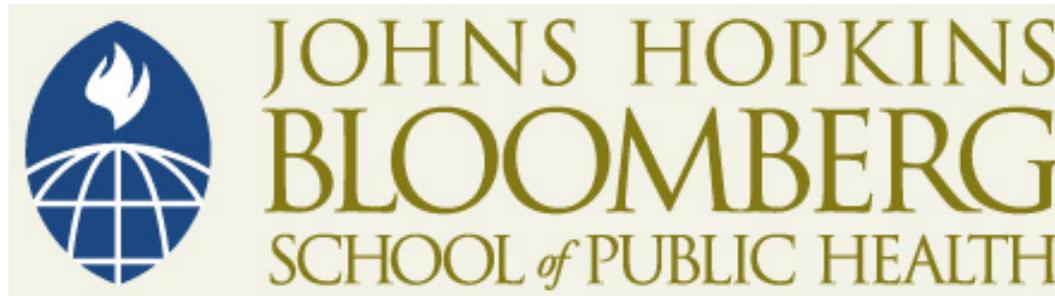


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Session 3:

Drug Manufacture, Industrial Pharmacy Considerations, Quality Assurance, and Regulation

Tom Layloff, Management Sciences for Health



JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH



USAID
FROM THE AMERICAN PEOPLE



MANAGEMENT SCIENCES for HEALTH

RPM Plus | *Rational Pharmaceutical Management Plus*

Objectives

- Be familiar with drug manufacturing requirements and industry regulations
- Describe Good Manufacturing Practices (GMP)
- Understand requirements for developing domestic manufacturing capabilities
- Differentiate between brand vs generics and the conditions for interchange
- Become familiar with the procedures to prevent and detect counterfeit products
- Describe relevant drug regulations
- Describe the Guiding Principles for small national drug regulatory authorities
- Understand basics of and issues relating to drug product quality assurance
- Understand differences relating to full-scale manufacturing, small-scale institutional/local production, and extemporaneous compounding

The Drug Universe

- Begins with the Active Pharmaceutical Ingredient (API)
- APIs are chemicals have been shown through clinical studies to have desirable properties when used appropriately.
- APIs are extracts from natural products or chemically or biologically synthesized.
- The Safety and Efficacy (S&E) of APIs are established almost universally through the exquisite guidelines developed through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), www.ich.org.
- The ICH guidelines are adopted into the laws and regulations of the ICH countries (European Union, Japan and United States) where essentially 100% of the drug research is conducted and which constitute over 85% of the world drug market.

ICH Quality Topics Checklist

Q1: Stability	Q1A(R): Stability Testing of New Drugs and Products (Revised)	Q1B: Photostability Testing	Q1C: Stability Testing for New Dosage Forms
	Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products		
Q2: Analytical Validation	Q2A: Text on Validation of Analytical Procedures	Q2B: Methodology	
Q3: Impurities	Q3A(R): Impurities in New Drug Substances (Revised)	Q3B(R): Impurities in New Drug Products (Revised)	Q3C: Impurities: Residual Solvents
Q4: Pharmacopoeias	Q4: Pharmacopoeial Harmonisation		
Q5: Biotechnological Quality	Q5A: Viral Safety Evaluation	Q5B: Genetic Stability	Q5C: Stability of Products
	Q5D: Cell Substrates		
Q6: Specifications	Q6A: Chemical Substances with its Decision Trees	Q6B: Biotechnological Substances	
Q7: GMP	Q7A: GMP for Active Pharmaceutical Ingredients		

More on APIs

- Chemically synthesized APIs (Fine Chemicals) are produced primarily in the Chindia economic block, Korea and Italy (near Milan).
- Biotechnology derived APIs are almost all manufactured in the ICH regions
- The clinical studies—Phase III—define the therapeutic window—more drug may be toxic and less may be ineffective.
- Summary: Clinical studies are used to define the safety and efficacy of a drug product containing the API and the therapeutic window.

