World Health Organization

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GUIDELINES ON THE CONDUCT OF SURVEYS OF THE QUALITY OF MEDICINES

(June 2015)

DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms (kopps@who.int) with a copy to Ms Marie Gaspard (gaspardm@who.int) by 20 August 2015.

Medicines Quality Assurance working documents will be sent out electronically only and will also be placed on the Medicines website for comment under "Current projects". If you do not already receive our draft working documents please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.

37   SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/15.630:

38   **Guidelines on the conduct of surveys of the quality of medicines**

Preparation of draft guidelines by Dr Jitka Sabartova, Prague, Czech Republic, based on the working documents QAS/12.510[1] and QAS/14.500[2] following discussion during meetings of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 2011-2014.	June 2015
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[1] Working document QAS/12.510: *Proposal for a procedure on sampling and market surveillance* (http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/).
[2] Working document QAS/14.590: *Recommendations on the content of a survey protocol for surveys of the quality of medicines* (http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/).

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75
76

77 **1. INTRODUCTION**

78

79 The quality of medicines is essential for efficient disease management. To ensure that good
80 quality medicines are available to patients in their countries, national medicines regulatory
81 authorities (NMRA) can apply various regulatory instruments. These are:

82

83 • Authorisation/registration for marketing with the assessment of products
84 documentation, inspection of manufacturers' compliance with the principles of good
85 manufacturing practices (GMP) and approval of products' information;
86 • Post-marketing surveillance activities including maintenance of products'
87 authorisation/registration through variations or renewals, regular inspections of
88 manufacturers, wholesalers/distributors/retailers, quality control testing, and
89 pharmacovigilance; and
90 • Implementation of regulatory actions should any quality problem be found.

91

92 Quality surveys may serve as an important source of information about the quality of
93 medicines available to patients. They can be organized by NMRAs, international
94 organizations, procurers, non-governmental organizations or academic and research groups.
95 Not all countries have a stringent system of medicines regulation in place and information
96 from quality surveys is specifically important for countries with weaker systems.

97

98 Data on the quality of medicines, if properly collected, interpreted and used, are vital for the
99 planning of effective interventions to improve the quality of medicines. Surveys give
100 snapshots of the medicine quality situation but the accuracy, reliability and interpretation of
101 the data obtained depend on the survey design, organization of sample collection, and
102 available resources. Medicine quality surveys are costly and available resources may restrict
103 the number of collected samples, tested parameters, techniques to be used for analysis, or
104 number of staff available to conduct the survey and analysis. Therefore it is important to
105 optimize use of resources by focusing on medicines and parameters that pose higher risk to
106 patients and apply risk analysis during planning of the survey. Also co-operation with
107 partners, joint organization of surveys in several countries, and sharing testing capacities,
108 experience and information can enhance the effectiveness of quality surveys.

109

110 These guidelines outline the steps to consider when preparing and conducting a survey of
111 medicines quality. It provides recommendations and examples of various methodological
112 approaches with discussion of their advantages and disadvantages, and suggestions on
113 preparation of reports from such surveys.

114

115 **2. GLOSSARY**

116

117 **sample collected within a quality survey.** A sample means a product in given
118 presentation (identified by its name, content of active pharmaceutical ingredient/s (API),
119 dosage form, strength, batch number and manufacturer) collected at the specific sample
120 collection site. It means that the same product characterized by the same name, content of
121 APIs, dosage form, strength, batch and from the same manufacturer collected in two different
122 sites represents two samples. Each sample must consist of the number of dosage units (e.g.
123 tablets, capsules, ampoules, vials, bottles) required by the sampling plan.

124

125   **pharmaceutical outlet.** A pharmaceutical outlet means any point (licensed or
126   unlicensed) of sale or provision of medicines for individual patients or other medicine
127   providers.
128
129   **sampling plan.** A sampling plan contains detailed identification of sites where samples
130   will be collected, medicines to be sampled, minimum number of dosage units to be collected
131   per sample, number of samples to be collected per medicine, and total number of samples to
132   be collected in the area for which the sampling plan is prepared. It contains also detailed
133   instructions for sample collectors.
134
135   **3.   OBJECTIVES OF THE SURVEY AND INITIAL PLANNING**
136
137   Detailed objectives must be set at the start of planning since all the activities and requirements
138   within the survey should be derived from its objectives. Objectives for a quality survey should
139   reflect the reasons why the survey is conducted and should be formulated in a way enabling to
140   identify medicines to be surveyed, sites of sample collection, surveyed areas/regions/countries
141   and tests to be conducted. Clearly defined objectives are essential for setting up conditions for
142   sampling and testing which should be described in detail in the survey protocol.
143
144   There is a wide range of possible objectives, just to mention a few examples:
145
146   • to evaluate quality of selected medicines available in the market in selected
147   areas/regions/countries at various levels of distribution/supply chain with the aim to
148   assess the exposure of patients to poor-quality medicines and propose appropriate
149   actions;
150   • to compare quality of domestically produced medicines with imported ones in order to
151   recommend appropriate regulatory actions and adjust pharmaceutical policy in the
152   country;
153   • to identify possible causes of inferior quality of specific products to which patients are
154   exposed. To propose possible strategies and implementation plans to address the
155   problems identified by the survey;
156   • to test quality of selected medicines in order to support the national medicines
157   regulatory authorization (NMRA) in identification of manufacturers non-compliant
158   with quality standards and in adoption of regulatory measures;
159   • to find out if within a selected category of medicines any spurious/falsely
160   labelled/falsified/counterfeit products penetrate to the market in selected
161   areas/regions/countries, and what may be the health impact for patients. To propose
162   possible strategies and implementation plans to prevent harm to patients.
163
164   To ensure that a survey provides the requested information it is useful, in addition to a
165   primary objective, to set questions to be addressed within the survey. Some examples of such
166   questions may be:
167
168   • what proportion of sampled medicines fails quality testing?
169   • What proportions of sampled medicines fail quality testing at different levels of the
170   regulated distribution chain and in the informal market?
171   • What proportions of medicines sampled at different geographical regions fail quality
172   testing?

173 • What proportions of sampled domestically produced and imported medicines fail
174 quality testing?
175 • Which specific quality tests do the selected medicines fail?
176 • Are any of the deficiencies critical, i.e. could they substantially affect treatment
177 efficiency and/or cause harm to patients?
178 • What is the registration status of sampled products and what proportions of registered
179 and unregistered products fail quality testing?
180 • What are the supply chains by which poor-quality medicines are distributed and what
181 are the market segments they serve?
182 • Are there any indicators of poor storage and distribution conditions which influence
183 quality of sampled medicines?
184 • Are there poor-quality medicines in the selected area, border checkpoint, etc.?
185 • What is the proportion of poor-quality medicines being sold and/or proportion of
186 pharmaceutical outlets selling poor-quality medicines in a particular area?
187 • Does the proportion of poor-quality medicines or the proportion of pharmaceutical
188 outlets selling poor-quality medicines exceed a predetermined level?
189 • Has the quality changed for a medicine, or medicine category, or in an area (in case of
190 repeated random surveys with consistent design)?
191
192 Setting reasonable objectives and appropriate design of a survey needs initial planning. Some
193 examples of questions which should be considered in the planning phase are:
194
195 • *What is already known about the quality and risk of inferior quality of the target*
196 *medicines?*
197 The information may be sought in scientific literature, alerts of medicines quality, and
198 published studies through searches, e.g. in PubMed or Google Scholar. In the case that
199 an NMRA is involved in the survey, it is important to gather information from
200 inspectors, assessors, laboratory and pharmacovigilance experts and design the survey
201 in cooperation of such a multidisciplinary team. Also discussions with pharmacists and
202 other health-care professionals may help to prioritize surveys.
203
204 • *What is the distribution/supply system of the target medicines?*
205 Distribution/supply chains vary in individual countries and even in one country may
206 be different for various medicines categories. In order to design the survey properly it
207 is important to understand how the target medicines are supplied in the surveyed area
208 and how they reach patients. Knowledge of the distribution/supply chain of the target
209 medicines enables risk-based selection of sampling sites best serving the survey
210 objectives. Complex supply chains pose higher risk of quality deterioration and should
211 be prioritized in market surveillance activities. Information on distribution/supply
212 chains should be available to NMRAs, ministries of health, provincial health
213 departments and health centres or other governmental organizations. In the public
214 domain some information can be found at the World Health Organization (WHO)
215 Essential Medicines and Health Products department website
216 (http://www.who.int/medicines/areas/coordination/partnerscoordination/en/). Several
217 international nongovernmental organizations are mapping pharmaceutical outlets in
218 various areas and publishing the information on their website, e.g. Population Services
219 International - PSI (http://www.psi.org/) or, specifically for antimalarials, ACTWatch
220 (http://www.actwatch.info/). If the survey should focus on unlicensed outlets, it may
221 be necessary to perform an initial pre-survey to map their locations.

