Risk-based sampling for Minilab users

Guideline

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This document is intended to help you implement the risk-based sampling approach and set up your own (adapted) SOP as agreed during the Minilab Workshop Nairobi 2019.

Content

1. What is risk-based sampling?

Working on the improvement of medicine safety, the availability of resources (e.g. money, personnel) sets a limitation to our efforts. Therefore, we can't test every single tablet which is added to the stock but will choose a few packages for testing. This is what the term of sampling describes.

"Risk-based sampling" is defined as a statistical process in which the required sample size is calculated according to the maximum risk acceptable. The higher the danger arising from one product, the more units of this product should be checked. In comparison: in statistical sampling the required sample size is calculated according to the number of units available and is therefore identical for all products, irrespective of their risk.

An example: An organization buys 100 units of three different medicines of which one medicine bears a high risk, one a medium risk and one a low risk. Using statistical sampling, of each product the same amount of samples would be checked (e.g. 3 of each). Using risk-based sampling more units of the riskier products would be checked (e.g. 1 unit of the low-risk product, 3 of the middle-risk product and 5 of the high-risk product). In both cases a total amount of 9 samples is tested.

Therefore, risk-based sampling uses the limited resources more efficiently to detect products of unacceptable quality without increasing the total number of units tested.

This practical guide on a "risk-based sampling approach" for Minilab users comprises the sampling from the organization´s own stock as well as sampling directly from the market.

Source:

International Symposium for Risk-Based Sampling, Baltimore, 2017
https://www.eppo.int/media/uploaded_images/MEETINGS/Meetings_2017/inspectors/08_Eyre.pdf

2. Which risks do we face?

Concerning medicines various risks can occur. They can be categorized as shown in the following figure:

This guideline will focus on process, product and supplier associated risks as they occur before the delivery to the organization and are therefore detectable by controlling the incoming goods for which the Minilab is mainly used.

Process associated risks:

- Poor process flow
- Human error
- Software anomalies
- Communication failure
- Exposure to adverse conditions during handling, storage and transport

Product associated risks:

- Chemistry
- Formulation stability
- Bioavailability

Supplier associated risks:

- Risks associated to product history
- Regulatory actions
- Customers' perception

Source: Presentation Risk-based sampling approach, JMS-Uganda, held throughout Minilab Workshop Nairobi 2019

3. How to implement risk-based sampling in your organization?

1. Risk assessment

As the aim of risk-based sampling is to put a special effort on the analysis of higher risk products, in a first step it is necessary to find out which products are of high risk. You can use the attached checklist (see section 5) or the team's knowledge and experience to assess the risk of each product.

If you use the checklist, in the end count the number of "yes" you ticked. The risk increases with the number of "yes" you ticked.

2. Evaluation of the risk assessment

After assessing the risks of your products, it can be helpful to summarize the results. One way of summarizing is to categorize all your products into three classes: products of low, middle and high risk. There are 24 questions on the checklist. Please define a threshold for the classes, e.g.:

- 0 – 3 times "yes" low risk
- 4 – 10 times "yes" middle risk
- >10 times "yes" high risk

You may also want to specify criteria which immediately put a product to the high risk category (e.g. a "product with a history of quality incidents" shall be immediately classified as high risk product. Regardless of how many times "yes" was ticked).

3. Adapting your testing schedule

Taking into account the amount of samples you usually analyze, distribute this amountover the three categories. Make sure that from now on most of the samples come from the high-risk category, some from the middle-risk category and few from the low-risk category. An example: On average 15 samples tested per month could lead to 8 of high risk, 5 of middle risk and 2 of low risk.

4. SOP writing

This general guideline should help you set up an SOP adapted to the requirements of your organization. Use the examples given in this guideline to calculate your own numbers.

4. Collecting samples outside your DSO

Procurement

The sampling should be conducted wherever the highest risk is expected. Keep in mind aspects like urban/rural, different sectors of the medical sector, different stages of the supply chain and different products. In order to identify products with a higher risk you can refer to the list in section 5. It is a good advice for the sampling person to keep the identity hidden and pretend to be a usual customer (mystery shopper approach). For a profound analysis, an amount of 100 tabs/caps/vials is preferable but at least 30 units should be bought to allow Minilab testing and confirmatory analysis afterwards. According to the current MoU for Difaem Minilab partners (2019), each organization will be supported in the procurement of samples by up to 100€ per year, upon request and submission of receipts.

