



A study of the quality of cardiovascular and diabetes medicines in Malang District, Indonesia, using exposure-based sampling

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1 A study of the quality of cardiovascular and diabetes medicines in Malang District,
2 Indonesia, using exposure-based sampling
3

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30 **A study of the quality of cardiovascular and diabetes** 31 **medicines in Malang District, Indonesia, using exposure-** 32 **based sampling**

33 **Abstract**

34 **Background**

35 The World Health Organization (WHO) has warned that substandard and falsified medicines
36 threaten health, especially in low- and middle-income countries (LMIC). However, the
37 magnitude of that threat for many medicines in different regions is not well described, and
38 high-quality studies remain rare. Recent reviews of studies of cardiovascular and diabetes
39 medicine quality recorded that 15.4 % of cardiovascular and 6.8% of diabetes samples failed
40 at least one quality test. Review authors warn that study quality was mixed. Because they did
41 not record medicine volume, no study reflected the risk posed to patients.

42 **Methods and Findings**

43 We investigated the quality of five medicines for cardiovascular disease and diabetes in
44 Malang district, East Java, Indonesia. Our sample frame, based on dispensing volumes by
45 outlet and price category, included sampling from public and private providers and
46 pharmacies, and reflected the potential risk posed to patients. The content of active ingredient
47 was determined by High Performance Liquid Chromatography, and compared with the
48 labelled content. Dissolution testing was also performed.

49 We collected a total of 204 samples: amlodipine (88); captopril (22); furosemide (21);
50 glibenclamide (21); and simvastatin (52), comprising 83 different brands/products. All were
51 manufactured in Indonesia, and all samples met specifications for both assay and dissolution.
52 None was suspected of being falsified.

53 **Conclusions**

54 While we cannot conclude that the prevalence of poor-quality medicines in Malang district is
55 zero, our sampling method, which reflects likely exposure to specific brands and outlets,
56 suggests that the risk to patients is very low; certainly nothing like the rates found in recent
57 reviews of surveys in LMICs. Our study demonstrates the feasibility of sampling medicines
58 based on likely exposure to specific products, and underlines the dangers of extrapolating
59 results across countries.

60

61 **What is already known on this topic**

62 The World Health Organisation suggests that as many as one in 10 medicines in low- and
63 middle-income countries are of poor quality, but studies of the prevalence of substandard
64 and falsified rarely take into account patient exposure.

65 Medicines for non-communicable diseases and studies from large middle-income
66 countries are under-represented in existing studies.

67 **What this study adds**

68 We showed that it is feasible to sample medicines based on patient exposure. Our
69 exposure-based study of cardiovascular and diabetes medicines in Indonesia, a lower-
70 middle income country that is the world's fourth most populous, found that all met quality
71 standards.

72 **How this study might affect research, practice or policy**

73 Adopting exposure-based methods for sampling and/or calculating the prevalence of
74 substandard and falsified medicines would improve our understanding of the potential
75 public health impact of poor-quality products globally.

76 **Introduction**

77 In 2017, the World Health Organization (WHO) warned that substandard and falsified
78 medicines posed a significant threat to health and to budgets, especially in low- and middle-
79 income countries. The warning, based on data from its newly-strengthened case-reporting
80 system and a review of 100 studies of medicine quality (some unpublished), was summarised
81 in a press release headlined: "1 in 10 medical products in developing countries is substandard
82 or falsified" [1–3].

83 The WHO noted nine major limitations in its own review, many centring around
84 heterogeneity in definitions, sampling designs and testing. In 2009, scholars proposed
85 Medicine Quality Assessment Reporting Guidelines (MEDQUARG), along with sampling
86 and survey methods [4]. A 2013 review which rated medicine quality studies published
87 between 1948 and 2013 against the MEDQUARG guidelines found that only 15 of 44 meet
88 what the paper's authors define as minimum standards for research design and reporting
89 (scoring 6 or more on the MEDQUARG checklist) [5]. Standards have improved since the
90 guidelines were published, according to McManus and colleagues, who identified a further
91 34 studies published between 2013 and 2018; just one of these scored less than 6 [6]. They
92 note, however, that the studies use a variety of sampling methods and quality definitions,
93 complicating the interpretation of results.