222
223 • *What is health-seeking behaviour for the target medicines?*
224   For some surveys it may be important to also understand where different categories of
225   patients tend to buy their medicines and what kind of product they buy. In many
226   countries the medicines market is heavily segmented with different markets for people
227   of different spending power and ethnicity. For example, the wealthier people may go
228   to pharmacies or private clinics, whilst the poorest go to grocery shops or street
229   peddlers and people of middle income may go to hospitals. There will also be brands
230   of the same product at different prices aimed at different market segments. If such
231   information is needed, an initial pre-survey should be performed.
232
233 • *What is the patients' exposure to the target medicines?*
234   The higher volumes of medicines used the bigger impact the inferior quality will have
235   on patients. Therefore medicines with high consumption volumes should be prioritized
236   in market surveillance activities. It may be difficult to obtain consumption volumes in
237   some countries but some estimates based on distribution volumes or information from
238   various disease control programmes can be used.
239
240 • *What registered medicines are available in the surveyed area?*
241   It may be useful for the evaluation of survey results to have available lists of registered
242   medicines in the surveyed countries. These lists are available to NMRAs or ministries
243   of health and sometimes are published on their websites. It should be taken into
244   account that most countries also apply a policy of making available unregistered
245   medicines under certain conditions, e.g. specific medicines used in public health
246   programmes or donated may not be necessarily registered.
247
248 • *What brands for the target medicines are available in the surveyed area/in the*
249   *selected outlets?*
250   If the objectives of the survey require a wide picture of the quality of medicines
251   available on the market, samples produced by as many manufacturers as possible
252   should be collected and more sampling sites may be necessary to visit. It is normally
253   very difficult to know in advance how many brands of a specific medicine (containing
254   the same API in the same dosage form) are sold on the market and which their market
255   share is. A pilot study asking for a product list at the selling points may help to collect
256   the data needed to better plan the survey.
257
258 For correct understanding of all parties involved in the survey and proper interpretation of its
259 results, any limitations of the survey should be always stated and explained.
260
261 **4.   SURVEY MANAGEMENT AND TIME FRAME**
262
263 Ideally, the authorities (ministry of health/NMRA) of surveyed countries should be involved
264 or should agree with the survey plan before it commences. Responsibilities and tasks of
265 persons having key roles in the survey organization (e.g. survey coordinator, focal persons in
266 individual areas/countries) should be identified at the beginning and should include those with
267 the responsibility for monitoring the conduct of the survey, performing analysis, processing
268 results and preparing the final report. Communication lines and means should be agreed in
269 advance.
270

271 It is recommended before starting the sample collection to organize a meeting with
272 participation of focal persons to explain and discuss the project, survey protocol and provide
273 detailed instructions to ensure survey consistency. After data analysis and before publication
274 of the report it is useful to hold a meeting with appropriate stakeholders to discuss the results
275 and the actions needed.
276
277 It is important to take into consideration when the samples will be collected. There is no
278 information on seasonal changes in the frequency of poor-quality medicines, but they may
279 occur. For example, it is possible that falsified antimalarials are more common during the
280 malaria season. Access to outlets in rural areas may be impaired in the rainy season due to
281 floods and landslides. In addition, seasonal environmental conditions may have an influence
282 on the quality of the medicine collected. Humidity and temperature may influence specific
283 products and should be considered when planning the timing of the survey.
284
285 Issues such as the utilization of results and their public availability should be clearly
286 understood by responsible authorities and all parties involved in the survey from the
287 beginning. Relevant regulatory measures in individual countries lie within the responsibility
288 of the NMRA, when applicable in collaboration with the police or other enforcement bodies
289 (falsified medicines or criminal negligence). Therefore, if an NMRA does not organize the
290 survey directly, it should be provided with the results before publication to be able to
291 investigate in line with the regulatory practice and legislation with the relevant manufacturer
292 and, if appropriate, adopt necessary regulatory measures.
293
294 A publication plan including authorship of any papers to be submitted for peer-reviewed
295 publication and a distribution list of those to whom the report will be disseminated should be
296 agreed at the beginning of the survey. A policy should be adopted concerning public release
297 of data which might be considered confidential. The default position should be to distribute as
298 widely and openly as possible.
299
300 Medicines quality surveys aim primarily to enforce medicines quality standards and reduce
301 harm to patients, and represent market surveillance or generation of new scientific knowledge.
302 Normally, they are not subject to an ethical approval. But as the requirements for ethical
303 clearance vary between countries, they should be checked in target countries before planning
304 a specific survey.
305
306 The survey plan with key milestones and persons responsible for individual steps should be
307 predefined together with an estimated timeframe (Table 1). It is necessary to plan the financial
308 resources expected for the whole survey before commencing.
309
310 **Table 1. Example of the plan of survey activities**

Activity	Timeframe	Responsible person
Selection of areas/region/countries and medicines to be surveyed		
Preparation of survey protocol		
Agreement with authority/ies in surveyed country/ies		
Selection of testing laboratory/ies		

Finalization of testing protocol in agreement with testing laboratory/ies		
Meeting held with focal persons from the target areas to discuss the survey protocol		
Preparation of detailed sampling plans		
Preparation and pilot test of data collection instructions and procedures, if needed		
Training and supervision of personnel collecting samples		
Collection of samples and transport to testing laboratory/ies		
Database of information on collected samples (including scanned pictures or photographs of the dosage form, label and package leaflet)		
Testing of samples		
Compilation of results		
Data analysis		
Report drafting		
Meeting held with appropriate stakeholders to discuss the results and the actions needed		
Report finalization		
Distribution and publication of the results		

311
312 5. METHODOLOGY
313
314 Medicines quality survey methodology and conduct may pose important challenges due to,
315 e.g. insufficient sample size, incorrect sampling and/or testing. This may lead to inaccurate
316 results and policy recommendations. Survey results may influence national policies and have
317 a direct impact on individuals and public health. Therefore careful methodological and ethical
318 considerations should guide the survey preparation and the people involved should comply
319 with the instructions and appropriate ethical standards.
320
321 Any survey should be conducted according to a predefined survey protocol. In principle, the
322 survey protocol should, apart from the background and explanation of the survey objectives
323 and limitations, contain the following information.
324
325 5.1 Selection of areas to be sampled
326
327 Different geographical areas should be sampled unless the objectives expressly justify
328 targeting one area only. Samples should not usually be collected only in the capital city, as
329 situations in rural and suburban areas often differ. Depending on the survey objectives, the
330 following variables may be considered for area selection:
331

