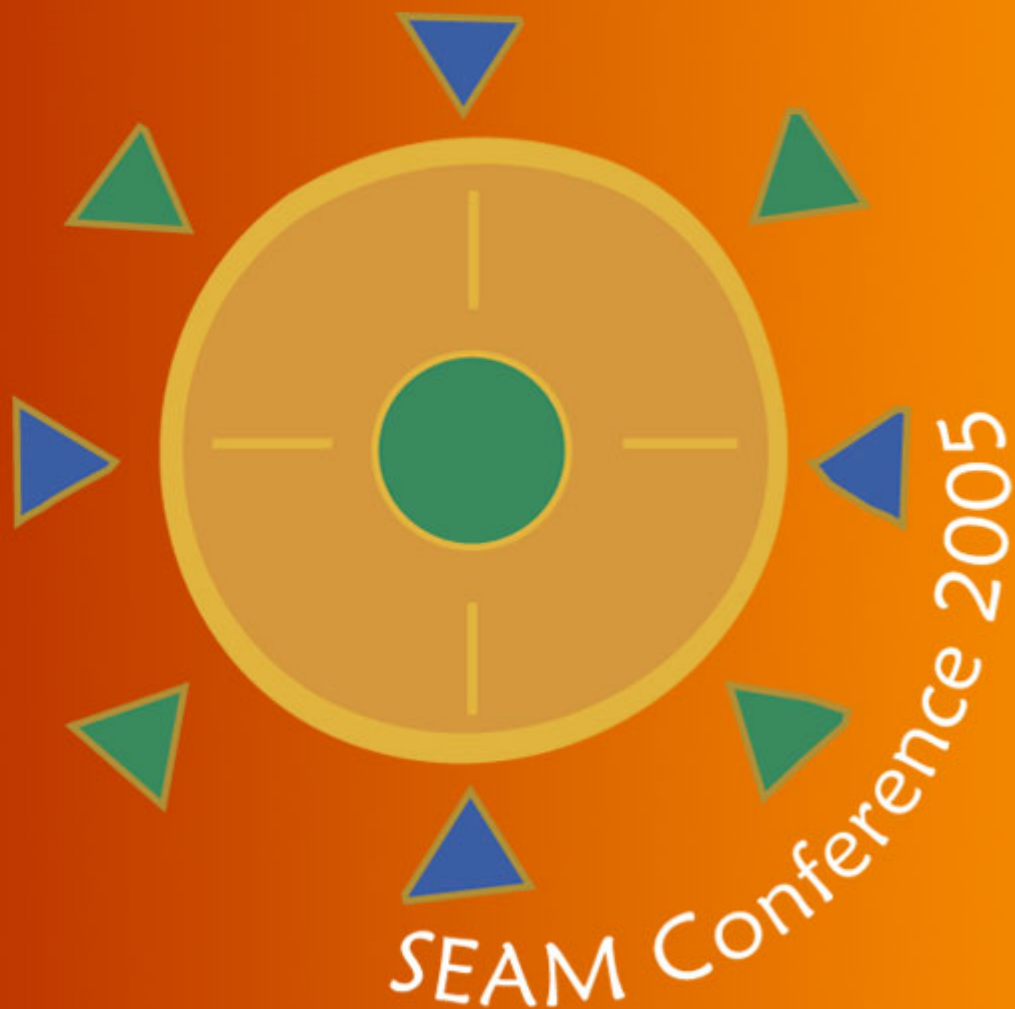




Accra, Ghana • June 20–22

Targeting Improved Access

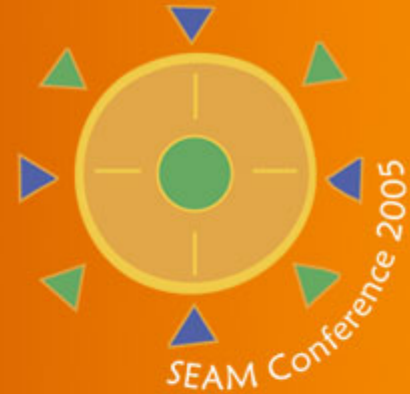


MANAGEMENT SCIENCES *for* **HEALTH**

SEAM | Strategies for Enhancing Access to Medicines

Funding for the SEAM Program is provided by the Bill & Melinda Gates Foundation.