Transportation, storage

Please transport and store the samples under the conditions indicated for the product. Pay special attention to humidity, light and temperature (usually dark, <60% relative humidity, between 15°-25°C). Protect the product from physical damage and cross contamination. It might therefore be advisable to bring tight and padded containers when going out for buying samples. When storing the samples within your stock, make sure they don't get mixed with the medicines for sale, e.g. by labelling them and keeping them in the quarantine area!

Time from sampling to analysis

The analysis should take place quickly after sampling in order to avoid any quality losses due to storage time. In case of intermediate storage (for a certain limited time), the indicated storage conditions should be adhered to.

Analysis

Please follow the Minilab Manual.

Documentation

Documentation of product information should be done quickly after purchasing, to avoid loss or mix up of any details such as the purchase price. A Sampling Form is attached to this guideline.

For reporting results back to Difaem, you can additionally use the Minilab forms such as the *Testing results map* or *Form A (for suspicious products)*. Please make sure you are using the 2019 version of these forms. Don't forget to take pictures.

Retention, Disposal

After testing, keep the left over samples separated from your medicines for sale. Keep suspicious samples until the entire follow-up process is finished. As in this case authorities (local, national, international) should be informed, it might helpful to keep the samples in case the authorities want to perform additional testing. Afterwards discard them so that they will not accidentally end up in the supply chain again, preferably by destroying them. For those samples that were found to be of good quality, discuss in the pharmaceutical team whether to discard them or release for use in your organization.

Sources:

Newton PN, Lee SJ, Goodman C, Fernández FM, Yeung S, Phanouvong S, et al. (2009) Guidelines for Field Surveys of the Quality of Medicines: A Proposal. PLoS Med 6(3): e1000052. https://doi.org/10.1371/journal.pmed.1000052

WHO (2007) Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide. http://apps.who.int/medicinedocs/en/m/abstract/Js18424en/

WHO (2005) Guidelines for Sampling of Pharmaceutical Products and Related Materials. WHO Technical Report Series, No. 929, 2005, Annex 4. https://apps.who.int/medicinedocs/en/m/abstract/Js21440en/

5. Checklist

Process associated risks	YES	NO
Product with history of quality incidents (recall, warning, customers complaint)		
Product exposed to adverse conditions		
Returned product		
Newly introduced to market		
Medicine on high demand		
Product from a region with a high prevalence of falsified products		
Insufficient, non-protective package (e.g. loose, in a paper bag)		

Product associated risks	YES	NO
Medicine with formulation instability		
Medicine with increased resistance potential		
Heat sensitive product		
Light sensitive product		
Humidity sensitive product		
Cold sensitive product		
Other stability problems		
Bioavailability problems		
Physical or mechanical damage visible		
Great potential to harm		
Failure in visual inspection		

Supplier associated risks	YES	NO
Supplier/manufacturer from non-stringent regulatory jurisdiction		
Supplier/manufacturer with a known quality incident or regulatory recall in the last two years		
New supplier/source (first order of this product)		
Brand name medicine with limited safety and efficacy data		
Unusually cheap supply		
Supply from an informal source (street market, black market)		

Please see section 6 for examples of products with process and product associated risks.

6. Examples for medicines with "product associated risks"

Examples for checking "product associated risks"