332 • population density;
333 • incidence/prevalence of the disease for which the target medicines are indicated;
334 • level of risk of poor-quality medicines, e.g. higher risk can be at trade routes across
335 country borders, areas where poor-quality medicines have been previously found,
336 areas where formal health services are limited, areas where the NMRA has little or no
337 resources to monitor the distribution of medicines;
338 • degree of urbanization;
339 • income level of the population in the target area;
340 • areas with complex distribution systems.
341
342 Sampling several countries according to the same survey protocol gives a broader picture of
343 quality of medicines in the region and enables comparisons between countries.
344
345 Selection of the sampled areas should be explained and justified.
346
347 **5.2   Selection of medicines to be surveyed**
348
349 The category of medicines to be surveyed may be characterized in various ways, e.g. by the
350 content of APIs, therapeutic group classification, formulation, specific programme under
351 which they are supplied, manufacturer or distributor declared on the label. If collection of
352 commonly used products is required, a pre-survey investigation of treatment-seeking
353 behaviour may be necessary. Collaborating with other sectors, such as national disease control
354 programmes, may help to identify products used commonly.
355
356 Selection of medicines is driven by the survey objectives and public health considerations.
357 The potential public health impact of poor-quality medicines should be key guides for
358 selection. To optimize use of available resources the survey should focus on medicines posing
359 higher risk to patients, e.g. where the therapeutic index is narrow, substandard quality could
360 lead to a significant change of the health outcome or categories particularly vulnerable to
361 counterfeiting. To estimate risks posed by individual medicines an analysis should be
362 performed, considering the following aspects:
363
364 • probability of occurrence of a quality problem, taking into account:
365   o complexity of manufacture,
366   o stability of the medicine – risk of quality deterioration considering local
367   conditions of distribution and use,
368   o compliance of manufacturers of the target medicines with good manufacturing
369   practices (GMP) principles,
370   o complexity of distribution chain for the target medicines and likelihood of non-
371   compliance with approved storage conditions during distribution and storage;
372
373 • exposure of patients to the medicine and seriousness of potential health impairment,
374   considering:
375   o extent of exposed population – number of patients and length of treatment, and
376   volumes used,
377   o vulnerability of target population – susceptibility of treated population to the
378   undesired effects of the medicine,
379   o complexity of the dosage form in relation to the route of administration,

380   o   therapeutic properties and risk, such as safety margins and risk of side effects, risk
381   of therapeutic failure, acute versus chronic exposure, risk of development of
382   resistance.

383
384 Sample collectors should be provided with instructions as regards the dosage forms and
385 strengths of the selected medicines to be collected. Unless the objectives of the survey require
386 to focus on the particular brand/s, it should be defined how to select samples if more brands
387 are available in the sample collection site.

388
389 The number of medicines selected for the survey depends on available resources (both
390 financial and human) and care should be taken to keep the survey manageable.

391
392 **5.3   Selection of sample collection sites**

393
394 *5.3.1 Types of sample collection sites*

395
396 Pharmaceutical outlets vary greatly in type both within and between countries and may be
397 classified according to the countries' medicine legislation. To allow comparison between
398 regions/countries, outlets can be classed as:

399
400   •   public (government);
401   •   formal (licensed), i.e. registered private for profit and private not for profit
402   (nongovernmental organizations (NGOs));
403   •   informal (unlicensed).

404
405 Another classification of sample collection sites may be according to the level of the supply
406 chain:

407
408   •   Level 1 − points of entry to the market, e.g. warehouses of importers or manufacturers,
409   central medical stores, NGO central stores, procurement centres or other facilities
410   supplied directly within various programmes, central wholesalers/distributors;
411   •   Level 2 − wholesalers/distributors, pharmacies and other regulated retailers,
412   dispensing facilities, hospitals, health centres, sub-health centres, district hospitals,
413   clinics, polyclinics, cabinets, treatment centres, health posts, community health
414   workers;
415   •   Level 3 − informal outlets selling medicines outside the approved distribution system,
416   e.g. kiosks, street vendors, grocery shops, drug stores, itinerant sellers.

417
418 Sampling should usually be performed in both the public and private sectors as well as in the
419 "informal market", i.e. include both licensed and unlicensed outlets. Types of sites for sample
420 collection should be selected in a way to best serve best the survey objectives and the
421 selection should be explained.

422
423 Quality of samples collected in the supply chain close to the point of sale to patients (Levels 2
424 and 3) may be influenced by distribution and storage conditions. However, these will be the
425 closest in terms of quality to the medicines that patients actually take. If medicine quality
426 problems are found and suggest degradation, collection of additional samples of the same
427 product at higher levels of the chain, e.g. in central wholesalers and central medical stores,
428 may highlight the importance of supply chain management.

429
430   Samples collected at points of entry to the market (Level 1) should be less affected by the
431   conditions they may encounter during in-country distribution, but are relatively distant from
432   the actual quality of medicines that patients will have access to and take. Sampling at this
433   point in the supply chain has the advantage of identifying the quality of products as supplied
434   by manufacturers and detecting quality issues before the products reach patients. Corrective
435   actions may be more easily put in place if the results are quickly available.
436
437   Once the types of sample collection sites are selected, the areas/regions/countries to be
438   sampled need to be mapped and the sites where samples will be actually collected in the
439   survey should be identified (by address and facility type). Good local knowledge of the
440   distribution/supply chain structure for the target medicines is needed and cooperation with
441   NMRAs and relevant disease control programmes in this respect is very important. If the
442   survey objectives require collection of samples offered by itinerant sellers, it may not be
443   possible to map their "territory" and a pre-survey investigation, e.g. in households, may be
444   needed. Another option would be to include a list of the outlets where itinerant vendors buy
445   their medicines.
446
447   ### 5.3.2 Sampling designs
448
449   Various designs can be used for selection of sample collection sites. The choice depends on
450   the objectives of the survey, the risks and consequences associated with inherent decision
451   errors and biases and available resources.
452
453   #### 5.3.2.1   Convenience sampling
454
455   Convenience sampling is a non-probability sampling technique based on the judgement of the
456   survey organizer. The sites, however, should not be identified just because of their convenient
457   accessibility and proximity. There should be defined rules guiding the selection to best reflect
458   the survey objectives. Whenever convenience sampling is used it should be reported how the
459   sites were identified and which types and proportion of the outlets the selection represents.
460
461   Convenience surveys are simple and do not necessarily need complete lists of outlets in
462   defined areas which may be difficult to obtain especially for unlicensed or mobile outlets.
463   However, they are inherently prone to biases which have to be considered when interpreting
464   the survey outcomes. It is a technique predominantly used for selection of sample collection
465   sites by, e.g. NMRAs for market surveillance. To utilize resources in a most efficient way
466   NMRAs focus on outlets where the risk of poor-quality medicines occurrence is high. When
467   selecting such sites the risk analysis should consider, e.g. the way of medicines distribution to
468   the site, transport conditions, storage conditions and handling products in the site, experience
469   of the NMRA with the distribution chain and sites.
470
471   The results of convenience sampling cannot be generalized to other areas, even within the
472   same country, or reliably interpreted over time. However, convenience surveys may provide
473   the evidence to support regulatory actions or signal of a quality problem. If convenience
474   sampling does indicate a medicine quality problem further investigation or regulatory actions
475   can be initiated. If a wider picture is needed subsequent surveys with probability sampling can
476   be designed. If convenience surveys do not demonstrate a problem one should bear in mind
477   that this may be a false negative result. It is important to explain the limitations of this
478   technique in reports and scientific papers.