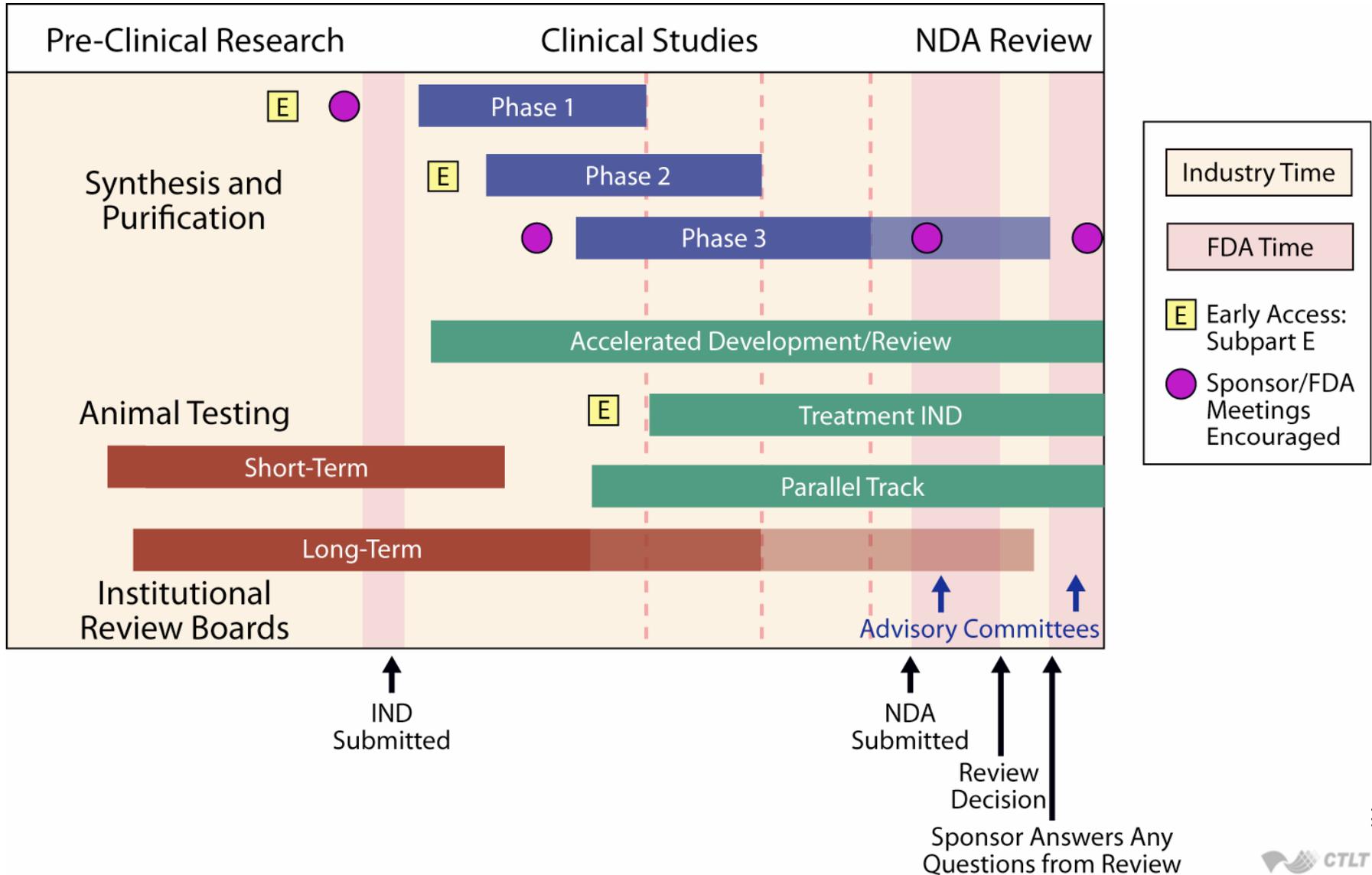
Drug Products

- Excipients used to formulate APIs into drug products are generally food grade chemicals—Bulk Commodities. Excipients are used to make the drug more convenient, palatable or effective
 - 325 mg Tylenol Excipients--cellulose, corn starch, magnesium stearate, sodium starch glycolate
- **Some Common Dosage Forms:** Capsules, Tablets, Chewable Tablets, Granules, Creams, Gels, Ointments, Injections, Powder for Injection, Oral Solutions, Suspensions, Syrups, Powder for Suspensions, Suppositories, Inhalers, Powder for Inhalation

New and Generic Drugs

- Generic drugs are off-patent products
- New and Generic Drugs frequently are give proprietary trade names for market leverage. Tylenol brand acetaminophen and Bayer brand aspirin are good examples of trade name off patent products. In Namibia I encountered at a pharmaceutical distributor 28 trade named amoxicillin products.
- The names of the API are assigned in the International Non-proprietary Names (INN) by WHO or in the United States Adopted Names (USAN) established by the AMA, USP and APhA.

New Drug Development



Drug Regulation

- Commerce Issues
 - When you purchase a 100 tablet bottle of 325 mg Aspirin do you get 100 tablets?
 - Does each Aspirin tablet contain 325 mg of Aspirin?
 - 325 mg is a pharmaceutical “term of art.”
 - Each tablet contains 85-125% and on the average they contain 90-110%.
 - Chemically 325 mg means 324.6-325.4 mg.
- Therapeutic Issues
 - Do the tablets disintegrate and release the drug for absorption?
 - Are there undesirable impurities present in the formulation?

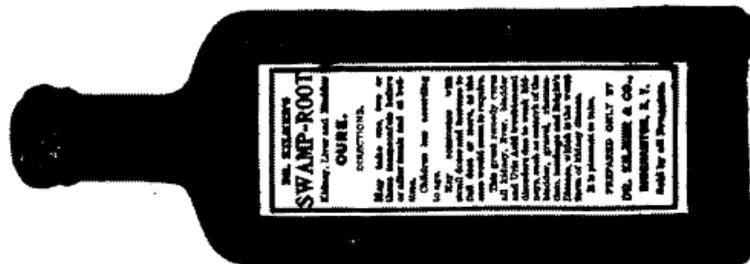
Commerce Issues

- Initially defined in pharmacopoeias which were established by practitioners to govern commerce in therapeutic “weeds and seeds.” The United States Pharmacopeia was established in 1820 by practitioners to govern their commerce.
- Pharmacopoeias contain monographs which define testing procedures and limits for assessing product quality.
- There are approximately 30 national pharmacopoeias from Argentina to Yugoslavia in addition to the African, European and International Pharmacopoeias.
- Identity, assay, dosage uniformity, API release from matrix, sterility, impurities, etc.
- Since the USP already was the basis for commerce in the US when the 1906 FDA legislation was enacted, it was cited for regulation and law enforcement of quality standards.
- The 1906 FDA legislation was a commerce law. It prohibits interstate commerce in misbranded and adulterated foods and drugs.

Cascara Sagrada is the dried bark of *Rhamnus purshiana* De Candolle (Fam. Rhamnaceae).

- Usually in flattened or transversely curved pieces, occasionally in quills of variable length and from 1 to 5 mm in thickness. The outer surface is brown, purplish brown, or brownish red, longitudinally ridged, with or without grayish or whitish lichen patches, sometimes with numerous lenticels and occasionally with moss attached. The inner surface is longitudinally striate, light yellow, weak reddish brown, or moderate yellowish brown. The fracture is short with projections of phloem fiber bundles in the inner bark.

