Screening Tests to Detect Counterfeit Products

Thomas Layloff
Quality Assurance Manager

Supply Chain Management System (SCMS)
“Providing Quality Medicines for People Living with and Affected by HIV and AIDS”

Supply Chain Management System Project

Partnering to Improve Supply Chain Performance
The President’s Emergency Plan for AIDS Relief (PEPFAR)

• **Targets**
  - Prevent 7 million new HIV infections
  - Provide treatment for 2 million HIV-infected people
  - Provide care to 10 million people infected and affected by HIV/AIDS, including orphans and vulnerable children

• **Scope**
  - 15 initial focus countries
  - 5 years
  - Up to $15 billion
Supply Chains: A Critical Component in the Global Response to HIV/AIDS

SCMS Mission

We will strengthen or establish secure, reliable, cost-effective and sustainable supply chains to meet the care and treatment needs of people living with or affected by HIV and AIDS. In collaboration with in-country and international partners, we will:

- Deploy innovative solutions to assist programs to enhance their supply chain capacity
- Ensure accurate supply chain information is collected, shared, and used; and
- Provide quality, best-value health care products to those who need them.
Supporting Partners Through Technical Assistance

- Systems assessment and work planning
- Quantification/forecasting
- Procurement
- Quality Assurance
- Freight forwarding and inventory management
- Distribution
- Logistics MIS
- Human and organizational capacity
- Sustainability planning
- Assistance to manufacturers and suppliers

Procuring and Delivering Commodities

- Global Planning
- Aggregated Quantification
- Developing specifications
- Establishing long-term contracts and aggregating orders to realize economies of scale
- Procuring in advance of client orders
- Obtaining diverse goods
- Employing high-volume, cost-effective shipping routes
- Clearing customs efficiently
- Using regionally based storage to enable rapid response
- Using small, frequent, and scheduled shipments to protect national infrastructure
- Offering tailored delivery solutions
- Minimizing points-of-care stockholding
- Recording and accessing consumption data
- Supporting production of home-based care kits
- Collaborating with global food and nutrition programs
Where Is SCMS?

Around the world, but initially focused on:

Supply Chain Management System

Reasons for Counterfeit

- To make lots of money
- To avoid losing money
- To disrupt health care systems

... the largest counterfeiting operations net millions of dollars and involve networks of front companies able to distribute thousands of boxes of medicines at a time.
Counterfeiting Detection Approaches

- The Technologist/Technology Choices Should Be Based on the Assessment Needs

- The Assessment Tools Selected Should Depend on the Questions Which Need to Be Addressed
Tomato Plants
Hand Tools

Types of Counterfeit

- Specially-manufactured counterfeits
  - Sophisticated production facilities
    - Excellent labeling
    - All processes in-control
  - *Generally no or wrong active ingredient*

- Hacker-manufactured counterfeits
  - Poor quality products
    - Non-uniform colors
    - Poor labeling
    - Poor compression – powder, capping
  - *Generally no or wrong active ingredient*
    - *Prescription Drugs in Herbal Products*

- Re-labelers, Product Substitution, etc.
Health Risks Posed by Counterfeits

• With Pharmaceutical Health Interventions The Most Significant Risks With Counterfeit or Authentic Products Are Getting **No Drug** Or The **Wrong Drug**.
  – July 20, 2006 -- About 1.5 million Americans are injured each year because of errors in their medications, an Institute of Medicine (IOM) report concluded Thursday.
  – The report estimates that such errors in hospitals alone cost the health system well over $3.5 billion per year. That does not include errors made at doctors' offices, pharmacies, long-term care facilities, and in patients’ own homes.

• Moderately Substandard Products Pose Less Risk Because of Large Therapeutic Windows for Most Products

Consumers Detecting Counterfeits

• Margaret Glavin, US FDA Office of Enforcement: “consumers should be alert to detect counterfeits and closely check their prescription drugs”
  – Check:
    • Is the color different?
    • Does it have a different taste or a different smell?
    • Are the pills cracked or chipped?
    • Does the packaging look as thought it’s been compromised?
    • Is the label funny, on crooked, or different from what a previous label looked like?
Another Example

- The labeling change that recast 110,000 bottles of low-strength $22-a-bottle Epogen as high-strength $445-a-bottle Procrit netted an estimated $46 million for counterfeiters before the scheme was discovered in May 2002.

- Only 8,000 bottles were seized in a Texas warehouse.

Counterfeit PROCRIT®

- PROCRIT (epoetin alfa)* 40,000 U/mL vials in four-pack boxes, lot number P002641 and expiration September 2003. …
- Analysis shows that they contain a clear liquid with active ingredient. However, the concentration of active ingredient is approximately 20 times lower than expected for PROCRIT 40,000 U/mL vials.
- It appears that counterfeiters may be acquiring PROCRIT 2,000 U/mL vials and relabeled the product with counterfeit 40,000 U/mL labels.

Authentic Folding Carton (Blue):
Text alignment on bottom of folding carton appears with a right-hand margin between end of text and edge of carton.

Counterfeit Folding Carton (Black):
Text alignment on bottom of folding carton must be shifted to extreme right side of panel without a right-hand margin.