479

480 Examples of convenience sampling include some surveys conducted in Africa[3,4] and South
481 East Asia.[5,6]

482

483 *5.3.2.2 Random sampling*

484

485 Random sampling is a probability sampling technique that, with sufficient sample size, will
486 give reliable estimates (with confidence intervals) of the prevalence of outlets selling poor-
487 quality medicines. Formulas for calculation of a sample size for random sampling can be
488 found in the literature.[7] The disadvantages of random sampling are the large sample sizes
489 needed, necessity of complete lists of the locations of the target outlets and the additional
490 costs in labour and time. In addition, it is important to recognize that a random survey will
491 only produce reliable and useful information if the list of outlets and actual within-outlet
492 sampling is in concordance with the primary aims of the survey. For example, a random
493 survey of the quality of medicine in the private sector when most patients obtain this medicine
494 in the public sector would not be useful, nor would a random survey using overt shoppers for
495 a medicine which the outlet staff know should not be sold to patients. Comparisons with
496 subsequent estimates using the same sampling design should be valid and will allow the
497 evaluation of interventions.

498

499 Stratified sampling is a probability sampling technique wherein the researcher divides the
500 entire group of investigated subjects (e.g. outlets) into different subgroups (layers/strata), then
501 randomly selects the final subjects proportionally from the different subgroups. Stratified
502 sampling can be used to adjust for potential differences, e.g. sales volume, type of customers
503 or geographical, trade and socioeconomic variables (such as rural versus urban, private versus
504 public outlets and one geographic area versus another) may be considered. Stratification
505 requires adjustment of the sample size calculation. Sampling proportional to number of outlets
506 will be more efficient compared to simple random sampling. It is important that the
507 randomization procedure uses formal random number tables or statistical software. Examples
508 of this technique are described in a stratified random survey in Lao People's Democratic
509 Republic.[8] Other examples of random surveys are from Nigeria[9] and the United Republic of
510 Tanzania[10]

511

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     countries of sub-Saharan Africa – QAMSA. 2011:
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10   Kaur H, et al. A Nationwide Survey of the Quality of Antimalarials in Retail Outlets in Tanzania. PLoS One,
     2008. **3**(10): p. e3403.

512   *5.3.2.3   Lot quality assurance sampling*

513

514   An alternative approach to formal random sampling, simpler and less expensive, which needs
515   smaller sample sizes, uses lot quality assurance sampling (LQAS). It can be used to determine
516   whether the prevalence of outlets selling poor-quality medicines exceeds a certain threshold.

517

518   LQAS is designed to allow determination as to whether a lot of goods meets desired
519   specifications without having to inspect the entire lot. Thus, the sample size in LQAS is
520   defined as the number of outlets or medicines ("goods") that are selected for each site/region
521   ("lot") and the only outcome is that the site/region is "acceptable" or "unacceptable". Setting
522   the level of risk taken by not inspecting each and every item enables the researcher to accept
523   or reject an entire lot after inspecting a randomly selected sample of items. Therefore the
524   sample size in LQAS is based on defined threshold values that classify good and bad
525   outcomes and the probability of error that the researchers are willing to tolerate.

526

527   Acceptable probabilities of error must be specified, i.e. the risk of accepting a "bad" lot
528   ("consumer risk") and the risk of not accepting a "good" lot ("provider risk"). These risks are
529   commonly referred to as Type I (alpha) and Type II (beta) errors, respectively. The former is
530   often set to 0.05. This means that if the null hypothesis (that the site has fewer outlets selling
531   poor-quality medicines than the specified value) is true, there is a 5% chance that a site with
532   an unacceptable proportion of outlets selling poor-quality medicines will be "accepted" or go
533   undetected. In general, Type I risk is set lower than the Type II risk.

534

535   Once the threshold values and probabilities of error have been considered a sample size and
536   decision value can be obtained. The decision value is the number of outlets selling poor-
537   quality medicines that need to be found before an area is considered unacceptable. LQAS still
538   requires random sampling, preparation of complete lists of the locations of the outlets and has
539   the disadvantage that it does not estimate an exact prevalence. The advantage is that it
540   requires relatively smaller sample sizes. Sampling can stop once the number of outlets selling
541   poor-quality medicine is exceeded, greatly reducing sampling time and costs.

542

543   As LQAS will only provide a binary result formal random sampling may be required to
544   examine longitudinal changes in the prevalence of poor-quality medicines accurately. It can
545   also be useful when the exact prevalence of poor-quality medicines is known as a way to
546   monitor the situation.

547

548   There has been almost no discussion as to what proportion of outlets selling poor-quality
549   medicines should be regarded as unacceptable. Ideally there should be zero-tolerance for
550   outlets selling poor-quality medicines, as even a 1% prevalence of such medicines for
551   potentially fatal diseases, such as malaria, tuberculosis and HIV, is disastrous for individual
552   patients.

553

554

555 Examples of this approach in various areas can be found in several publications,[11,12] a LQAS
556 toolkit is available from the Liverpool School of Tropical Medicine.[13]

558 *5.3.2.4 Sentinel site monitoring*

560 Sentinel site monitoring involves following the quality of medicines in a particular locality
561 through time. There are no common rules as to whether these sites should be chosen on the
562 basis of potentially important variables such as rural versus urban and private versus public
563 outlets, or as to sampling design (i.e. convenience or random samples or LQAS). The power
564 of this methodology resides in allowing longitudinal changes to be followed in one place but
565 data from fixed sentinel site monitoring should be interpreted with caution. Sentinel site
566 monitoring suffers from the disadvantage that shop owners may soon realize that they are
567 being sampled, change their behaviour accordingly and thus are no longer representative.
568 Examples of this approach include the survey in the Mekong region.[14]

570 **5.4   Sampling plans**

572 Sampling plans should be prepared for each area/region/country involved in the survey and
573 should in compliance with requirements of the survey protocol identify:

575 • individual sites where collectors should collect samples (by facility type and address,
576 possibly including global positioning system (GPS) coordinates);
577 • medicines to be sampled (by APIs, dosage form, strength, and, if needed, also package
578 size);
579 • minimum number of dosage units to be collected per sample;
580 • number of samples to be collected per medicine;
581 • total number of samples to be collected in the relevant area/region/country.

583 Sampling plans should also contain detailed instructions for collectors. Examples of sampling
584 plans for surveys organized by WHO can be found in the published survey reports.[15]

586 *5.4.1 Number of dosage units to be collected*

588 The number of dosage units that should be collected per sample depends on the survey
589 objectives, surveyed medicines, tests to be conducted, testing methods to be employed and
590 available resources. To protect integrity of samples and avoid quality deterioration before
591 testing, dosage units should not be taken out of the original primary and secondary packaging
592 and only intact and unopened packages should be collected. Sampling plans normally define

11 Hani MJ Khojah, Henrik Pallos, Naoko Yoshida, Manabu Akazawa, Hirohito Tsuboi, and Kazuko Kimura.
The Quality of Medicines in Community Pharmacies in Riyadh, Saudi Arabia: A Lot Quality Assurance
Sampling (LQAS)-Based Survey, Pharmacology & Pharmacy, 4(7), 511-519, 2013, doi:
10.4236/pp.2013.47074.
12 Lemeshow S. and Taber S. Lot quality assurance sampling: single- and double-sampling plans. World Health
Stat. Q, 1991. 44(3): p. 115-32.
13 Liverpool School of Tropical Medicine LSTM, The LQAS Generic Toolkit. 2014:
http://www.lstmliverpool.ac.uk/research/departments/international-public-health/metre/lqas-generic-toolkit/.
14 Phanouvong S. Mekong Malaria Initiative. Antimalarial Drug Quality Monitoring and Evaluation. Indicators,
in USP. 2004: http://pdf.usaid.gov/pdf_docs/pnadh147.pdf.
15 World Health Organization Prequalification of Medicines Programme. Quality Monitoring:
http://www.who.int/prequal/.

593 the minimum number of dosage units to be collected per sample. In relation to the available
594 package size the appropriate number of packages is collected.