Targeting
Improved
Access



Accra, Ghana • June 20–22

Multitier Approach to Drug Quality Assurance

Tom Layloff, SEAM, MSH

Funding for the SEAM Program is provided by the Bill & Melinda Gates Foundation.



MANAGEMENT SCIENCES *for* HEALTH

SEAM | *Strategies for Enhancing Access to Medicines*

The Regulatory Universe

What Needs to Be Done?

Inspection:
Product and
Supply Chain

Product
Evaluation

Product
Screening

Registration

Postmarketing Surveillance
Pharmacovigilance

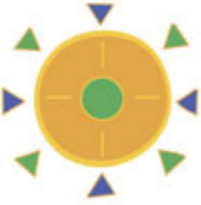
Prescribing
Dispensing

Management

QA

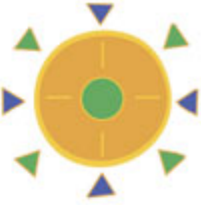
Product
Testing

Compliance
Enforcement



Do Something

- ❖ In law enforcement, doing something is always better than doing nothing.
- ❖ A police car parked by the side of the road will cause speeders to slow down.
- ❖ Don't advertise your limitations.
- ❖ Move resources to shift targets.
- ❖ Keep the market uncertain of your targets.



Evaluation/Registration

- ❖ Products must be safe and effective
- ❖ LEVEL 2 evaluation for new chemical entities
 - ❖ Scientific elegance of International Conference on Harmonisation (ICH)
 - ❖ Astounding resource requirements
- ❖ LEVEL 1 evaluation for established chemical entities



ICH Guideline Topics

- ❖ Quality
- ❖ Safety
- ❖ Efficacy
- ❖ Multidisciplinary

Safety (S) - Guidelines

- ❖ S1 - Carcinogenicity Studies
- ❖ S2 - Genotoxicity Studies
- ❖ S3 - Toxicokinetics and Pharmacokinetics
- ❖ S4 - Toxicity Testing
- ❖ S5 - Reproductive Toxicology
- ❖ S6 - Biotechnological Products
- ❖ S7 - Pharmacology Studies
- ❖ S8 - Immunotoxicology Studies
- ❖ M3(M) - Joint Safety/Efficacy (Multidisciplinary)
Topic

Efficacy E - Guidelines

- ❖ E1 and E2 - Clinical Safety
- ❖ E3 - Clinical Study Reports
- ❖ E4 - Dose-Response Studies
- ❖ E5 - Ethnic Factors
- ❖ E6 - Good Clinical Practice
- ❖ E7 - Clinical Trials

- ❖ E7 - Studies in Support of Special Populations: Geriatrics
- ❖ E8 - General Considerations for Clinical Trials
- ❖ E9 - Statistical Principles for Clinical Trials
- ❖ E10 - Choice of Control Group and Related Issues in Clinical Trials
- ❖ E11 - Clinical Investigation of Medicinal Products in the Pediatric Population
- ❖ E12A - Principles for Clinical Evaluation of New Antihypertensive Drugs (Consensus Draft Principle)
- ❖ E14 - The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Evaluation Levels

