



Pharmaceuticals: Quality Assurance in the Distribution Chain

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Introduction

Pharmaceuticals are an essential element of health care. In developing countries, up to 66% of public and private health expenses are used to buy medicines.[1] Unfortunately, data show that a lot of this money is wasted on fake and substandard drugs. WHO estimates that about 25% of the drugs sold in developing countries are fake. In some countries rates up to 40% and higher have been reported [2,3], including life saving medicines against diseases such as malaria and bacterial infections. As a consequence, thousands of people die every year because the drugs they take do not have the anticipated therapeutic effect. [2, 3] This human tragedy together with the significant economic impact makes it obvious that drug quality assurance throughout the entire supply chain must be a priority for every national drug regulatory authority.

Ensuring the quality of medicines is a multi-dimensional task. It includes

- licensing and control of manufacturers
- a registration process for medicines that assures product quality, safety and efficacy
- a procurement system with in-built quality controls, such as supplier prequalification and pre-/post shipment quality testing
- purchasing from qualified and known suppliers
- accreditation and control of distributors and retailers, by inspectors who are well trained, sufficiently paid and backed up by law enforcement personnel so that they are not easily bribed or intimidated
- a transparent logistics chain with automated inventory system and clearly defined procedures, limiting the number of people who are physically handling drugs
- reduction of distribution tiers in the supply chain
- market surveillance and a mechanism to report drug quality issues and recall drugs that do not meet quality standards
- legislation that allows for severe punishment of crimes such as drug counterfeiting
- law enforcement capacity to prosecute those who risk other people's lives for their own financial benefit by producing or distributing unsafe drugs
- public education about the dangers of fake and substandard drugs

This paper deals only with quality assurance questions for products that are in circulation already. It does not address the manufacturing or registration level; neither does it discuss the legal framework or the political economy of pharmaceutical regulation. There are separate HNP Briefs on other aspects such as counterfeit drugs and on local manufacturing of medicines - complementary to this one.

Accreditation of suppliers

An important step to ensure the quality of pharmaceuticals in the supply chain is to create minimum professional standards and a system of controls for those who handle these sensitive products. Such standards and controls should apply to every facility or business in the public and private sector that is involved with making, purchasing, storing, testing, shipping or dispensing medicines.

Accreditation is a formal process based on a set of rules and SOPs (Standard Operating Procedures) for every level, describing for example

- organizational requirements, for example a minimum organizational chart with essential functions
- educational level and training requirements for key staff
- physical conditions of warehouses, dispensaries, trucks, etc.
- workplace conditions and wages for workers
- up-to-date equipment, tools, documents and other essential means to maintain operations
- "good practice" procedures for every task, including guidelines for documentation and self control

Facilities or businesses that have been formally accredited - after passing an inspection that confirms the adherence to the standards above - are then licensed to legally handle or dispense pharmaceutical products. Accreditation should be renewed in certain intervals and withdrawn if standards are no longer met.

Although such a rigorous approach is a long shot from today's reality in many developing countries, it should be seen as a policy goal. A strategy of stepwise implementation might be desirable, which could give pre-existing players time to upgrade their facilities and processes. A first step could be to simply legalize all acting players (who meet basic criteria for legal

business operations), then enforce re-licensing within a reasonable timeframe.

Such an accreditation system places a significant capacity requirement on the Ministry of Health, Drug Regulatory Authority or other body responsible for the implementation. If capacity is too limited for such a system to be supported by the public sector, collaboration with professional societies and trade associations may be an alternative way to achieve the same policy objective. These groups should have a strong self-interest to enhance the reputation and professional standards of their membership and sanction or exclude those, who do not live up to the standards. Negotiating and contracting skills on the side of the public sector are required to make this “outsourcing” model work.

Distribution logistics and quality

Many developing countries have a long distribution chain for drugs - it touches several warehouses and hand-over points. Tracking of supplies is difficult under such circumstances. Theft, diversion or introduction of expired, sub-standard and counterfeit products into the trade becomes relatively easy. Therefore, streamlining logistics and introducing modern tracking technology should be a policy objective for the public as well as the private sector. Relatively inexpensive and simple technology solutions exist and may even be applied in a given country already in another sector, for example for branded food and beverage products or other fast moving retail items. Costs for the necessary hard- and software have come down significantly. They need to be assessed against the background of potential losses generated by an outdated pharmaceutical logistics system. If there is motivation and a good plan for improvements, a low-income country government might get financial aid from donors such as the Global Fund to fight AIDS, Malaria and TB (GFATM) specifically for upgrades of the logistics system.

