



Session 3: Common Quality Assurance Problems



World Health
Organization



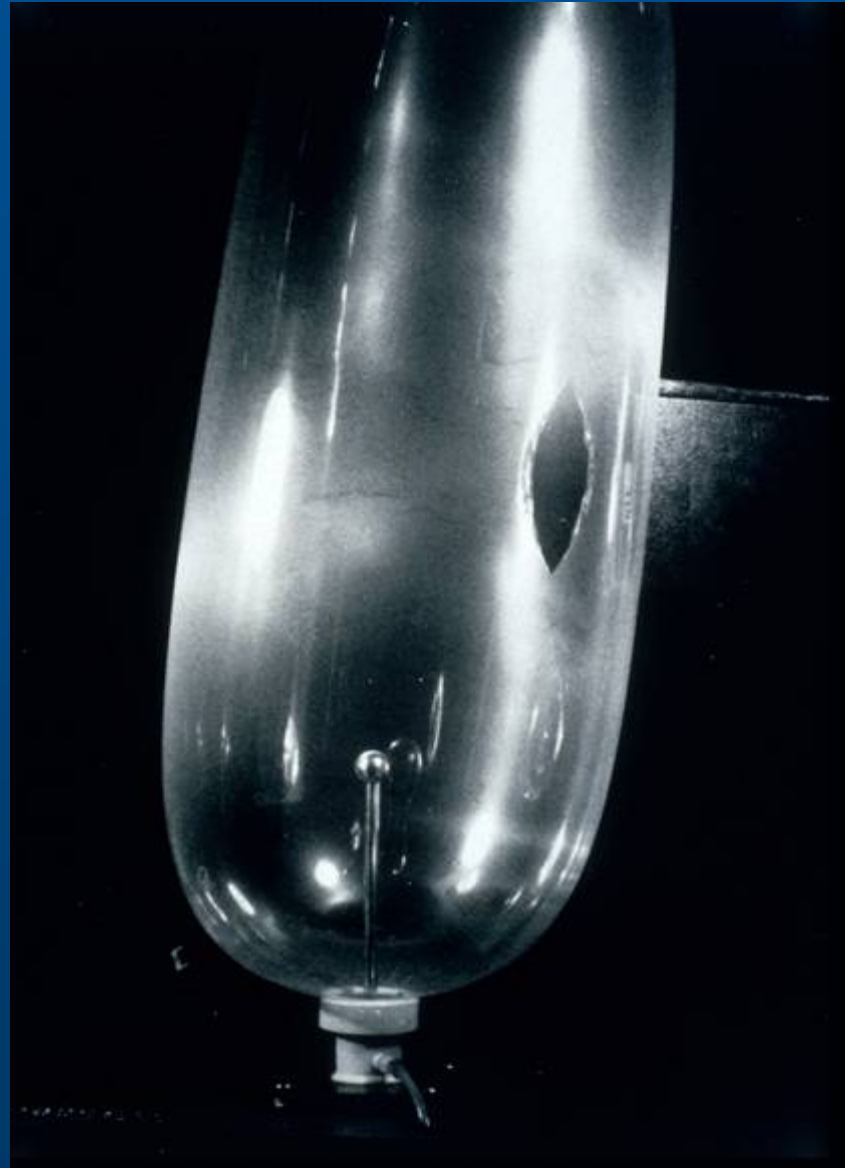
UNFPA



A catalyst for global health



Physical Defects



Counterfeit Product



Authentic



Fake

Active Ingredients



Other Ingredients



Storage and Handling



Storage and Handling



Storage and Handling



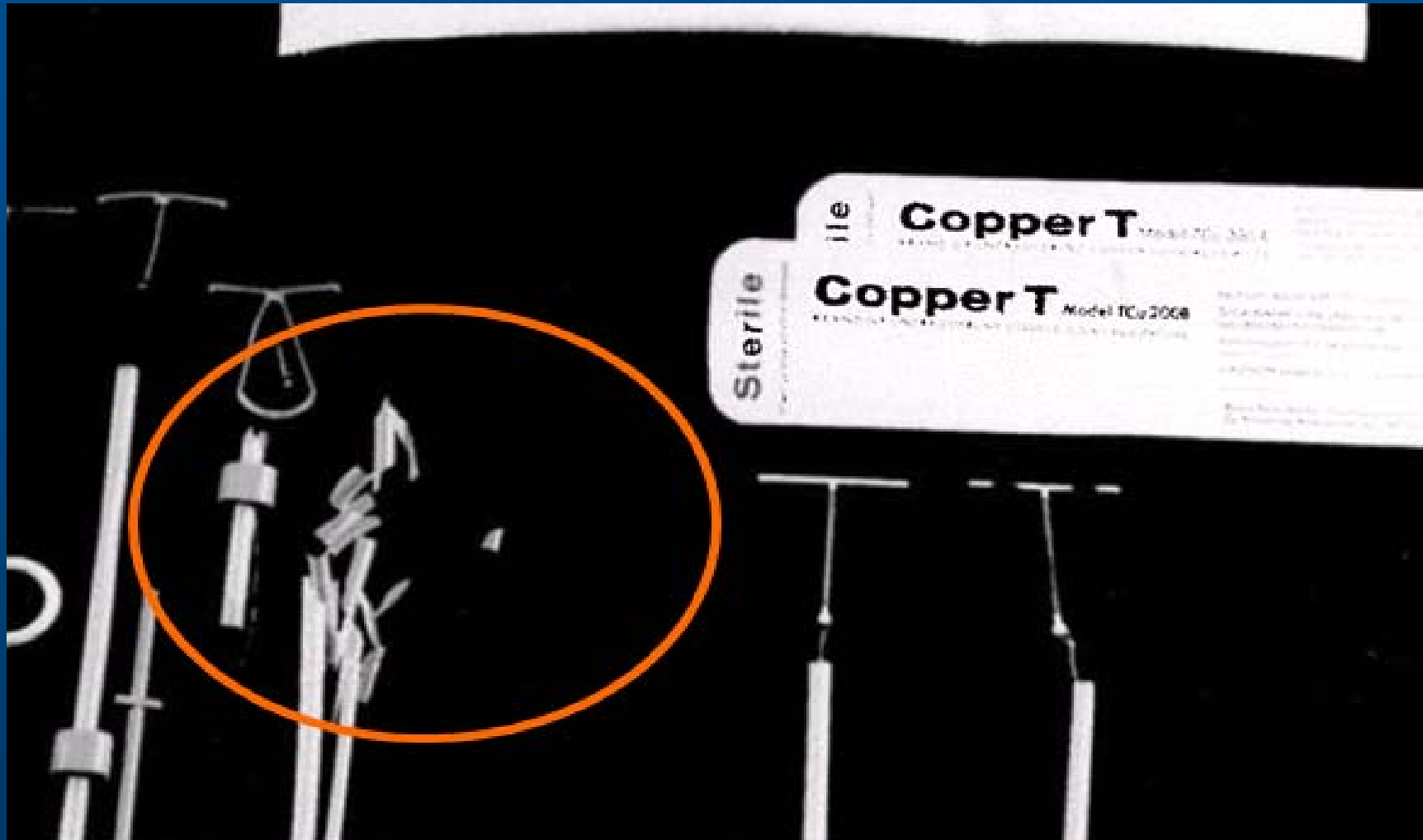


Storage and Handling





Substandard Components



Inadequate Packaging



Condom Case Study

In 2005, the program “PREVENT” (a fictitious name) began subsidized social marketing of condoms in Mexico. Its purpose was to sustain condom distribution where donor funding was being phased out. The Ministry of Health’s (MOH) procurement agency, the Central Medical Stores (CMS), was their primary in-country partner for all activities.

The US Agency for International Development (USAID) had provided bulk condoms to the CMS in the past, but was now providing “seed money” through PREVENT to start the process of phasing out their support. To start, PREVENT would procure a one-year condom supply, and provide the goods to CMS. The goods would be repackaged under various brand names, and CMS would manage and promote sales and distribution to pharmacies, public health facilities, and nongovernmental organization programs. CMS would retain any profit from the revenues for their future condom procurement. A memorandum of understanding (MOU) was under development between CMS and PREVENT, but it was not finalized.

The program late in getting started, so Mr. Martinez, the PREVENT program manager, negotiated sole source procurements with two manufacturers, Otamax of Japan and Kutchu of Korea. He communicated by email with the two manufacturers on price and delivery issues, but did not finalize the communications into a purchase contract document. He also assumed that the National Drug Authority (NDA) accepted product registered with its neighbor, the United States Food and Drug Administration (USFDA), even if it was not yet registered in Mexico. The only written reference to quality standards was an email indicating that the condoms “should meet ISO standards” or be registered with the USFDA or the NDA.

Mr. Lopez, the CMS procurement manager, mentioned that the amount of condoms that had been estimated for the program seemed too low, so Mr. Martinez negotiated costs for 200 million units or two full 40-foot ocean freight containers from each manufacturer. When the goods arrived at the port, Ms. Santiago, the chief pharmacist with CMS, received the attached notice of quarantine indicating that the arrival would be subject to testing.