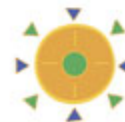
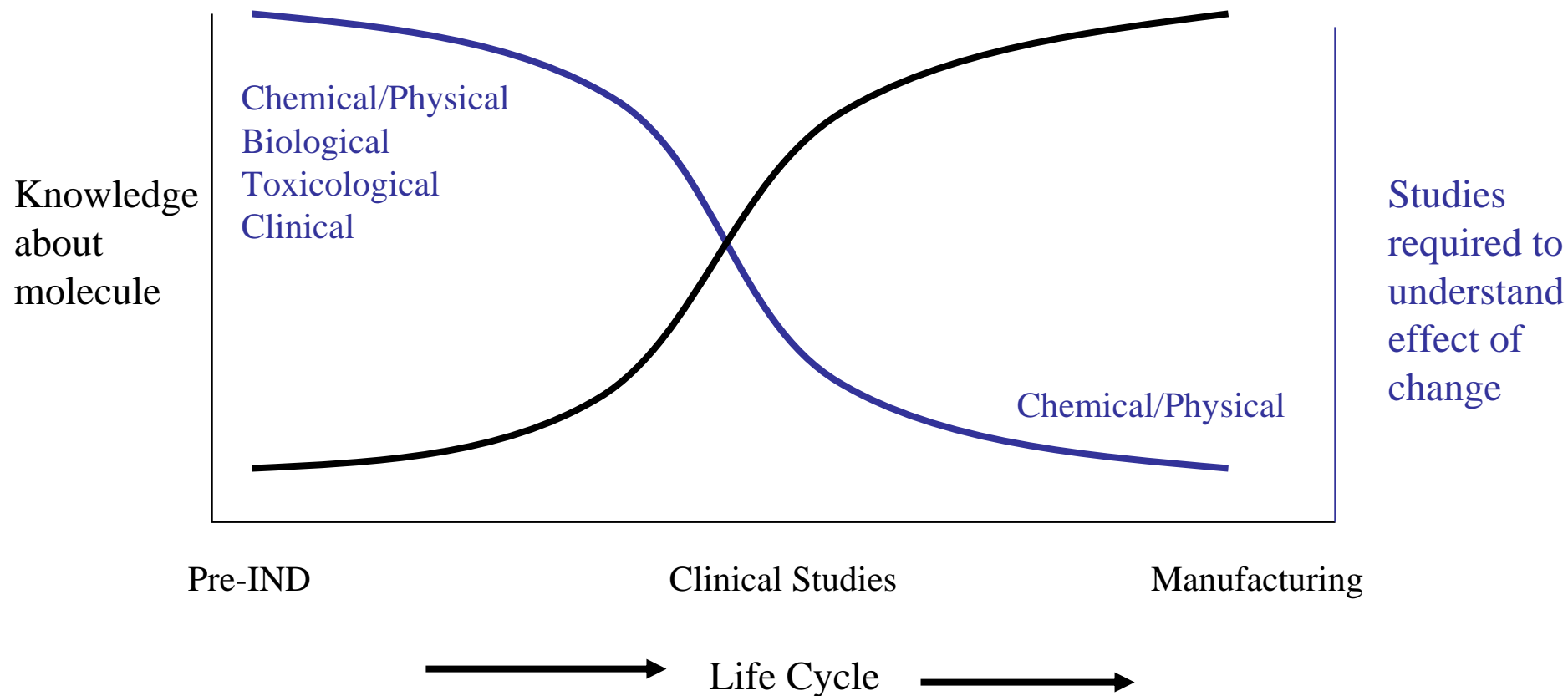
❖ LEVEL 2: No History to Acceptance

- Never before tested in humans
- Animal studies
- ICH schedules
- Safety and efficacy of new chemical entity

❖ LEVEL 1: Established Drugs

- Shown in ICH region to be safe and effective for intended use
- WHO prequalified; history of safe and effective use
- Bioequivalence issues

Knowledge vs. Studies



New vs. Generic Review Process

New Drug Requirements (ICH)

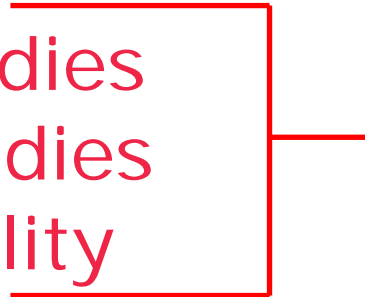
LEVEL 2

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal studies
7. Clinical studies
8. Bioavailability