94 MEDQUARG became the basis for methodological guidelines for field surveys of medicine
95 quality published by the World Health Organization (WHO) in 2016 [7]. The guidelines
96 cover various sampling designs (convenience, simple or stratified random sampling, lot
97 quality assurance, and sentinel site monitoring), expressing a preference for random sampling
98 where feasible. More recently, researchers have proposed surveillance methods focused on
99 capturing medicines at highest risk of being substandard [8].

100 Broadly speaking, these sample designs aim to estimate the prevalence of substandard
101 medicines (which are made by registered pharmaceutical companies in regulated factories but
102 do not meet the quality standards set out in their market authorization paperwork, either
103 because they were poorly made or because they have degraded since manufacture) or of
104 falsified medicines. The latter are made, repackaged, or sold by criminals who seek
105 deliberately to misrepresent the identity, composition, or source of the product [9].

106 Prevalence of poor-quality medicines is usually expressed as the number of samples failing
107 testing, divided by the number tested, though some designs calculate the proportion of outlets
108 dispensing poor quality medicines [4].

109 MEDQUARG guidelines suggest reporting information on volumes of sales (potentially
110 allowing the risk of exposure to be calculated), and at least one study has weighted
111 prevalence by sales volume [10]. However, none of the WHO-proposed sampling designs
112 adequately captures the risk posed to patients. For a given level of physical harm caused by a
113 poor-quality medicine, the risk of exposure is determined not only by the prevalence of poor-
114 quality medicines, but also by the likelihood that a patient will consume the type and
115 particular brand of medicine at fault. A small number of brands or outlets may account for a
116 large fraction of patient consumption. In addition, consumption varies by type of medicine
117 and health condition; for example, medicines for chronic conditions are likely to be taken

118 indefinitely, while patients generally only take antimicrobials when experiencing an
119 infection.

120 *Cardiovascular and diabetes medicines*

121 Medicines for chronic conditions are under-represented among medicine quality studies; just
122 6.2% of the 48,218 tested medicines included in the WHO review were for non-
123 communicable diseases [2]. A 2019 review identified just five field-based quality surveys
124 including medicines for diabetes, covering 31 countries and totalling 527 samples, of which
125 6.8% were substandard or falsified[11]. Two of the five surveys used random sampling
126 designs. The medicine most commonly tested in the reviewed studies was metformin; 5.4%
127 of 258 metformin samples collected across four surveys failed at least one quality test.
128 glibenclamide featured in two surveys; 9.2% of 239 samples failed at least one test. A 2021
129 review of CVD medicine quality studies identified 27 prevalence surveys published between
130 1996 and 2020. The studies covered 23 active ingredients, in medicines collected in 28 low-
131 or middle-income countries [12]. Overall, 525 out of 3414 samples (15.4%) failed at least one
132 quality test to which they were subjected. However, the authors are careful to note: "we do
133 not state that 15.4% of cardiovascular medicines globally are SF [substandard or falsified]".
134 Some 63% of all CVD medicine samples were collected in Africa, many in a study that used
135 stricter criteria for tolerated deviations than permitted by the commonly-used United States
136 Pharmacopeia (USP) standards [13]. Failure rates in Africa were higher than in other regions.
137 Of close to 4,000 samples included in the two reviews, just 212 were collected in Southeast
138 Asia, and only four in Indonesia, the world's fourth most populous county, where prevalence
139 of hypertension and diabetes among adults aged 45 or more are 52.8% and 13.5%
140 respectively.[14] The four samples, collected between 2009 and 2012, were labelled as a
141 Japanese brand of candesartan; all were judged falsified [15].

142 *Cardiovascular disease prevention in Indonesia*

143 In an attempt to reduce the burden of CVD in Indonesia, the Ministry of Health has since
144 2012 supported a prevention and early detection program, including the prescription of
145 medication to prevent cardiovascular events [16]. Members of Indonesia's nation-wide health
146 insurance system *Jaminan Kesehatan Nasional* or JKN (which at the start of 2022 covered
147 235.7 million people, around 80% of the population) are entitled to free medication.
148 However, to access it they must follow cumbersome bureaucratic procedures, and medicines
149 are not always available [17,18].