When the testing was complete, the two lots from Kutchu did not meet ISO 4074 standards for latex thickness and air burst limits. The NDA rejected the goods for entry. The two lots from Otomax passed all NDA tests, and were allowed entry. PREVENT paid for the Otomax goods, and not for the rejected Kutchu goods.

When the Otomax goods were released to CMS, it was discovered that they were already in consumer packaging, making it very difficult and costly to perform the repackaging for the social marketing brand names. They were also bright pink in color. CMS refused to accept the goods from PREVENT, stating that they did not meet basic requirements for the social marketing program activities. A significant legal dispute emerged between PREVENT and CMS, and the program eventually failed to launch.

GOVERNMENT OF MEXICO



NATIONAL DRUG AUTHORITY

Notice of Product Quarantine

Date: September 28, 2005

Importer Data

Consignee: PREVENT
2 Health Center Plaza
Opposite Ministry
Juncalito, MEXICO
Contact: Mr. G. Lopez

Consignee NDA registration number: not registered

Bill(s) of Lading: SEA087345 and K126687

Exporter/Product Data

Arrivals from the following origin(s): Kutchu of Korea
Otamax of Japan

**National Drug Authority registration number:
(or United States Food and Drug registration)** Kutchu, no NDA or USFDA status
Otamax, no NDA status, incomplete
Evidence of USFDA status

Reason for Quarantine

- 1) Importer is not registered to import or distribute medical devices or pharmaceutical materials.
- 2) Products are either not registered or lack sufficient evidence of registration for import and distribution.

1. Discuss and name (at least) five procurement mistakes that contributed to the eventual failure of this transaction.

2. What mistakes were made regarding registration and other requirements for importing medical devices?

3. Discuss and name two to three ways that understanding and using prequalification systems could have improved this situation.

Condom Case Study Answer Key

1. Discuss and name (at least) five procurement mistakes that contributed to the eventual failure of this transaction.
 - *There was no contract for the final procurement between the buyer (PREVENT) and the seller (the two manufacturers) stipulating any of the terms and conditions, including packaging, physical characteristics, color, etc.*
 - *There was no contract between PREVENT and CMS specifying product requirements, especially those needed to facilitate the repackaging and general acceptability of the goods.*
 - *The forecast was increased beyond the means of most warehouses.*
 - *The program sole-sourced goods without waivers and without an acceptable justification.*
 - *The procurement manager and the chief pharmacist should have been the key operators of this transaction, or at least should have had substantial involvement.*
 - *The program manager handled the procurement independently and without transparency, making the resource difficult.*

2. What mistakes were made regarding registration and other requirements for importing medical devices?
 - *It was not a safe assumption that a neighboring country's approval would be accepted as a proxy, even if it is a country with a stringent regulatory authority. Mexico in fact does accept registration from the USFDA in lieu of substantial dossier reviews, but products still must complete the registration process in Mexico to be allowed.*
 - *The program did not check to see what regulatory requirements the donor or the host country government required.*
 - *Without a contract or any specifying of quality requirements, the manufacturer was also somewhat delinquent in not requesting the information. Since condoms are classified in most countries as a medical device, manufacturers have substantial knowledge of this. While they are not completely responsible for the error, they are responsible for negligence in shipping to a country where they were not registered.*

3. Discuss and name two to three ways that understanding and using prequalification systems could have improved this situation.
 - *If the funder and host country government relied on systems of prequalification, the USFDA registration may have been sufficient to allow entry of the Otomax condoms without the testing and demurrage costs incurred.*
 - *Had the program been aware of quality assurance as a critical issue, they might have opted to solicit from a list of prequalified suppliers, instead of sole-sourcing to the two that they happened to know.*
 - *If the manufacturers were part of a prequalification system, they may have been triggered to investigate their eligibility prior to shipping to the country.*

Oral Contraceptive Case Study

In 2005, the Family Planning and Health program (FPH—a fictitious name) was supplying contraceptives to 15 countries in various regions. Despite a publicly advertised international tender for oral contraceptives (OCs), they received only two valid responses. Other bids were received but the products were generics that did not have approval status with either the U.S. Food and Drug Administration or the European Directorate for the Quality of Medicines-European Pharmacopoeia, as required by the program funder. To ensure coverage FPH awarded contracts to both qualifying bidders, Hyacinth Laboratories and Sterotech Ltd.