Category	Example	Source
Medicines with formulation instability	Dispersible formulations, suppositories, liquids	http://www.ub.edu/farmaciaclinica/projectes/webquest/WQ0/docs/ishak.pdf
	Reconstituted antibiotic formulations	
Medicines with increased resistance potential	In general: antiinfectives such as antibiotics, antimalarials, antimycobacterials. Please research your regional situation!	https://apps.who.int/iris/bitstream/handle/10665/251715/9789241511469-eng.pdf?sequence=1
Heat sensitive products	Cloxacillin, Phenoxymethylpenicillin	Experience of EPN Minilab Network members
	Amoxicillin+Clavulanic acid, Doxycycline, Erythromycin, Tetracycline	http://diyhpl.us/~nmz787/pdf/Journal_of_Antimicrobial_Chemotherapy_1995_Traub_149-154.pdf
	Artemether, Dihydroartemisinin	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4856632/
	Ritonavir	https://www.msh.org/sites/msh.org/files/mds3-ch19-qualityassurance-mar2012.pdf
	Metronidazol	https://www.audor.de/wp-content/uploads/2015/10/AUDOR_Wirkstoff-Ratgeber.pdf
Light sensitive products	Aciclovir, Atenolol, Co-trimoxazol, Efavirenz, Lamivudin	http://www.ub.edu/farmaciaclinica/projectes/webquest/WQ0/docs/ishak.pdf
	Lisinopril	http://www.ecv.de/download/download/Zeitschriften//pharmind/volltext/PI-2012-09-1520-Grosse-Patientenindividuell.pdf
	Cloxacillin, Phenoxymethyl penicillin	Experience of EPN Minilab Network members
	Levofloxacin	https://www.nature.com/articles/s41598-019-40201-9
	Metronidazol	https://www.ptaheute.de/rezeptur/rezeptursubstanzen-von-a-bis-z/rezeptursubstanz/metronidazol/
	Moxifloxacin	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4245426/
	Chloroquine, Primaquine, Nifedipine	http://dx.doi.org/10.1155/2016/8135608
	Amlodipine	https://labs.pcure.se/substance/amlodipine
	Prednisolon, Chloramphenicol, Erythromycin, Tetracyclin, Sulfonamid	http://media.dav-medien.de/sample/9783769260731_p.pdf

	Clindamycin, Furosemide	Plausibilitätscheck-Rezeptur, Ziegler, DAV 2016
Humidity sensitive products	Acetylsalicylic acid, Aciclovir, Diclofenac, Efavirenz	http://www.ub.edu/farmaciaclinica/projectes/webquest/WQ0/docs/ishak.pdf
	Prednisolone, Simvastatin, Atenolol, Bisoprolol, Lisinopril	http://www.ecv.de/download/download/Zeitschriften//pharmind/volltext/PI-2012-09-1520-Grosse-Patientenindividuell.pdf
	Chloramphenicol, β-Lactam-Antibiotics, Cephalosporin-Antibiotics	https://www.researchgate.net/publication/315721033_DEGRADATION_PATHWAY_OF_PHARMACEUTICAL_DOSAGE_FORMS
	Metronidazole, Chloramphenicol	http://media.dav-medien.de/sample/9783769260731_p.pdf
	Clindamycin, Erythromycin, Hydrochlorothiazide, Tetracycline, Paracetamol	Plausibilitätscheck-Rezeptur, Ziegler, DAV 2016
Cold sensitive product	Vaccines, eye drops and other liquid formulations (do not freeze)	
Other stability problems	Not suitable for loose packaging (e.g. patient bags): Clarithromycin, Fluconazol, Omeprazol, Quinine, Salbutamol, Zidovudin	http://www.ub.edu/farmaciaclinica/projectes/webquest/WQ0/docs/ishak.pdf
	Unstable under tropical conditions: Aminophylline, Ampicillin, Benzylpenicillin, Cefalexin, Chlorphenamin, Gentamicin	http://apps.who.int/medicinedocs/en/d/Jh1813e/3.2.5.html
Bioavailability problems	Clindamycin, Aminophylline, Gentamicin, Rifampicin, Streptomycin, Kanamycin	Narrow therapeutic index drugs, view entire list here https://www.drugbank.ca/categories/DBCAT003972

Examples for checking "supplier associated risks"

Countries with stringent regulatory authorities

- Members: European Union, Japan, United States
- Observers: Switzerland, Canada
- Associates: Australia, Norway, Iceland, Liechtenstein
- List of countries with stringent regulatory authorities
  http://www.stoptb.org/assets/documents/gdf/drugsupply/List_of_Countries_SRA.pdf

Reference prices for medicines

- International drug price indicator guide http://mshpriceguide.org/en/home/

7. Sampling Form

Name of your organization	
Date of sampling	
Location of sampling	
Name of sampling person	
Name of product	
Strength	
Active ingredient	
Dosage form	
Package size	
Purchase price + currency	
Manufacturer acc. to label	
Country of manufacturer	
Batch number	
Mfg. date	
Exp. date	
Source (e.g. private vendor, open market)	
Name of vendor	