Authentic PROCRT vial P004677:
Aluminum wrap under red cap is smooth without dents.

Counterfeit product vial P004677:
Aluminum wrap under red cap is not smooth and may appear to be dented.
Sample Headlines Reporting Counterfeits

Turmeric For Ampicillin
Mefloquine Substituted With Sulphadoxine-Pyrimethamine

Bottles Of Combivir Actually Contained Ziagen
Antimalarials, Antibiotics, Snake Antivenom With No Active Ingredients

Lipitor Counterfeit Pills Were Indistinguishable From Real Pills
Wheat Flour Contraceptive Pills
Artesunate Products With No Drug

Viagra pills mainly of dry wall

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

- Incorrect ingredient: 16%
- Incorrect amount: 17%
- Other errors: 7%
- No active ingredient: 60%

60% No active ingredient + 16% Incorrect ingredient = 76% Would fail ID/TLC test
17% Fail assay
93% of these substandard drugs might be detected by ID and TLC testing
The German Pharma Health Fund (GPHF) Minilab
Minilab Testing

- 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

TLC Method Inventory

- GPHF Minilab 40 drug products

- Kenyon inventory additional 47 products

- 87 TLC methods from acetylsalicylic acid to ziduvodine using inexpensive non-toxic solvents

- Minilab and Kenyon use reference tablets (unofficial) for testing
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 only available option.
- Product testing is the most expensive tool in the regulatory process.
- Product testing is frequently contested in courts, so chain-of-custody and rigorous adherence to good practices and legal standards are mandatory.

Well Made Counterfeits

- Even experts who were brought in by the "Dateline" investigation had trouble distinguishing “well-made” counterfeit pills from the authentic ones.
- Chemical tests were finally needed to definitively identify the fakes.
- Citing the high costs of testing. "It costs Pfizer about $1,000 per tablet."
NBC Dateline June, 2006

Product Testing Poses a Very Significant Deterrent

Costa Rica

- Social Security Fund purchases in 1977 vs. 1991
  - Product testing program was instituted
Control of Imports

- Control is more easily effected at ports-of-entry (POE) before the product is dispersed in the market.
- Denial of entry can be decided if reliable data available.
- Need to determine rapidly if product:
  - Contains correct active pharmaceutical ingredient(s), including correct quantity
- Need assessment resources close to POEs to speed turn-around and avoid without-cause entry delays.

Thin Layer Chromatography (TLC)

- Component of two-tier testing strategy
  - Primary screening
    - Visual detection
    - At POE or other non-central sites
    - Semi-quantitative
  - Secondary testing
    - Instrumented detection
    - At laboratory facility
    - Quantitative
TLC – Disadvantages

- Detects no more than three or four compounds in a single sample at a time
  - HPLC and GLC can detect up to hundreds of compounds in a single sample

- Methods must be validated against legal reference methods
  - Most legal reference methods use HPLC or GLC
Secondary Testing

- Legal reference methods (e.g., HPLC) more complex and costly than TLC
- Can only be performed on a fraction of product batches on the market
- Unsuitable for POE or primary screening

<table>
<thead>
<tr>
<th>Drug</th>
<th>USP Method</th>
<th>TLC Method</th>
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<tbody>
<tr>
<td>Rifampin</td>
<td>100.00 (uses chloroform)</td>
<td>1.50</td>
</tr>
<tr>
<td>Chloroquine diphosphate</td>
<td>4.10 (uses acetonitrile)</td>
<td>1.50</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1.00</td>
<td>1.50</td>
</tr>
<tr>
<td>Theophylline</td>
<td>6.60</td>
<td>1.50</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>5.30</td>
<td>1.50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>117.00</strong></td>
<td><strong>7.50</strong></td>
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Summary of Costs

<table>
<thead>
<tr>
<th></th>
<th>Training/Qualification</th>
<th>Number of Samples Per Run</th>
<th>Capitalization/Analysis</th>
<th>Consumable Costs/Analysis</th>
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<tbody>
<tr>
<td>GLC</td>
<td>Medium</td>
<td>One</td>
<td>High</td>
<td>Medium/Low</td>
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<tr>
<td>HPLC</td>
<td>High</td>
<td>One</td>
<td>High</td>
<td>High</td>
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<tr>
<td>TLC</td>
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<td>Primary-1 or 2</td>
<td>Very Low</td>
<td>Low</td>
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<tr>
<td></td>
<td></td>
<td>Secondary-Up to 70</td>
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Conclusions

• Testing needs to be part of an overall drug product quality assurance strategy.

• The TLC approach offers a technically sound and inexpensive way to detect products containing no or the wrong drug.

• Because of the rapid rise time and simplicity TLC screening is especially useful at POEs.
FIGURE 1
Graph showing the results of antimalaria drugs screened/tested from October 2002 to April 2005

FIGURE 4
Graph showing the results of antibiotic screened from November 2003 to April 2005
FIGURE 5
Graph showing total number of the type ARV’s screened from March 2005-April 2005
For Additional Information

- Tom Layloff: tlayloff@pfscm.org
- SCMS Website: www.scms.pfscm.org

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