CERTIFICATE OF PURITY



This is to Certify that Dr. Kilmer's Swamp-Root, the great kidney, liver and bladder remedy, is purely vegetable and does not contain any calomel, mercury, creosote, morphine, opium, strychnine, cocaine, nitrate potash (salt-petre), bromide potassium, narcotic alkaloid, whiskey, wine or any harmful or habit producing drugs. Swamp-Root was discovered through scientific research and study by Dr. Kilmer, who graduated with honors and is now actively engaged in the practice of his profession, which calling he has successfully followed many years. } State of New York, County of Broome, } S. S.
City of Binghamton, }

Jonas M. Kilmer, senior member of the firm of Dr. Kilmer & Co., of the City of Binghamton, County of Broome, State of New York, being duly sworn, deposes and says that the guarantee of purity of Swamp-Root, as described in the foregoing certificate, is in all respects true.

Subscribed and sworn to }
before me April 28. 1898. }

Jonas M. Kilmer



James O. Haines
Notary Public

Dr. Kilmer's Swamp-Root is not recommended for everything, but if you have kidney, liver or bladder trouble, it will be found just the remedy you need. Swamp-Root makes friends.

Each bottle contains the same standard of purity, strength and excellence. You may have a sample bottle of Swamp-Root free by mail, if you have not already had one. When writing to Dr. Kilmer & Co., Binghamton, N. Y., be sure to mention reading this generous offer in this paper.

If you are already convinced that Swamp-Root is what you need, you can purchase the regular fifty-cent and one-dollar size bottles at drug stores everywhere. Don't make any mistake, but remember the name, Swamp-Root, Dr. Kilmer's Swamp-Root, and the address, Binghamton, N. Y. on every bottle.

US FDA Legal Tipping Points

- **1938** Safety legislation enacted following the elixir sulfanilamide fiasco. Sulfanilamide was dissolved in ethylene glycol to prepare a toxic elixir. Drug products introduced into commerce after 1938 had to be shown to be safe. Products marketed prior to 1938 were grandfathered and the onus was on FDA to demonstrate lack of safety for action. Relived again by accident in Haiti with the acetaminophen elixir prepared with impure glycerol.
- **1941** Nearly 300 deaths and injuries result from distribution of sulfathiazole tablets tainted with phenobarbital. The incident prompts FDA to revise manufacturing and quality controls drastically, the beginning of what would later be called good manufacturing practices (GMPs).
- **1962** Efficacy legislation enacted following the thalidomide disaster. Drug products introduced into commerce after 1962 had to be shown to be effective for intended use. Drug products in commerce before 1962 were reviewed for efficacy. Panels of experts were established by the National Academy of Sciences-National Research Council to conduct the Drug Efficacy Study Implementation (DESI).

A Generic Drug Is

- A generic drug is a drug that is bioequivalent to an innovator drug with respect to pharmacokinetic and pharmacodynamic properties.
- Generic drugs must contain the same active ingredient at the same strength as the innovator brand, be bioequivalent, and are required to meet the same pharmacopeial standards as applicable.
- Generic drugs are identical in dose, strength, route of administration, safety, efficacy, and intended use.

Hatch-Waxman Amendments to FFD&C Act

- **1984** Legislation enacted to require FDA to approve applications to market generic versions of brand-name drugs after expiration of patents and exclusivities without repeating the research done to prove them safe and effective thereby avoiding expensive pre-clinical and clinical trials. Abbreviated New Drug Applications (ANDA).
- **1992** Generic Drug Enforcement Act imposes debarment and other penalties for illegal acts involving ANDA.
- Bolar Pharmaceutical Company, pleaded guilty in 1991 to charges that it submitted false test results to win Federal approval for some generic drugs.

New vs. Generic Review Processes

New Drug (ICH) Requirements

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

Generic Drug Requirements

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

1990s Generic Drug Fall-Out

- Circa is a cleaned-up reincarnation of Bolar Pharmaceuticals, a generic drug maker whose chairman went to jail after the company was caught faking a test for the Food and Drug Administration. And Pharmaceutical Resources is the renamed Par Pharmaceuticals; officers of Par were convicted of bribing F.D.A. regulators.
- FDA Manager Charles Chang, admitted receiving about \$15,000 worth of gifts, including furniture, computer equipment and an expense-paid trip to Hong Kong, to help speed applications for generic drugs through the approval process.
- Vitarine officials admitted that the data showing equivalence actually came from tests on the brand-named drug, not the generic.

Preparing an API for Patient Use

- To serve the patient's needs the API must be provided in the right amount in an appropriate vehicle.
- Compounding: Good Compounding Practices. In the US the practice of medicine and pharmacy is governed by state boards.
- “Production”
- Manufacturing: Current Good Manufacturing Practices. In the US API and drug product manufacturing are governed by the US FDA.

Compounding

Compounding involves the preparation, mixing, assembling, packaging, and labeling of a drug or device in accordance with a licensed practitioner's prescription under an initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice. Compounding includes the following:

- a. Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.
- b. Reconstitution of commercial products that may require the addition of two or more ingredients as a result of a licensed practitioner's prescription drug order.
- c. Manipulation of commercial products that may require the addition of one or more ingredients as a result of a licensed practitioner's prescription drug order.
- d. Preparation of drugs or devices for the purposes of, or as an incident to, research, teaching, or chemical analysis.