150 Some Indonesians are thus obliged to buy these medicines, and medicines for other
151 conditions such as diabetes, from pharmacies or elsewhere; others choose to do so for
152 convenience or because they prefer branded medicines which are not provided free. Some
153 vendors do not comply with good pharmaceutical practice, for example in terms of
154 temperature control, or are not regulated by health authorities [19].

155 Since an auction-based, single-winner procurement platform for JKN medicines known as e-
156 catalogue was introduced in 2014, the volume of medicines procured by the state has risen,
157 and the price paid by Indonesia's public sector for many essential medicines has fallen
158 dramatically, to levels that producers complain are unsustainably low [20,21]. This, together
159 with a number of medicine falsification scandals in the private sector, raised concerns
160 (expressed in the news media and by professional medical associations) about the quality of
161 the medicines taken by Indonesian patients [22]. Public concern about medicine quality
162 appears at odds with regulatory data. Indonesia's medicine regulator Badan Pengawasan Obat
163 dan Makanan (BPOM) has been certified by WHO as Maturity Level 3, the second highest
164 level [23]. BPOM is relatively well resourced, with a 2020 budget of US\$107 million (72%
165 spent on oversight of medicines and food); over 5,000 staff; and laboratories in every
166 province. Annual post-market surveillance was suspended during the COVID-19 epidemic,
167 but in 2019 BPOM reported 340 of 17,123 sampled medicines were out of specification

168 (1.98%), far below the "1 in 10" intimated by WHO for low and middle income countries
169 [24].
170 Substandard cardiovascular and diabetes medicines may fail to deliver the correct dosage of
171 active pharmaceutical ingredient (API), thus increasing the risk of cardiovascular events or
172 compromising glucose control, and endangering patients. At a population level, the extent of
173 the threat depends on the number of patients exposed to specific brands of medicine that are
174 poor quality. Because quality may also be affected by handling and storage, the outlet from
175 which medicines are acquired may also influence exposure. However, sampling methods
176 designed to reflect population exposure have not, to our knowledge, been tried in medicine
177 quality surveys, and no studies of the quality of CVD or diabetes medicines in Indonesia
178 exist.
179 Aiming to fill this gap, we designed a exposure-based study that sampled the five medicines
180 most commonly used by patients at high risk for CVD in eight villages in Malang district,
181 East Java, testing them to ascertain whether they met the quality specifications listed in
182 United States Pharmacopeia and Farmakope Indonesia VI for percent of active ingredients
183 (assay) and for dissolution -- a proxy for availability of active ingredients in the body after
184 consumption. Four of these medicines target cardiovascular disease while one was a diabetes
185 medicine, reflecting frequent co-morbidity with the two diseases.

186 **Methods**

187 We report according to MEDQUARG guidelines. The annotated checklist is available at
188 <https://doi.org/10.7910/DVN/EBQYUB>, file 01.

189 **Study setting and background**

190 The study was based around eight villages in Malang district, a district of 2.5 million people
191 in Indonesia's second most populous province, East Java. The eight villages, which include
192 urban, semi-urban and rural areas, hosted previous research about CVD risk management.
193 [25,26] Researchers screened 99.24% of all adults aged ≥ 40 in the eight villages in 2018;
194 among the 22,093 people screened, 6,579 adults were identified as at high risk for CVD. For
195 the 2,534 who reported taking any CVD medicine, information was also collected about
196 which medicines they consumed, by API and dosage.
197 In the study area, patients at high risk for CVD and diabetes may acquire all study medicines
198 for free from public primary health centres, including village-level outreach posts. Most of
199 these medicines are procured through a single national government-run e-catalogue platform
200 and distributed from the District Medicine Warehouse. With rare exceptions (mostly for
201 patented medicines) all are unbranded generics identified by their international non-
202 proprietary name (INN). If the warehouse is out of stock, primary health centres may buy
203 their own INN medicines using capitation funds, a mechanism through which JKN pays
204 public primary health centres and private clinics that accept publicly insured patients a fee
205 per registered participant to deliver preventative services and health care, including
206 medicines.[27] The public hospital provides INN medicines free to JKN-insured patients,
207 paying out of a flat-rate diagnostic-related reimbursement package. Hospitals charge non-
208 insured patients for both INN and branded medicines. They may procure medicines for JKN
209 patients through e-catalogue, independently of the District Medicine Warehouse, or may buy
210 other brands directly from distributors.
211 Some 50.2% of Malang district residents were JKN members in 2020, well below the
212 national average of 79%. Of those reporting using outpatient services, just 32.7% said they
213 used JKN insurance [28,29]. Most of the remainder sought care from private health care
214 providers -- doctors, midwives or nurses. Many doctors provide prescriptions for medicines
215 which patients then buy from pharmacies. A rapid survey of health care providers (see below)