595

596 In surveys aiming to provide evidence to support regulatory actions, which are often
597 organized by NMRAs or with their participation, pharmacopoeial tests performed in
598 compliance with pharmacopoeial procedures are commonly used. In such surveys the
599 principles of Good practices for pharmaceutical quality control laboratories[16] should be
600 followed and the number of dosage units per sample should allow:

601

602 • conducting the planned tests;
603 • investigation and confirmatory testing for those found to be out-of-specification
604 (OOS);
605 • retention samples to be used in case of dispute.

606

607 To fulfil these requirements, quite high numbers of dosage units per sample should be
608 collected (e.g. 100 tablets, 40 injection solution ampoules or powder for injection vials,
609 depending on the medicine and requested tests), which may be difficult to obtain in some
610 outlets. It may also suggest to the outlet owner that the buyer is not an ordinary shopper in
611 cases when the survey objectives request a mystery-shopper approach. The minimum number
612 of dosage units to be collected per each selected medicine should be agreed with the testing
613 laboratory. The advantage of surveys using pharmacopoeial procedures is the possibility to
614 apply quality acceptance criteria as defined in pharmacopoeias. The disadvantage is rather
615 time- and resource-demanding laboratory testing leading to lower numbers of samples which
616 can be included in the survey.

617

618 Other types of surveys are quality screening surveys using basic, simple tests, non-destructive
619 techniques (such as Raman and infrared (IR) spectroscopy) or unofficial testing methods
620 (non-pharmacopoeial or not approved by the NMRA during registration process) to assess the
621 identity of the API and estimate its content. Such surveys cannot be used as a basis for
622 regulatory actions but may precipitate further investigations with appropriate protocols. The
623 advantage is that only a few dosage units can be collected per sample, a higher number of
624 samples can be collected and the mystery-shopper approach can be used, if needed. The
625 disadvantage is that when testing only a few individual dosage units, usual pharmacopoeial
626 quality acceptance criteria are difficult to apply, e.g. when estimating the content of the API
627 by testing a few individual tablets only, pharmacopoeial criteria for the assay cannot be used.

628

629 Testing of individual dosage units to assess the content of API raises the question of how
630 many dosage units, within a medicine sample, need to be analysed. The variability of
631 individual units can be very high, especially within a sample of poor-quality medicine.
632 Various statistical approaches to representative medicine sampling especially for forensic
633 analysis purposes are described by, e.g. United Nations (UN) Office on Drugs and Crime,[17]

[16] Good practices for pharmaceutical quality control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization. WHO Technical Report Series, No. 957, 2010, Annex 1:
http://www.who.int/prequal/info_general/documents/TRS957/GPCL_TRS957_Annex1.pdf.

[17] United Nations Office on Drugs and Crime. Guidelines on Representative Drug Sampling, Laboratory and Scientific Section, Editor. 2009: http://www.unodc.org/documents/scientific/Drug_Sampling.pdf.

634   Scientific Working Group for the Analysis of Seized Drugs,[18] European Network of Forensic
635   Sciences Institutes,[19] or in some publications.[20]

636

637   Sampling procedures ensuring that representative samples are taken by authorities,
638   procurement agencies, manufacturers or customers for acceptance of consignments, batch
639   release testing, in-process controls, special controls, inspection for customs clearance/
640   deterioration/adulteration or for obtaining a retention sample are described in the WHO
641   guidelines for sampling of pharmaceutical products and related materials.[21]

642

643   **5.5   Sample collection**

644

645   *5.5.1 Overt sampling versus mystery-shopper approach*

646

647   The decision on who should collect samples will depend on the survey objectives, regulatory
648   status of the target medicines and what is known about the knowledge and attitude of sellers
649   (whether he/she knows that the outlet is selling poor-quality medicines and understands the
650   health, legal and ethical implications). If outlet staff are anxious to avoid poor-quality
651   medicines and are informed about the survey objectives, overt sampling with feedback would
652   allow more data to be collected on poor-quality medicines and their risk factors and lead to
653   direct improvement in the medicine supply. Overt sampling may be the only possible method
654   in some circumstances, such as if samples are collected where people are seen first by
655   clinicians or in the public sector.

656

657   However, many outlets in countries with weak medicines regulation sell expired or
658   unregistered medicines, which may make outlet staff suspicious and anxious about
659   investigations. If the seller knows or is concerned that his/her stock contains illegal or poor-
660   quality medicines and that the buyer is potentially linked to the NMRA, this may influence
661   which medicines are offered. An additional concern is that in many resource-poor countries
662   the medicine market is heavily segmented with different markets for people of different
663   spending power and ethnicity. Even within a single outlet there will often be several different
664   brands of the same medicine at different prices aimed at different market segments. In such
665   cases a covert, mystery-shopper approach may be appropriate.[22] The identity and purpose of
666   the buyer should not be generally known by the outlet being evaluated. Sampling should
667   usually be performed by nationals of the country concerned although there may be some
668   situations, such as suspicion that migrant workers may take inferior medicines, where this
669   would not be applicable. It may not be safe for people living in the same wider community to
670   act as purchasers. In contrast, in some remote rural locations, it would be difficult for
671   someone who is not local to request medicines as this would cause suspicion. The safety of
672   those acting as mystery shoppers should be considered, the risk assessment performed and
673   instructions appropriate to local conditions developed.

---

[18]   Administration, U.S.D.o.J.D.E. Scientific working group for the analysis of seized drugs (SWGDRUG).
Recommendations, 2011: http://www.swgdrug.org/Documents/SWGDRUG%20Recommendations%206.pdf.

[19]   Calculator for qualitative sampling of seized drugs: http://www.enfsi.eu/documents/enfsi-dwg-calculator-
qualitative-sampling-seized-drugs-2012.

[20]   Frank R, Hoffman C, and Hinkley S. Representative Sampling of Drug Seizures in Multiple Containers.
ASTM International, 1991. 36(2).

[21]   WHO guidelines for sampling of pharmaceutical products and related materials. In: *WHO Expert Committee
on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization,
2005, Annex 4 (WHO Technical Report Series, No. 929).

[22]   Madden JM et al. Undercover careseekers: Simulated clients in the study of health provider behavior in
developing countries. Social Science & Medicine, 1997. 45(10): p. 1465-1482.

674
675   The mystery shopper mimics a "normal shopper" for the community in which the outlet is
676   located and should dress, speak and behave appropriately for the community. They should use
677   a standard scenario, e.g. pretending to be a visitor from another part of the country who needs
678   some medicines for a specified disease, for a specific reason and for a stereotyped patient. The
679   mystery shopper should be prepared to explain the real purpose of the visit to protect
680   himself/herself in case that his/her identity is revealed. After leaving the surveyed place the
681   mystery shopper should record details of the purchase. Price, name of the provider/outlet,
682   estimation of temperature at the place should be documented as well as conditions of the
683   purchase, e.g. how many people were in the outlet, how long it took, what was the interaction
684   between the mystery shopper and outlet staff, was it easy to convince the provider to sell
685   medicines, and other information requested by the survey objectives. Collected medicines
686   should be properly identified and stored, e.g. in a plastic bag labelled with the name of the
687   outlet.
688
689   The mystery shopper should brief the focal person for the surveyed area after return from each
690   outlet. The focal person should transcribe the reported interaction with translation as
691   appropriate. Translations should use a meaning-based translation method, rather than a literal
692   or interpretative approach. The original text with translation should be double-checked for
693   accuracy by other members of the team and kept.
694
695   Examples of overt sampling include some surveys in Asia[23,24] and the example of mystery-
696   shopper approach can be found in the survey conducted in Lao People's Democratic
697   Republic.[6]
698
699   *5.5.2   Sample collection*
700
701   The focal person for each area/region/country will arrange for training of collectors to be
702   familiar with the project, survey protocol, national sampling plan and instructions for
703   collection of samples. Staff from the NMRA and the different national disease control
704   programmes may provide a useful insight into the survey planning.
705
706   Data collection instructions and procedures should be well understood by the collectors
707   (translated in the language of collectors, piloted and revised, if needed). The following
708   principles should be included in detailed instructions for collectors:
709
710   •   the minimum number of dosage units per sample and number of batches to be
711   collected from each collection site for each selected medicine as indicated in the
712   sampling plan should be adhered to;
713   •   the target medicines, their dosage forms, strengths, package sizes should be defined.
714   As outlets may have more than one brand of a particular medicine available,
715   instructions should be provided on how to decide if a selection has to be made. It
716   should be taken into consideration that mystery shoppers requesting a very specific