- Both contracts were for levonorgestrel and ethinyl estradiol OCs.
- Hyacinth registered its OC in 7 of the 15 countries under the special program brand name “Femerol.”
- Sterotech registered its OC under the special program brand name “Femital” in the remaining eight countries.

In June 2005, Hyacinth advised that it had quarantined the batch of Femerol scheduled for shipment because of unusual test results detected in their internal quality control processes. The company suspected the problem was related to the active pharmaceutical ingredients (API). The company was performing additional tests on the finished product and on the API. The additional tests would take at least 90 days, with no guarantee that they would be able to release the product.

The pipeline analysis showed the affected countries had approximately six months of OC stock in their pipeline, and all would all incur stock-outs if shipments did not resume within 90 days.

To solve this problem within the 90-day window, FPH considered the following options:

- a. Attempt registration in the seven countries for Femital from Sterotech and provide an identical product.
- b. Identify alternate manufacturers of levonorgestrel and ethinyl estradiol OCs already registered in the countries, which would require independent quality testing to support waivers from the funder regarding registration requirements.
- c. Identify an alternate OC formulation (not levonorgestrel and ethinyl estradiol) that met the registration requirements, and request a sole-source waiver.
- d. Wait 90 days and risk a stock-out if the problem led to a rejection of the batch in question.

After carefully considering the implications of each of the options, FPH management opted to wait 90 days and risk a possible stock-out. Unfortunately, the testing on the batch revealed that the particle sizes in the key raw material were significantly out of the acceptable range, and the batch was rejected. A stock-out of OCs occurred in the seven countries receiving Femerol.

Oral Contraceptive Case Study Answer Key

1. Discuss each of the four options FPH had considered, and note at least one or two problems associated with each of the options.

Option 1: Attempt registration in the seven countries for Femital from Sterotech and provide an identical product. The three main problems are:

- *It is highly unlikely that they could accomplish registration in seven countries within the 90-day window.*
- *Prescribers and consumers are likely to reject the substitution without substantial evidence that it is an identical product. Even though it is essentially similar, there can be small differences in non-active ingredients and packaging that would affect consumer satisfaction.*
- *Social marketing programs run partly on brand recognition. Since this would be as different brand, it is likely to create questions regarding cost and appropriateness for the program.*

Option 2: Identify alternate manufacturers of levonorgestrel and ethinyl estradiol OCs already registered in the countries, which would require independent quality testing to support waivers from the funder regarding registration requirements.

- *The problems with substitution are the same as with option 1.*
- *The problem with seven waivers from the funder is that it would not be feasible to gather the supporting documentation and have the waiver reviewed within 90 days.*

Option 3: Identify an alternate OC formulation (not levonorgestrel ethinyl estradiol) that met the registration requirements, and request a sole source waiver.

- *The problems with substitutions in a social marketing program are the same as for Options 1 and 2.*
- *It may be possible to achieve a sole source waiver in 90 days if all documentation was available.*
- *Substituting a different formulation has medical implications that would require significant management from prescribers, and could potentially have a negative effect on consumers.*

Option 4: Wait 90 days and risk a stock-out if the problem led to a rejection of the batch in question.

- *While this was the option chosen by the program, the risk was that the batch would ultimately be rejected, and they had not prepared themselves with any type of backup option.*

2. List and discuss two to three ways that a harmonized regulatory system could have made options one and two more feasible.
 - *If the COUNTRY used prequalification programs, it is likely that the project could have registered both manufacturers' products from the early stage of the project, creating a "back up" system.*
 - *If the DONOR had used a broad prequalification program instead of strictly adhering to approval from the USFDA, it would have expanded the options available to this program, again, allowing for back up plans, possibly even from local manufacturers.*
 - *They may have had to pursue a source-origin or sole-source waiver, but this is far less cumbersome than attempting a new product registration.*

Checklist of Common Quality Assurance Problems in Reproductive Health Medicines and Devices

1. Expired goods
2. Contraband goods
3. Inadequate or inappropriate packaging
4. Loss of potency due to inappropriate handling in manufacturing or supply chain management
5. Medicines—substandard product:
 - Incorrect active ingredient
 - Incorrect amount
 - No active ingredient
6. Devices (IUDs):
 - Packaging
 - a. Substandard packaging of IUDs (materials or package seams)
 - b. Evidence of non-sterility in packaging (tears or holes in packaging, visible foreign particles in packages, or test results indicating a non-sterile product)
 - Errors in physical attributes, such as size, color, thickness, shape, or missing components
 - Material defects, such as holes, tears, and weak spots in condoms; or burs, breaks, and brittle material for IUDs