USP Compounding Practices

< USP >	Abbreviated Title
795	Nonsterile Compounding
797	Sterile Compounding
1075	Good Compounding Practices
1150	Pharmaceutical Stability
1160	Compounding Calculations
1191	Dispensing Stability

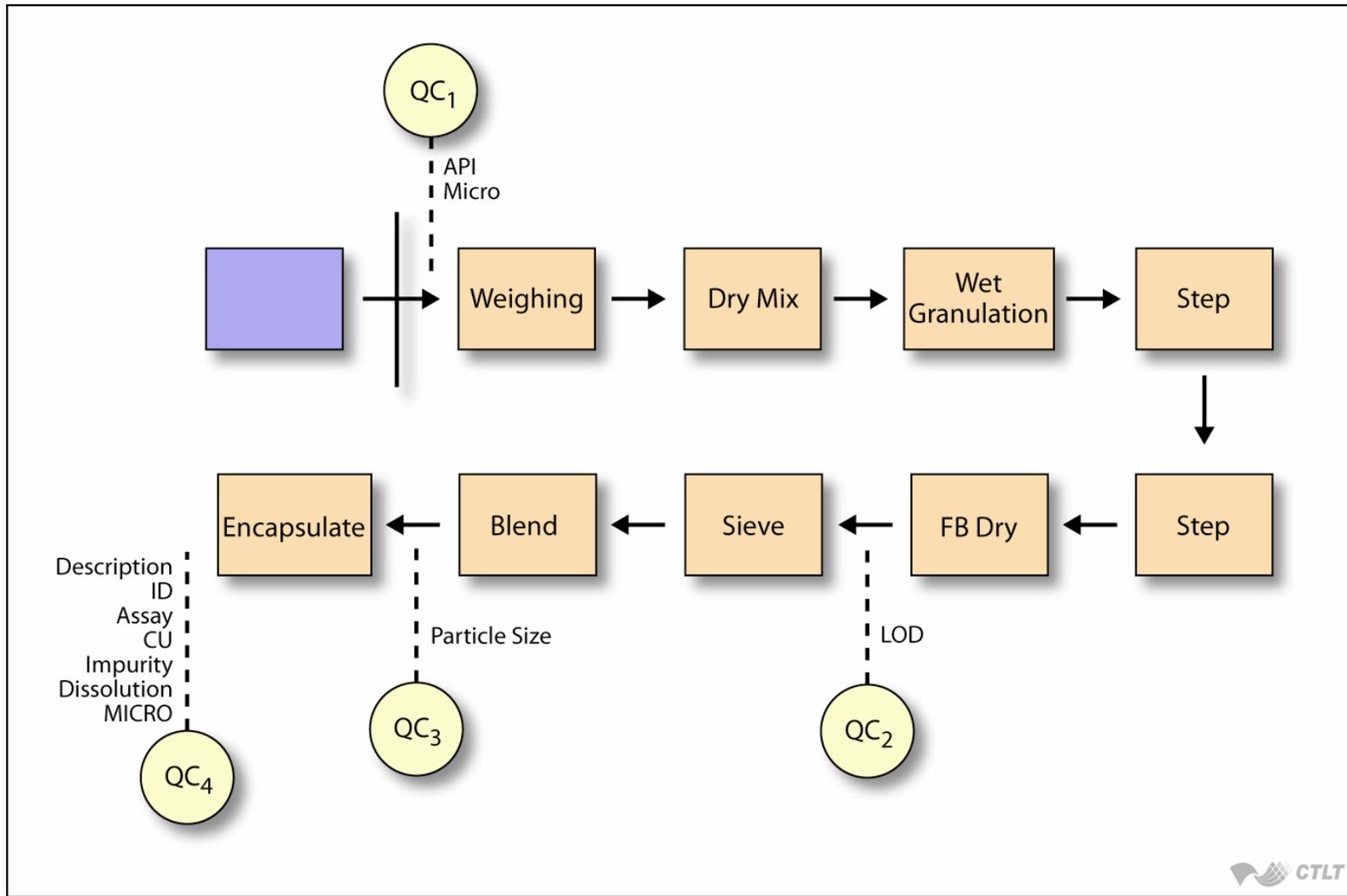
Manufacturing

- Manufacturing involves the production, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction of the drug from substances of natural origin or by means of chemical or biological synthesis.
- Manufacturing also includes
 1. any packaging or repackaging of the substance(s) or labeling or relabeling of containers for the promotion and marketing of such drugs or devices;
 2. any preparation of a drug or device that is given or sold for resale by pharmacies, practitioners, or other persons;
 3. the distribution of inordinate amounts of compounded preparations or the copying of commercially available drug products; and
 4. the preparation of any quantity of a drug product without a licensed prescriber/patient/licensed pharmacist/compounder relationship.

Drug Manufacturing

- Mechanized Formulation
- API and Excipients are Blended and Processed into Products.
- Generally in Drug Manufacturing no chemical reactions are conducted.

A Manufacturing Process



Adapted by CTLT from GK Raju - MIT

Granulation and Milling

- Granulation end-point
- Flow characteristics, bulk density etc
- Homogeneity of granule
- Moisture content
- Particle size

Good Manufacturing Practices (GMP)

- GMPs are intended to assure the production of a uniform, consistent product. The WHO and US have published the flagship guidance. The manufacturing processes must be well-defined, documented and in demonstrated control.
- The GMP start with the quarantine of all received goods which after verification are released to production.
- The GMP end with the review of the finished product to assure that it complies with the stated requirements.
- It is estimated that the cost of quality manufacture costs 25-35% of sales.