Generic Drug Requirements

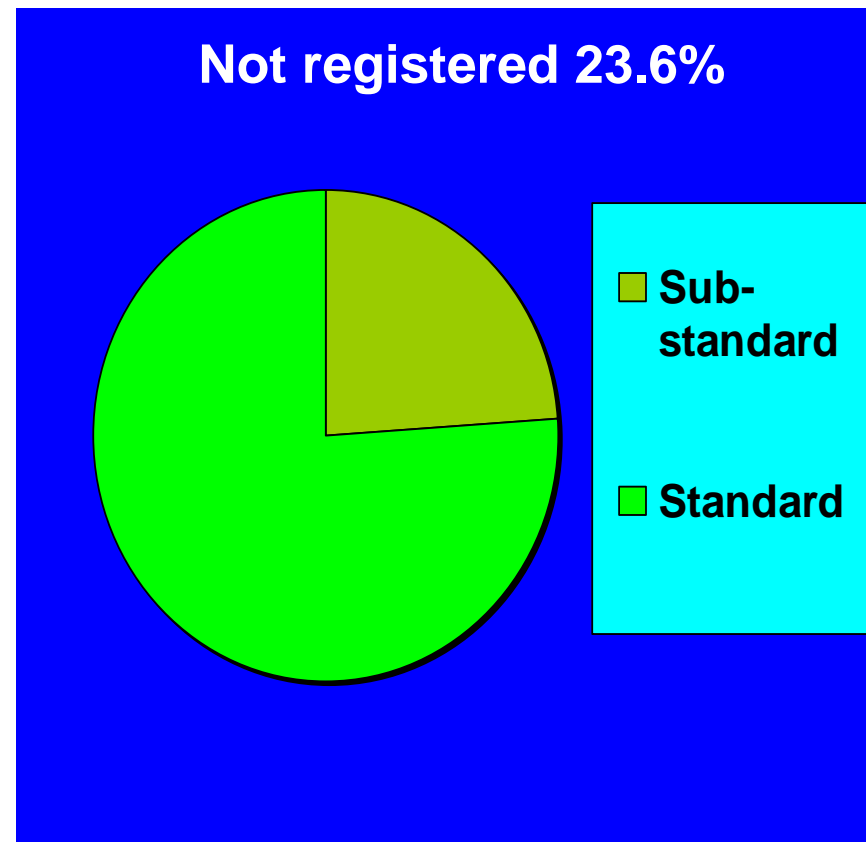
LEVEL 1

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence



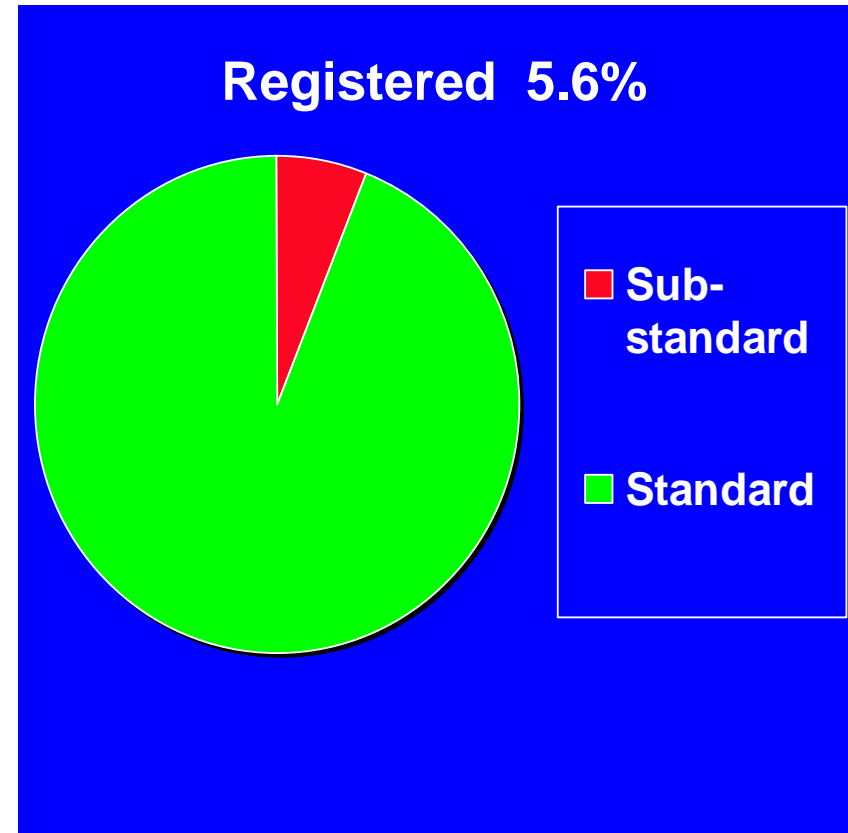
Just Looking Appears to Improve the Marketplace

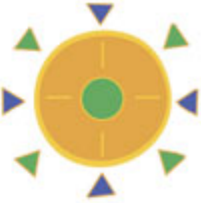
A Comparison Study of Testing Products Registered and Not Registered in Myanmar and Vietnam 1996–1997
WHO Data



Drug Registration Appears to Improve Drug Quality

- ❖ Product testing shows that registered products (5.6% substandard) are much less likely to be substandard than unregistered products (23.6% substandard).
- ❖ 75% reduction!!!