23   ACTwatch, Outlet Survey. Kingdom of Cambodia. 2011 Survey Report, in Outlet Survey Report (Endline),
     Cambodia, 06/11 – 08/11, P.S. Kathryn O'Connell, Editor. 2011, ACTwatch. Evidence for Malaria
     Medicines Policy: http://www.actwatch.info/sites/default/files/content/outlet-
     reports/ACTwatch%20Cambodia%20OS%20Endline_2011.pdf.
24   World Health Organization. Survey of the quality of anti-tuberculosis medicines circulating in selected newly
     independent states of the former Soviet Union. 2011:
     http://www.who.int/prequal/info_applicants/qclabs/monitoring_documents/TBQuality-Survey_Nov2011.pdf.

717   brand or product may alert sellers. However, such an approach may be required if
718   evidence suggests that only one brand of an essential medicine is afflicted by
719   falsification or substandard production. It may be useful to consider using a specific
720   written prescription for a number of items including the target medicine. This can
721   reduce raising suspicion of a verbal request. Using the written prescription format may
722   also enable studying the quality of dispensing, labelling directions and counselling;

723   • all units of one sample must be of the same batch number;

724   • the medicine samples should not be taken out of the original primary and secondary
725   packaging (though removal from large secondary packs is appropriate). Containers
726   such as bottles and vials should not be opened. In cases where medicines are sold
727   without package leaflets, or in unlabelled plastic bags coming from large sized boxes
728   (locally repacked), or as individual dosage forms, this should be recorded;

729   • ideally, samples collected should have at least six months remaining to expiry to allow
730   sufficient time for chemical analysis. However, the frequency of expired medicines is
731   also an important outcome measure and any expired medicine found in the outlet
732   should be recorded;

733   • the medicine labels and package leaflets should not be removed or damaged;

734   • each sample should be recorded separately using the sample collection form (for an
735   example see Appendix 1). Whenever the required information is not available it
736   should be indicated in the appropriate space on the sample collection form; any
737   observed abnormalities should also be recorded;

738   • each sample should be identified by a unique sample code, defined on the sample
739   collection form and specified on all original packages belonging to the respective
740   sample (legible and not covering the basic product information). The sample
741   collection form and all packages belonging to one sample should be kept together (e.g.
742   blisters inserted in a dedicated zip-lock plastic bag or envelope marked with the
743   appropriate sample code and trade name of the product). For large surveys, bar-code
744   systems may be helpful and reduce errors;

745   • when overt sampling is used, manufacturer's batch certificates of analysis should be
746   collected with samples, if available, and kept with the sample collection form;

747   • storage conditions at the site (temperature, humidity, access of light, any other
748   observation) should be described in the sample collection form. When overt sampling
749   is used collectors can measure temperature if not controlled in the site. Mystery
750   shoppers can estimate and record the temperature;

751   • samples should be collected and kept under controlled conditions in line with the
752   product label requirements. The cold chain has to be maintained, where required.
753   Samples should be kept protected from light, excessive moisture or dryness. Safety
754   measures against theft should be put in place; medicine boxes should be kept in a
755   locked area.

756

757 The time period, within which samples should be collected and the deadline for sending the
758 last sample to the testing laboratory, should be clearly indicated and followed.

759

760 Normally samples of collected medicines should be paid for by collectors. The cost of
761 collected samples needs to be taken into account when determining the numbers of samples to
762 be collected. In some countries NMRA inspectors have legal power to collect samples from
763 the market without reimbursement.

764

765 Collectors should be mindful of the stock of sampled products in outlets, and potential
766 difficulties of replenishment of sampled medicines through the supply chain, so as not to
767 jeopardize the availability of these medicines to patients. If there is a risk of product shortage
768 after sampling replacement of the sampled amount should be arranged immediately after the
769 survey or, less desirably, collection of that particular product in that outlet should be omitted.
770
771 In case of surveys seeking the proportion of poor-quality medicines sold to patients, outlet
772 product-specific sales volumes may be necessary. Collection of these data can be conducted
773 after sampling, especially when the mystery-shopper approach is used, and sellers should be
774 informed about the survey. This approach requires NMRA support as sales volumes are better
775 collected by inspectors or by officers of the authority.
776

777 **5.6   Storage and transportation of samples**
778

779 Storage and transportation of the samples to the testing laboratory should be done according
780 to the requirements set out in paragraph 2.3 of *WHO Guidelines for sampling of*
781 *pharmaceutical products and related materials.*[19] It should be done as quickly and straight as
782 possible so as not to jeopardize the quality of collected samples.
783

784 • The samples should be kept in their original packaging and under storage conditions as
785 specified on the label; freezing should be avoided and, where required, the cold chain
786 should be retained.
787 • For transport all samples should be packaged adequately and transported in such a way
788 as to avoid breakage and contamination during transport. Any residual space in the
789 container should be filled with a suitable material.
790 • In case of temperature-sensitive medicines, temperature data loggers may be included
791 within shipments to document adequate temperature in prolonged transit.
792 • A covering letter, copies of sample collection forms and, if available, copies of
793 manufacturer's batch certificate of analysis should accompany the samples.
794 • In the case that collectors are not transporting samples directly to the testing
795 laboratory, samples with the accompanying documents should be sent by a courier
796 service. For each shipment it should be clearly indicated that samples are sent for
797 laboratory testing purposes only, will not be used on humans or animals, have no
798 commercial value and will not be placed on the market. If the country, where the
799 laboratory is located, requires permission for importation of samples, the laboratory or
800 NMRA of the country may be able to assist to avoid long clearance procedures. The
801 testing laboratory should be informed of the shipment, with the tracking number as
802 provided by the courier service, to be able to follow the shipment and arrange
803 collection as soon as possible.
804 • Copies of sample collection forms and, if available, copies of manufacturer's batch
805 certificates of analysis should also be sent to the survey coordinator or person
806 preparing the survey report.
807

808 **5.7 Testing**

809

810 *5.7.1 Testing laboratory*

811

812 It is important that only quality control laboratories which demonstrate capability to produce
813 reliable testing results are used in quality surveys. Therefore laboratories for testing should be
814 properly selected and should meet the three following criteria:

815

816 • The laboratory works in compliance with WHO *Good practices for pharmaceutical*
817 *quality control laboratories*[14] – preferably a WHO prequalified laboratory[25] or a
818 laboratory where other evidence of equivalent working standards is available;
819 • the laboratory is capable and competent to perform tests required by the testing
820 protocol;
821 • the laboratory has sufficient capacity and agrees to test the required number of
822 samples within the specified period for the cost within the available budget.

823

824 The choice of the testing laboratory/ies should be explained in the survey protocol, reports
825 and publications. There can be one or more laboratories used for testing of samples collected
826 within the survey. If more laboratories are testing collected samples, samples should be
827 divided among laboratories in a way that all samples containing the same APIs are assigned
828 for testing to one laboratory. Many countries do not have a fully functioning quality control
829 laboratory and should consider making arrangements with a laboratory abroad.