Part 211 – Selected CGMP For Finished Pharmaceuticals

Subpart A - General Provisions

Subpart B - Organization and Personnel

211.22 Responsibilities of quality control unit.

211.25 Personnel Qualifications.

211.28 Personnel responsibilities.

Subpart C - Buildings and Facilities

211.46 Ventilation, air filtration, air heating and cooling.

211.58 Maintenance

Subpart D - Equipment

211.63 Equipment design, size, and location.

211.65 Equipment construction.

211.67 Equipment cleaning and maintenance.

211.68 Automatic, mechanical, and electronic equipment.

211.72 Filters.

Subpart E - Control of Components and Drug Product Containers and Closures

211.80 General requirements.

211.82 Receipt and storage of untested components, drug product containers, and closures.

211.84 Testing and approval or rejection of components, drug product containers, and closures.

211.86 Use of approved components, drug product containers, and closures.

Subpart F - Production and Process Controls

211.100 Written procedures; deviations.

211.101 Charge-in of components.

211.103 Calculation of yield.

211.105 Equipment identification.

211.110 Sampling and testing of in-process materials and drug products.

211.111 Time limitations on production.

211.113 Control of microbiological contamination.

211.115 Reprocessing.

Selected 211 CGMP Continues

Subpart G - Packaging and Labeling Control

211.122 Materials examination and usage criteria.

211.125 Labeling issuance.

211.130 Packaging and labeling operations.

211.134 Drug product inspection.

211.137 Expiration dating.

Subpart H - Holding and Distribution

211.142 Warehousing procedures.

211.150 Distribution procedures.

Subpart I - Laboratory Controls

211.165 Testing and release for distribution.

211.166 Stability testing.

211.173 Laboratory animals.

- **Subpart J - Records and Reports**

- **211.182** Equipment cleaning and use log.

- **211.184** Component, drug product container, closure, and labeling records.

- **211.186** Master production and control records.

- **211.194** Laboratory records.

- **211.198** Complaint files.

- **Subpart K - Returned and Salvaged Drug Products**

In Country Pharmaceutical Formulation Capacity

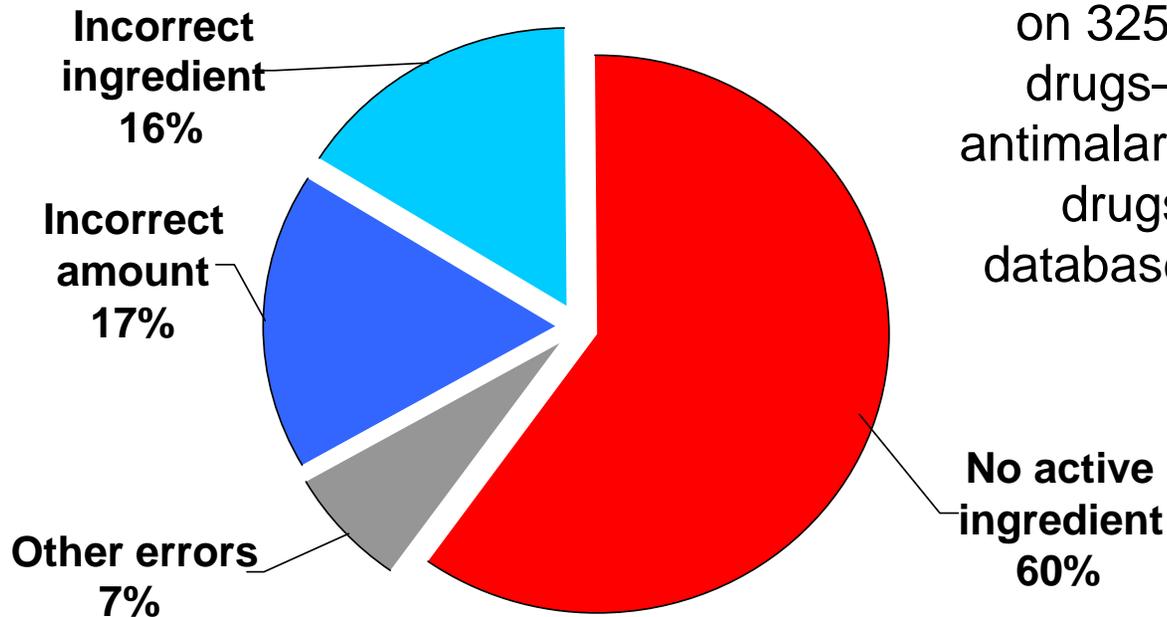
- Can GMP Formulation Plants Be Established in the Developing Countries??
- Can You Build Quality Toyota Vehicles In The US??
- Of Course
 - Fourth-largest automaker in America
 - 12 manufacturing plants in North America -- two additional facilities in the future
 - In 2004 at its North American facilities produced
 - > 1.44 million vehicles,
 - > 1.27 million engines and
 - nearly 390,000 automatic transmissions
- Ford Eliminating Up to 30,000 Jobs and 14 Factories
- Commercial viability is crucial for sustainability!!

Reasons for Poor Quality Pharmaceuticals

- Gaps in regulatory capacity: improper requirements and no capacity for implementation of requirements
- Global standards for generics: WHO has a comprehensive set of guidelines, but implementation varies
- Different quality requirements for export: very few countries effectively control quality of pharmaceuticals for export; certificates for export are issued more easily than are certificates for domestic markets
- Financial incentives: local manufacturers do not have sufficient incentives to meet international standards
- No enforcement actions.