One of the hurdles for the introduction of a modern system could be the reluctance of current players to change a situation that tolerates a certain amount of “leakage”, which can be turned into private profits. Low salary levels for government employees in many countries are a potential root cause for such practices.

Another problem might lie in the procurement method: It might be more efficient to have the supplier of the drug take responsibility for a part of the logistics chain, bypass the Central Medical Store and deliver directly to regional distribution hubs. This approach can lead to savings if compared on a “landed cost” basis, referring to the costs of a drug once it reaches the retail shelf. On the other hand, such a procurement strategy may require a change in budgeting and a close coordination

between various institutions that have so far existed in relative isolation from each other.

Box: The Catholic Drug Center in Ghana

Supported by Management Sciences for Health (MSH), the Catholic Drug Center in Ghana has re-organized its drug procurement in 2003. Certain high volume essential drugs are procured centrally, based on pooled orders from the field hospitals and clinics. The quarterly delivery, however, goes directly to five regional distribution centers, from where the dispensing pharmacists pick up their supplies. These regional centers use the GPHF Minilab (see page 4) for basic quality control of incoming shipments. The system is said to have reduced complaints about bad quality medicines and increased flexibility in case of demand fluctuations.[4]

Testing pharmaceuticals

Various types of tests are performed to confirm identity and quality of a drug sample taken from a shipment, a warehouse or a pharmacist’s shelf.

Testing parameters and specifications are described in detail in a “product monograph” for every drug. These monographs are published in collections called Pharmacopeias (detailed instructions how to make and identify pharmaceutical active compounds and preparations). The following is a simplified summary of the steps leading to the complete identification and evaluation of a particular pharmaceutical specimen[5]:

- Inspection, physical integrity: Are box, container, blister or other packaging elements intact? Is the label and information leaflet complete and do they correspond to a registered product? Is the pharmaceutical product itself (the tablet, liquid, powder or other) in a state that appears to be the original one (not broken, discolored, lumped together, disintegrated or otherwise altered)? Does packaging or product show any signs that raise the suspicion that it could be a counterfeit product?
- Dissolution: How long does it take for the drug to completely dissolve in liquid? This is an indicator for potential biological efficacy.
- Identification of the active compound: There are various test methods to establish the chemical identity of a drug substance. If positive, these tests prove that the correct substance is present, but they do not allow for quantification (however, semi-quantitative methods exist for field use, where a precise quantitative assay is not possible).
- Quantitative assays, measuring the exact amount of drug substance in a given unit, are being done with various methods against defined reference standards. These tests require stationary lab technology.

- Bioavailability and bioequivalence tests involve taking blood samples from test persons who have taken a particular drug. Such tests are not part of the routine drug quality monitoring. They are relevant at the level of registration, where they are used to demonstrate that a given product is likely to produce a predictable therapeutic effect, or is therapeutically equivalent to an already established product.

Identifying counterfeit (fake) drugs

"A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging." (WHO definition)

The most reliable method to identify counterfeit drugs is by running a complete test sequence according to the product monograph. There have been counterfeit drugs with a packaging that was so close to the original that visual inspection did not raise any suspicions. In some cases, counterfeits even contained the correct amount of active substance. However, in reality many counterfeits do not come from truly sophisticated forgers. Some show minor digressions from the original packaging, such as lower quality materials or bad print quality; differences in text size, font, dimensions; differences in size, shape or position of graphical elements; missing information about expiry date or manufacturer. Others fail the identification or the dissolution test, and most counterfeits can be identified through quantitative or semi-quantitative tests for the active ingredient: counterfeiters tend to avoid the cost for the active ingredient or minimize it by reducing the amount of ingredient to the minimum needed to get positive results of the identification test. (For more details, see HNP Brief #2 on counterfeit drugs.)

The National Drug Quality Control Lab

Usually under the control of the drug regulatory authority, the National Drug Quality Control Lab offers a partial or complete range of testing methods to cover the drugs that are in circulation in a given country.

In small and resource-constrained countries, the services of a regional facility outside the borders of the country may be used. In larger countries, there may be several regional labs that have the necessary equipment, know-how and accreditation to serve the authorities by providing the data needed to identify and eliminate fake or sub-standard drugs.

A drug safety lab needs to work according to a set of standards. WHO provides a comprehensive guide on Good Practice for National Pharmaceutical Control Laboratories (see "Additional information, resources").

Contracting private labs or university labs is an option if there is no public sector capacity. Clear terms of reference and a solid contract are necessary in this case. The authorities must at least have the capacity to assess the quality of a lab (see section on accreditation), even if they don't run their own – for example by employing a trained pharmacist with experience in drug quality assurance.