Registration

- ❖ Defines what products may be legally marketed in the country
- ❖ WHO prequalification Q&A states: “quality assessment is product and manufacturing site specific”
- ❖ Registration is product, manufacturer, and site specific

Testing

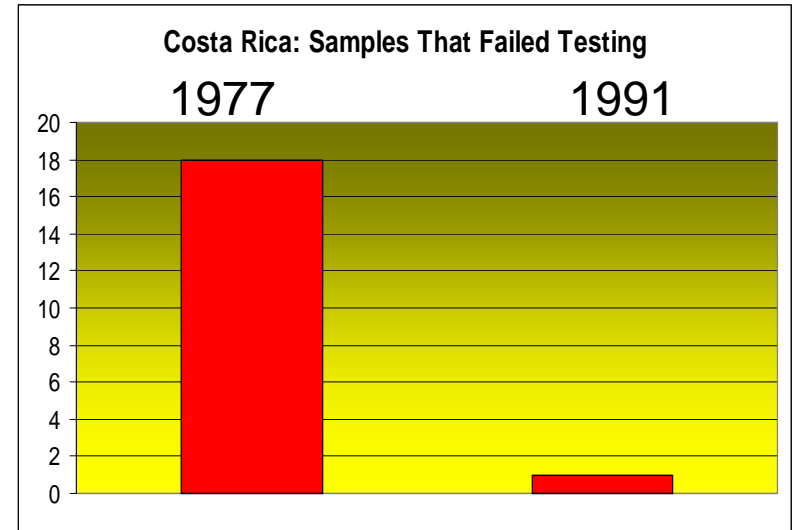
- ❖ Product testing is the most expensive tool in the regulatory process.
- ❖ Product testing is the only way to prove that a product is substandard or is counterfeit.
- ❖ Product testing is frequently contested in courts, so chain-of-custody and rigorous adherence to good practices and legal standards are mandatory.



Of Course Product Testing Also Poses a Very Significant Deterrent

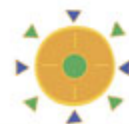
Costa Rica

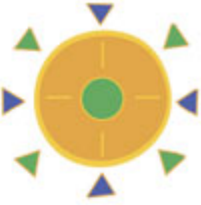
- ❖ Social Security Fund purchases in 1977 vs. 1991
 - ❖ Product testing program was instituted



Inspection and Testing Also Pose a Deterrent to Poor-Quality Products in the Market*

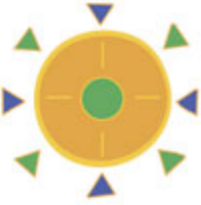
	Myanmar	Vietnam
Substandard drugs	16%	8%
Number of inspectors	2	61
QCL: Number of samples/year	32	31,000
<i>*Study in Myanmar and Vietnam 1996–1997 (WHO data)</i>		