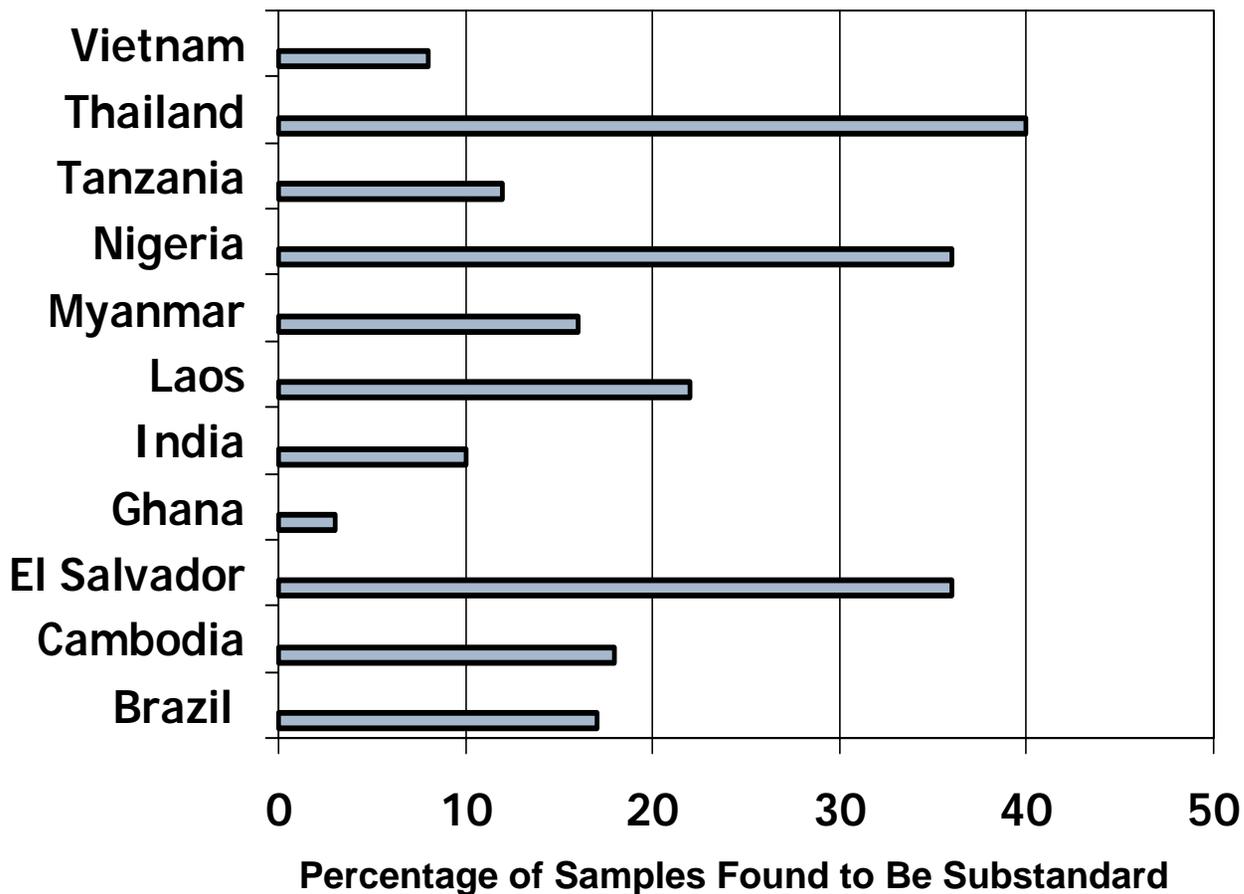
Substandard Medicines in Developing Countries

Percentage breakdown of data on 325 cases of substandard drugs—including antibiotics, antimalarials, and antituberculosis drugs—reported to WHO database from around the world



Rägo, L. 2002. *Ensuring Access to Drug Products That Are of Acceptable Quality*. PowerPoint presentation, WHO/EDM Technical Briefing, October 2, Geneva.

Substandard Medicines in Developing Countries



Therapeutic groups

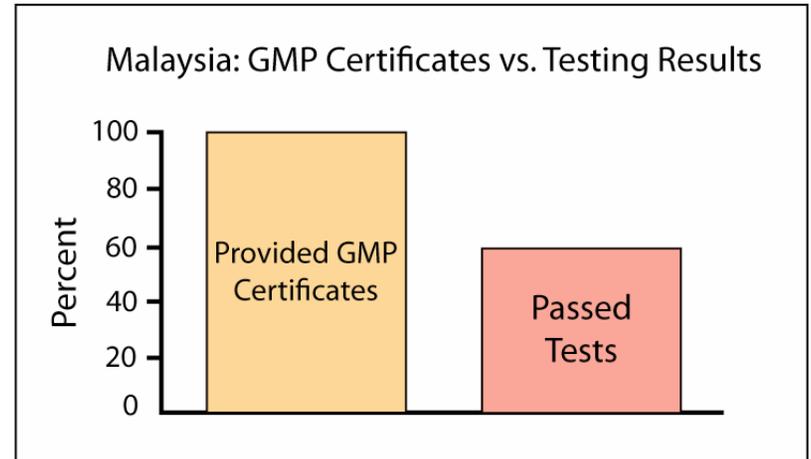
- Analgesics
- Antihypertensives
- Antimicrobials
- Antimalarials

Rägo, L. 2002. *Ensuring Access to Drug Products That Are of Acceptable Quality*. PowerPoint presentation, WHO/EDM Technical Briefing, October 2, Geneva.