Quality monitoring in the field

Systems for monitoring the quality of medicines in developing countries frequently focus on the entry point into the supply chain, for example at customs or at the Central Medical Store. This is not sufficient, because drugs might deteriorate during storage or transport, or retail pharmacists might buy drugs from unsupervised sources outside the official channels. However, limiting the number of entry points through which drugs can be imported legally makes it easier to establish effective controls on the imports.

Much more relevant for public health is the quality of drugs at retail or hospital level, i.e. close to the patient. Hence, drug samples must be taken in a random fashion from retail outlets such as pharmacies, drug stores, hospitals or even market stands if this is where drugs are sold. It is important that drug sellers cannot predict when an inspector turns up. The samples need to be inspected and tested. Business owners, who are caught selling substandard or counterfeit drugs, have to be punished hard enough to deter others, who might be tempted to engage in the same kind of business.

The sampling and testing methods and documentation have to be sophisticated enough to hold up in court. WHO provides detailed technical guidance documents for implementation of a quality monitoring system for the pharmaceutical supply chain – see "Additional information, resources".[6]

If measures such as closing a shop or confiscating inventory are required, a close collaboration with law enforcement authorities is needed.

Assuming that one inspector can visit 4 pharmacies per day, take samples and complete the necessary documentation, the capacity per inspector would be around 1000 pharmacies per year or 500 per half year. Once pharmacists or drug sellers know that at least once a year somebody comes and checks their inventory for fake and sub-standard medicines, and that they might lose license and business or even face time

in prison for selling bad quality products, they might be less tempted to buy products from questionable sources.

More labor intensive than the sampling is the processing and testing of the collected samples. Depending on the size of the country and the infrastructure, testing could be done in regional labs or in a central lab. Some countries have implemented a decentralized system using the German Pharma Health Fund (GPHF) Minilab (see box). If a sample fails the Minilab test, it is being sent to the National Drug Safety Lab. Also, 5-10% of samples that pass the Minilab tests should be evaluated at the next higher level: certain types of more sophisticated counterfeits can only be identified with full pharmacopoeial testing.

Box: The GPHF Minilab



The Minilab is a portable drug safety lab that allows identification of 40 essential drugs including modern anti-malarial and anti-retroviral (ARVs) medicines. It comes complete with reference substances and a detailed manual. Aid organizations and health care providers have already implemented Minilab based testing in a number of developing countries, together with training courses for local technicians who operate the labs on a day-to-day basis. For detailed information, see <http://www.gphf.org>

Building trust in the quality of medicines

The previous paragraphs show that effective monitoring of drug quality can be done with relatively limited resources in the field. The effect of these activities can be further leveraged if the general public is informed of the monitoring activities and their outcomes through the mass media. This will not only help force illegal traders into the underground and diminish their business opportunities. It will also build public trust in the quality of medicines in circulation, which is an essential cornerstone of any successful national drug policy. Professional media briefings and information campaigns require either the creation of a public relations officer position in the drug regulatory authority, or close collaborating with the national or regional government's press office.

Additional information, resources

WHO: Quality Assurance of Pharmaceuticals <http://www.who.int/medicines/organization/qsm/activities/qualityassurance/orgqas.shtml> and http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpfour_dist.html

WHO expert committee specifications, for example on sampling (QAS_066) and Good Distribution Practices (QAS_068): http://www.who.int/medicines/organization/qsm/expert_committee/expertcomm.shtml

WHO: International Pharmacopoeia: <http://www.who.int/medicines/library/pharmacopoeia/pharmacop-content.shtml>

WHO: Good Practices for National Pharmaceutical Control Laboratories: http://www.who.int/medicines/organization/qsm/strategy_quality_safety/trs902ann3.pdf

US Pharmacopoeia: <http://www.usp.org>

USP: Sampling of antimalarial drugs: <http://www.uspdqi.org/pubs/other/SamplingTool.pdf>

European Pharmacopoeia: <http://www.pheur.org/>

FIP (International Pharmaceutical Federation) Guidelines for Pharmacy Practice and other publications: <http://www.fip.org/>

DELIVER – resource center for health care logistics funded by USAID <http://www.deliver.jsi.com>

German Pharma Health Fund – Minilab <http://www.gphf.org> (GPHF is a charitable initiative of researched-based pharmaceuticals companies in Germany.)

References

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5. United States Pharmacopeia (USP): Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide; April 2005 (Draft)
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