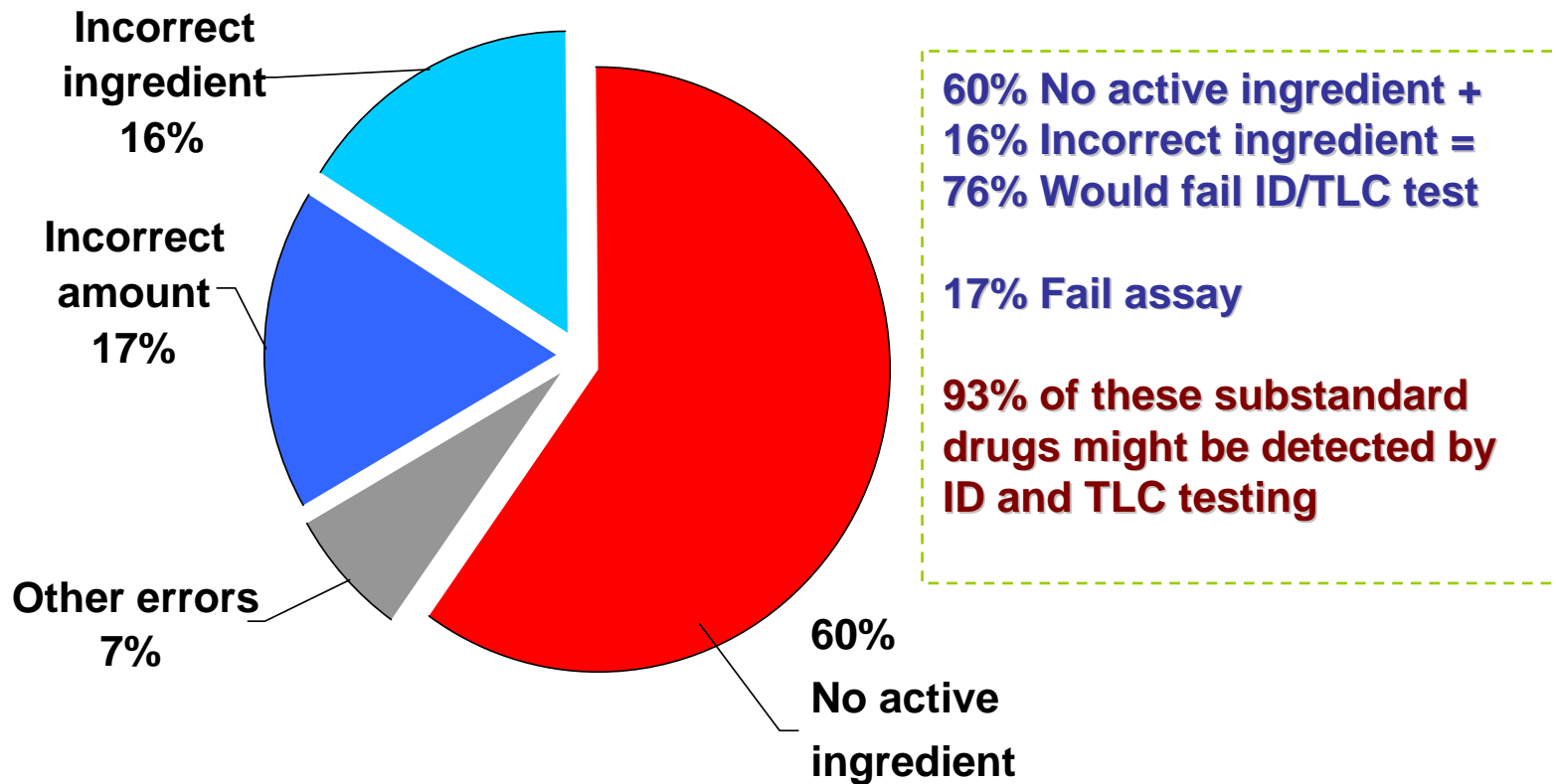


What to Test?

- ❖ Correct drug
- ❖ Correct amount
- ❖ Uniform dosage units
- ❖ Release from matrix—dissolution
- ❖ Impurities



325 Cases of Substandard Drugs, Including Antibiotics, Antimalarials, and Antituberculosis Drugs Reported to WHO



Minilab Testing

- ❖ Very capable of detecting over 76% of the substandard products—no drug or wrong drug
- ❖ Some capability to detect a part of the incorrect amount—visual detection depends on perception acuity of examiner
 - ❖ 0% to 80% and 100% plus

Other Attributes

- ❖ Impurity compliance to standards— chromatography frequently with mass spectroscopy. High tech with well-trained personnel.
- ❖ Dissolution testing. Laboratory tests very dependent on well-trained and skilled analysts.

Inspection

- ❖ Sterility—Very difficult to test. High defect level required for detection. Rely on inspection-validation.
- ❖ GMP—For nonlocal manufacture, expensive travel, personnel. Local manufacturers are less expensive.
- ❖ Product inspection—Least expensive and provides a reasonable level of protection.

Inspection Limitations

- ❖ From the WHO Prequalification Q&A
 - ❖ A product and manufacturer listed means that the product as manufactured at a particular site was found to meet WHO recommended standards, ***at the time of evaluation.***
- ❖ Paper records may not be accurate

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**Prescribing
Dispensing**

QA

Product
Testing

Management

**Compliance
Enforcement**

In Summary

Process	Tier 1	Tier 2	Tier 3
Evaluation/ registration	Established drug quality and bioequivalence	New chemical entity: Safety and efficacy, and bioavailability	_____
Inspection	Documentation/ physical examination	GMP	Terminal sterilization/ aseptic fill
Product quality assessment	Minilab-TLC	Monograph or drug application technologies— HPLC	Impurity assessments