Quality Assurance: Product Testing

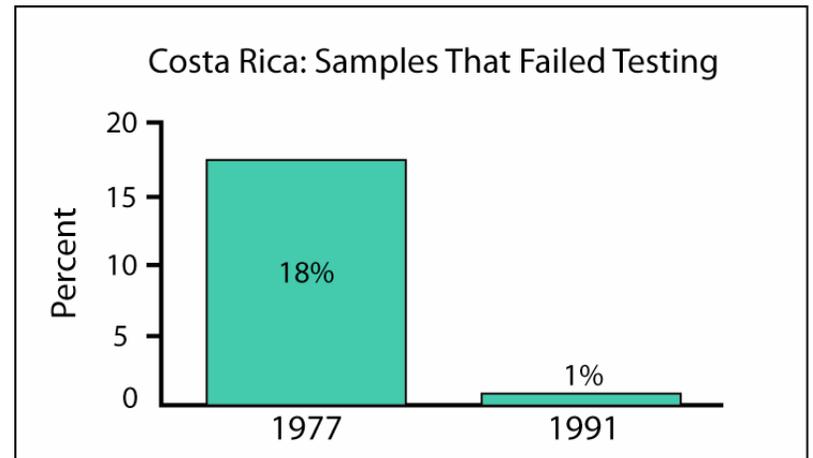
Malaysia

- Government Pharmaceutical Laboratory purchases in 1992
GMP certification and product testing

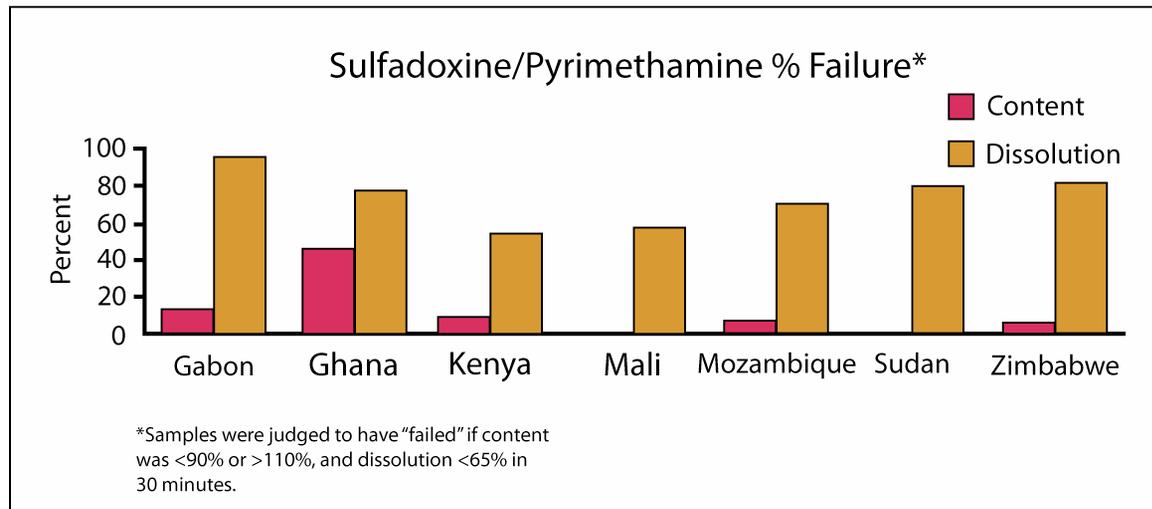
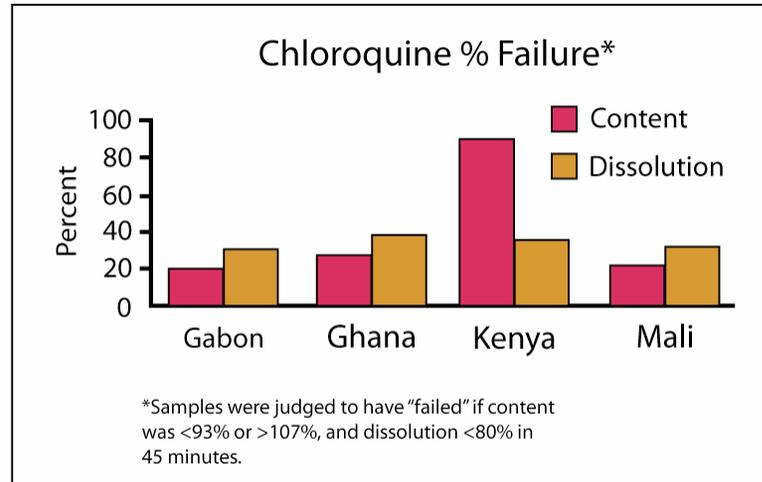


Costa Rica

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



Quality of Antimalarial Products: Both Content & Dissolution Are Problems



Current Testing Methods

- Color reactions
- Spectrophotometry
- Thin-layer chromatography (TLC)
- Gas chromatography
- High-performance liquid chromatography (HPLC)
- Others

Testing Standards and Methods

- Public vs. private standards (i.e., pharmacopeia vs. manufacturer/registration)
- Legal vs. credentialed methods (i.e., pharmacopeia vs. AOAC International)



Pharmacopoeial Assessments

- Rooted in the analytical methods developed in the drug discovery process – technology dependent
- Discovery technologies are very focused on API and impurity characterization (high-resolution systems)
- Relatively expensive systems:
 - Analytical equipment
 - Maintenance and other consumables
 - Reference materials
 - Personnel training

Implications for Resource-Limited Settings

- Being largely import-dependent, developing countries need to develop and maintain an effective product testing program. Two major hurdles are:
 1. Newer essential therapeutic drugs for which public standards/monographs are not available
 2. Multisource essential therapeutic drug products for which the legal reference methods require high- technology support
- Difficult to implement and sustain effective high-technology testing programs:
 1. Complexity of equipment and maintenance needs
 2. Access to reference materials, reagents, and other consumables
 3. Need for highly trained technical staff
 4. Cost to launch and maintain effective program

Product Testing: Simple Methods

Detecting Counterfeit and Substandard Drugs



The GPHE-Minilab®
Simple Test Methods for the Quality Assurance of Pharmaceuticals



Visual Inspection

- rapid drug quality control at low cost
- for the full range of essential drugs
- for hospitals, retail pharmacies, ...