830

831 The appropriate arrangement with the laboratory has to be made in advance. Within the usual
832 selection procedure and the resulting agreement the following should be clearly specified in
833 addition to the usual elements of such agreements (such as deadlines, financial arrangements
834 etc.):

835

836 • medicines and numbers of samples to be tested, tests to be conducted and
837 specifications to be used according to the testing protocol. If there are more testing
838 laboratories selected, a specific testing protocol should be prepared for each
839 laboratory;
840 • responsibilities of the laboratory during the survey as specified in section 5.7.4;
841 • confidentiality declaration of the laboratory;
842 • acceptance of a possible audit of the laboratory, access to records and retained
843 samples.

844

845 Once agreement/s is/are concluded, the survey coordinator should inform the focal persons in
846 areas/regions/countries participating in the survey about the name and address of the
847 laboratory/ies, the contact person/s in the laboratory and medicines assigned for testing to the
848 particular laboratory. The laboratory normally starts testing only when all samples containing
849 the same API in the same dosage form are received. Therefore it is important to set and
850 adhere to the deadline for sending samples to the testing laboratory.

851

852 *5.7.2 Tests to be conducted*

853

854 Laboratory testing of all collected samples should be performed according to the testing
855 protocol, which is a part of the survey protocol, and should be agreed with the testing

---

[25] The list of WHO-prequalified laboratories can be found at www.who.int/prequal.

856   laboratory/ies. Depending on the survey objectives, target medicines and available resources,
857   the tests to be applied to samples collected in the survey may include:
858
859   • verifying the identity;
860   • performing complete pharmacopoeial or analogous testing;
861   • performing special or specific tests.
862
863   In the case that testing should provide a full picture of the quality of target medicines, it
864   should be performed according to a pharmacopoeial or analogous monograph and the
865   following tests are, in principle, included:
866
867   • appearance, visual inspection;
868   • identity;
869   • assay for APIs declared on the label;
870   • test for related substances;
871   • for solid dosage forms – dissolution or disintegration, uniformity of dosage units (by
872   mass or content), fineness of dispersion in case of dispersible tablets;
873   • for liquid dosage forms – pH value and volume in containers/extractable volume;
874   • for parenteral products – sterility and bacterial endotoxins tests.
875
876   Inclusion of uniformity of content for single-dose dosage forms, or sterility and bacterial
877   endotoxins tests, which are costly, time demanding and need more dosage units to be
878   collected, should be considered in relation to target medicines and available resources. It is
879   impossible to achieve 100% certainty about sterility of the product through testing only and
880   inspections and enforcement of compliance with GMP principles may be more efficient tools
881   for verification in some cases.
882
883   Packaging of each collected sample, labelling and package leaflets should be inspected
884   visually for any signs of a spurious/falsely-labelled/falsified/counterfeit (SFFC) product. The
885   World Health Professionals Association published a checklist which may be used for this
886   purpose.[26] Laboratory analysis is not always successful in identifying falsified or substandard
887   medicines and any identified suspicious product should be further examined in cooperation
888   with the NMRA in the country of collection and the manufacturer declared on the label of
889   suspicious sample (for guidance on such investigation see WHO guideline QAS/15.631:
890   *Testing of substandard/spurious/falsely-labelled/falsified/counterfeit medicines* (draft in
891   preparation)).
892
893   Information on labels and in package leaflets can also be checked for quality and
894   completeness of essential information and compliance with requirements and approved
895   product information in the country of collection can be verified. However, when more
896   countries are involved in the survey it should be kept in mind that requirements on
897   information to be provided on medicines labels and package leaflets may differ.
898
899   Screening methods do not provide a full picture of the quality of medicines and may
900   underestimate non-compliant findings in comparison with laboratory testing.[1] However, they
901   enable testing of large number of samples in the field, e.g. to search for spurious, falsely-
902   labelled, falsified or counterfeit medicines. It is recommended to verify outcomes of screening

---

[26]   World Health Professions Alliance WHPA. Be aware. Tool for visual inspection of medicines.
        http://www.whpa.org/Toolkit_BeAware_Inspection.pdf.

903   by laboratory testing, at least for a random selection of those samples that pass screening and
904   for all those that fail.
905
906   *5.7.3   Test methods and specifications*
907
908   Test methods and specifications should be selected in a way to serve best to the survey
909   objectives. In general, when samples from different manufacturers are collected within a
910   quality survey, all samples containing the same APIs in the same dosage form are tested using
911   the same method and specification to enable comparison of samples from different
912   manufacturers. This specification is then used to decide on compliance or non-compliance of
913   tested samples for the purposes of the survey. It should be noted that individual manufacturers
914   may use different specifications and different methods for testing of their products and those
915   specifications and methods may be approved by regulatory authorities in individual countries.
916   Non-compliance with the specification selected for the survey does not therefore necessarily
917   imply non-compliance with the specifications approved in the country but it indicates the need
918   to look at the product and conditions of regulatory approval more closely and further actions
919   should be considered by the respective NMRA.
920
921   Wherever they are appropriate, pharmacopoeial methods and specifications should be used. A
922   national pharmacopoeia may be applicable if a survey is organized in one country. If more
923   countries are involved widely accepted pharmacopoeias (such as the International
924   Pharmacopoeia, British Pharmacopoeia or United States Pharmacopeia) may be appropriate.
925   In spite of efforts to harmonize pharmacopoeias there are still many differences. When a
926   monograph for the particular medicine is available in more pharmacopoeias the ability of the
927   respective methods and specifications to reveal quality problems should be considered and the
928   monograph selected accordingly.
929
930   If no monograph for the target medicine exists in pharmacopoeias or the existing monographs
931   do not provide for desired tests, a validated method of the laboratory should be used.
932
933   If samples suspicious to be an SFFC product should be tested, pharmacopoeial methods may
934   not be sufficient and further examination should be conducted (for guidance on such
935   investigation see WHO guideline QAS/15.631: *Testing of substandard/spurious/falsely-*
936   *labelled/falsified/counterfeit medicines* (draft in preparation)).
937
938   Once tests to be performed and methods and specifications to be used are selected, the testing
939   protocol should be finalized. For each of the target medicines it should contain the list of tests
940   to be conducted, reference to methods to be used and specifications to be employed.
941   Examples of testing protocols used for surveys organized by WHO can be found in the
942   published survey reports.[13]
943
944   *5.7.4   Receipt and testing of samples by a testing laboratory*
945
946   When samples are received, the testing laboratory should:
947
948   •   inspect each sample to ensure that the labelling is in conformance with the information
949   contained in the sample collection form or test request; an electronic databank (e.g.
950   scanned pictures or photographs of the medicines, such as of the tablets, packaging,
951   and package leaflet) is recommended;