Differentiation Test

- physical and chemical testing on the spot
- a laboratory assembled in two cases
- self-contained for in- and outdoor use



Colour Reactions

- trays containing ready-made reagents for use
- comes with step-by-step manuals and a full set of starter kit chemicals



Thin Layer Chromatography



BASIC TESTS FOR PHARMACEUTICAL SUBSTANCES



World Health Organization, Geneva

COUNTERFEIT DRUGS KILL!



WORKING TOGETHER FOR SAFE DRUGS:

- World Health Organization (WHO)
- International Federation of Pharmaceutical Manufacturers Associations (IFPMA)
- International Generic Pharmaceuticals Alliance (IGPA)
- World Self-Medication Industry (WSMI)
- CHMP/Pharmaciens Sans Frontières

Source: World Health Organization

Global Problem

How Do Producers Counterfeit?

1. Specially manufactured counterfeits

Sophisticated production facilities

- Excellent labeling
- All processes in-control

Generally no active ingredient

2. Hacker manufactured counterfeits

Poor quality products

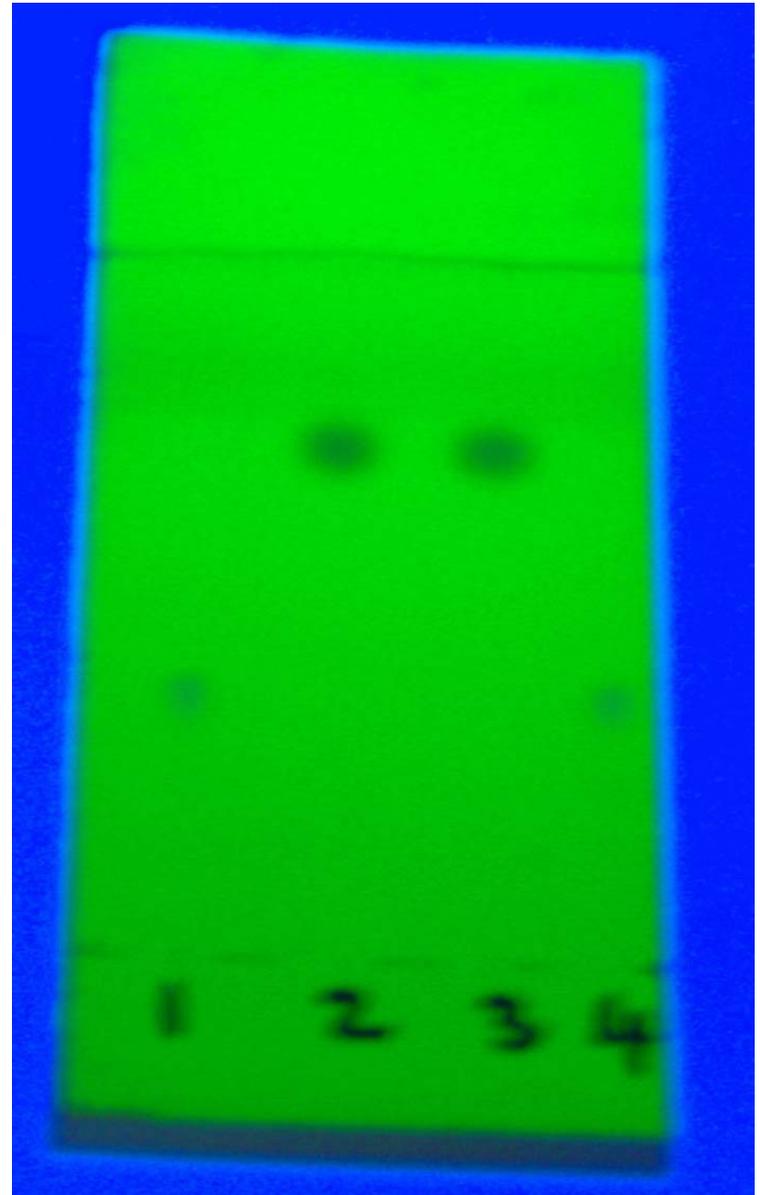
- Non-uniform Colors
- Poor labeling
- Poor compression – powder, capping

Generally no active ingredient

Detection of Counterfeit Medicines

- A perfect counterfeit product cannot be detected.
- A well-made and well-labeled counterfeit is very difficult to detect even if direct comparisons between authentic and fake products can be made.
- Testing may be the best available option.

- Counterfeit Detection by TLC--
Wrong Drug
- Metronidazole
 - Channel 1 = 100%
 - Channel 4 = 80%
- Quinine
 - Channels 2 & 3



Expired Chloroquine Injection Relabeled Quinine Dihydrochloride Injection



Photo courtesy of Thomas Layloff

Quality Assurance: Monitoring

- Product problem reporting
 - Suppliers
 - Health care providers
 - Consumers
- Supplier and product database
 - Supplier performance
 - Product problems
 - Clinical (ineffective, adverse events)
 - Pharmaceutical (physicochemical problems)

Quality Assurance: Evaluation and Enforcement

- Withdrawal of marketing authorization (product license)
- Delisting from prequalified status
- Rejection of shipment
- Product recall

Summary

- Many resource-poor countries are planning to purchase generics for ATM and other diseases, so product quality is becoming a growing concern
- There are a number of program implications if substandard or counterfeit products are purchased – poor treatment outcomes, potential liabilities, loss of public trust
- More open (international) procurement can be financially beneficial, but requires a more stringent QA system
- A three-tier testing program is a less expensive, viable option for quality control – big laboratories are not always necessary