952   •   store the samples in line with the conditions on product labels, including compliance
953   with any cold chain requirements;
954   •   conduct quality testing in line with the testing protocol and in compliance with WHO
955   Good practices for pharmaceutical quality control laboratories,[14] including
956   investigation and documentation of each OOS result according to the laboratory SOP.
957   If the OOS result is confirmed, it should be reported without delay to the survey
958   coordinator providing both results and investigation report;
959   •   complete analytical test reports/certificates of analysis containing information listed in
960   Appendix 2. The survey coordinator should define the format of the outcome (e.g.
961   separately for each sample or as a tabulated report);
962   •   keep document/s received with samples, records of testing of each sample including
963   all raw data and retention samples according to the requirements defined by the survey
964   coordinator (e.g. for at least six months if the sample complied with the specifications,
965   or for at least one year or until the expiry date (whichever is longer) if it did not
966   comply) and archive data according to the agreed conditions.
967
968 ## 6.   DATA MANAGEMENT AND PUBLICATION
969
970 To allow proper interpretation the data obtained during collection and testing of samples
971 should be summarized and well-arranged in a database (using Excel sheets or software for
972 epidemiological studies), linking each sample with all the gathered data and ensuring
973 consistency and security. Any errors should be avoided. For analysis of large sets of data
974 statistical software may be used. If relevant, personal identification of individuals who
975 participated in the survey (buyers, sellers, etc.) should be entered in the database using codes
976 only.
977
978 NMRAs of countries involved in the survey should be informed forthwith about confirmed
979 OOS results to be able to investigate in line with regulatory practice and legislation with the
980 relevant manufacturer or other party. It should be kept in mind that if testing methods and
981 specifications approved during registration process differ from those used in the survey, it
982 may be necessary to retest the particular product using the approved manufacturer's method,
983 where available. Once survey results are compiled, evaluated and summarized they should be
984 shared with the NMRAs involved as they may provide information on medicine quality
985 problems that will alert NMRAs and manufacturers. Before publication of the results it is
986 useful to hold a meeting with appropriate stakeholders to discuss the results and the actions
987 needed. The WHO Rapid Alert System should be informed when results are considered a
988 public health emergency.
989
990 A detailed survey report should be prepared including all testing results for collected samples
991 with interpretation. An example of the outline of the survey report content is provided in
992 Appendix 3. Recommendations for items to be addressed in reports of medicines quality
993 surveys can be also found in published literature.[27]
994
995 The report should be published as widely and openly as possible. The conclusions and
996 wording should be prepared with caution so as not to cause embarrassment or panic. The risk
997 that patients will stop taking genuine medicines and the public will lose faith in medicines or
998 the health-care system should be reduced by careful wording. Also any potential harm that

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[27]   Newton PN et al. Guidelines for field surveys of the quality of medicines: A proposal. PLoS Medicine, 2009.
6(3p. pp 0252-0257.

999 can be caused to manufacturers, suppliers or outlets should be considered to avoid any legal
1000 actions.

1001

1002

1003 # Appendix 1

1004 ## Example of the sample collection form[28]

1005 ### *SURVEY TITLE*

1006

1007 **Area/Region/Country:** _____   **Sample code:** _____
1008   (Area/region/country code/ medicine abbreviation/
1009   sequence number/sampling date ddmmyy)[29]

1010 Name of location/place where sample was taken:_____

1011 _____

1012 Address (with telephone, fax number and email address, GPS coordinates, if applicable):

1013 _____

1014 _____

1015 _____

1016 Organization and names of people who collected the sample:

1017 1. _____

1018 2. _____

1019 Product name of the sample: _____

1020 Name of active pharmaceutical ingredient(s) (INN) with strength:

1021 _____

1022 Dosage form (tablet, injection, powder for injection, etc.): _____

1023 Package size, type and packaging material of the container: _____

1024 _____

1025 Batch/lot number: _____

1026 Date of manufacture: _____   Expiry date: _____

1027 Regulatory status in the country, registration number, if applicable: _____

1028 _____

1029 Name and address of the manufacturer: _____

1030 _____

1031 _____

---

[28] The sample collection form should always be kept with the collected sample.

[29] Area/region/country code, e.g. for countries the two-letter code is used for the Internet country top-level domains; medicines abbreviations to be established; sample code system can be extended to be appropriate for a collection system in a particular area/region/country.

1032 _____

1033 Quantity collected (number of tablets/ampoules/vials and number of packages):

1034 _____

1035 *Initialize first page:*

1036 **Product name:** _____   **Sample code:** _____

1037

1038 Date the batch was received at the location: _____

1039

1040 Storage/climatic conditions at sampling site:

1041   Conditions controlled: Yes ☐   No ☐

1042   Temperature and humidity at the place where the sample was stored (at the time of sample
1043   collection):

1044 _____

1045 _____

1046

1047 Comments on suitability of premises where products are stored, abnormalities, remarks or
1048 observations that may be considered relevant, if any:

1049 _____

1050 _____

1051 _____

1052 _____

1053 _____

1054 _____

1055 _____

1056 _____

1057 _____

1058

1059 Date:

1060

1061 Signature of person/s taking   Signature of representative of the
1062 samples   facility where sample was taken
1063   *(only for overt sampling, optional)*

1064

1065 1. ....

1066   ....

1067 2. ....

1068

1069 **Note: Samples collected must remain in their original primary and secondary**
1070 **packaging, intact and unopened**

1071 # Appendix 2

1072 ## Content of the analytical test report/certificate of analysis

1073

1074 • Name and address of the laboratory performing the sample testing.

1075 • Name and address of the originator of the request for testing.

1076 • Number/code of the analytical test report/certificate of analysis.

1077 • Sample reference number assigned by the laboratory and sample code assigned at the
1078   time of sampling (specified in the sample collection form and packages belonging to
1079   one sample).

1080 • Date on which the sample was received.

1081 • Name of the area/region/country where the sample was collected.

1082 • Sample product name (trade name as appears on the label), dosage form, APIs,
1083   strength, package size (e.g. number of tablets in one blister and number of blisters in
1084   the secondary packaging, volume in one ampoule and number of ampoules in
1085   secondary packaging).

1086 • Description of the sample (both description of the product and of primary and
1087   secondary packaging, type and packaging material of primary container); if there is
1088   any sign of bad handling during the transportation, it should be mentioned.

1089 • Batch number of the sample, expiry date and, if available, manufacturing date.

1090 • Quantity of units received for the sample.

1091 • Name and full address of the manufacturer (as specified on the label or in the package
1092   leaflet).

1093 • Reference to the specifications used for testing the sample, including the limits.

1094 • In the case that a reference substance was used for quantitative determination, the
1095   substance should be specified (e.g. British Pharmacopoeia or United States of America
1096   Pharmacopeia reference substance or working standard).

1097 • Results of all the tests performed; for the evaluation and interpretation of results it is
1098   useful to request numerical results wherever possible, any observation made during
1099   testing and the following details:

1100   o for content uniformity, all results for individual units,

1101   o for dissolution test, results for all tablets tested,

1102   o for assay, results of each individual sample preparation (usually 3 sample
1103   preparations), average and the relative standard deviation (RSD); in case of an
1104   OOS result and retesting also the investigation report and results of retesting.

1105 • Conclusion whether or not the sample complies with the specifications set for the
1106   survey.

1107 • Date on which the test was completed.

1108 • Signature of the head of the laboratory or authorized person.

1109 **Appendix 3**

1110 **Outline of the content of a survey report**

1111 **Glossary and abbreviations**

1112 **Executive summary**

1113 **1.** **Introduction**

1114 1.1 Background

1115 1.2 Objectives of the survey

1116 **2.** **Methodology**

1117 2.1 Survey period

1118 2.2 Selection of medicines for sampling and testing

1119 2.3 Selection of areas/regions/countries

1120 2.4 Sampling design and selection of sample collection sites

1121 2.5 Sample collection and transportation

1122 2.6 Testing laboratories

1123 2.7 Quality tests performed and test methods and specifications used

1124 2.8 Definition of compliance of samples with standards

1125 **3.** **Results**

1126 3.1 Overview of samples collected

1127 3.1.1 Medicines

1128 3.1.2 Manufacturers and batches

1129 3.1.3 Sites of sample collection

1130 3.1.4 Storage and transportation conditions

1131 3.2 Registration status of sampled products

1132 3.3 Compliance with specifications

1133 3.3.1 Overall results

1134 3.3.2 Results of specific quality tests for individual products

1135 **4.** **Discussion**

1136 4.1 Testing methods and data quality

1137 4.2 Limitations of methodology

1138 4.3 Interpretation of the results

1139 4.4 Recommendations

1140 **5.** **Conclusions**

1141 **6.** **Other information** (conflict of interests, funding)

1142   **References**

1143   **Attachments – Detailed test results tabled for individual samples**