216 indicated that many doctors and midwives also sell prescription medicines directly to patients
217 themselves, although they are not authorized to do so in the study area. A further
218 unauthorised source of medicines are the medicine shops which sell prescription medicines in
219 violation of their over-the-counter-only licenses.

220 **Sample definition and sample size**

221 Following WHO norms,[7] we defined a single "sample" of medicine as:

- 222 • one product (API)
- 223 • of one dosage (strength and form)
- 224 • of one brand
- 225 • from one manufacturer
- 226 • and one batch number
- 227 • collected at one location, at one time.

228 Sampling of medicines differs from sampling of individuals, because if good manufacturing
229 and distribution practices are followed, quality should not vary within a batch. Exceptions
230 occur, for example when a genuine batch number is used on a falsified product, or if handling
231 and storage have varied significantly between samples, leading to differential degradation.
232 Broadly speaking, however, a single sample of a medicine should represent the quality of all
233 products of the same API, dose-form and brand, made by the same manufacturer, with the same
234 batch number, sampled in the same location at the same time. A single sample can thus
235 represent the risk of exposure to poor quality medicines for a large proportion of patients.
236 Our maximum target sample size, determined by budgetary constraints, was of 200 samples,
237 adequate collect at least one sample from all major sources of medicine in the study area (see
238 Figure 1). The Malang District Department of Health gave written permission for the study
239 (070/1102/35.07.103/2020). The study also received ethics approval from the Ethical
240 Committee, Ministry of Research, Technology, and Higher Education, Medical Faculty of
241 Brawijaya University (No.83/EC/KEPK/04/2020) and the Human Research Ethic Committee
242 of University of New South Wales, Sydney (HC200148).). The reflexivity statement in the
243 Supplementary Appendix provides further information about the relationship between
244 institutions. Patients were not directly involved in the design, conduct or reporting of this
245 study.

246

247 **Construction of sample frame: data sources**

248 To construct a sample frame reflecting the likelihood that a patient would take a particular
249 medicine, we collected secondary data from a variety of sources, and also conducted a rapid
250 survey of listed outlets and health care providers. The data, summarised in Table 1, were then
251 triangulated to develop a sample frame reflecting the likely distribution of patients
252 consuming different medicines, by INN status and source of acquisition.

253 We chose the study medicines based on a 2018 household survey data, in which over 6,500
254 high-risk patients reported which (if any) medicines they took to control blood pressure or
255 cholesterol.[25] We included all medicines and dosages taken by at least 10% of those
256 reporting medicine use. Because of high levels of co-morbidity, these included one medicine
257 (glibenclamide) to control blood sugar. In order of frequency the medicines were amlodipine,
258 simvastatin, captopril, furosemide and glibenclamide, all in oral tablets. The first three are
259 commonly prescribed in two dosages, the final two in just one, giving a total of eight
260 products (APIs and doses) to be sampled.

261 With the consent of the management (and where relevant, district health authorities), staff at
262 the District Medicine Warehouse (1/1) and a private medicines distributor (1/40) provided
263 information on volumes of the study medicines distributed each month. Two primary health
264 centres (2/5) and two pharmacies (2/75) provided data on volumes dispensed.

265 **Table 1: Data used to inform sample frame**

Data type	Source	Information provided	Time-frame
Household survey data	Provided by authors of Reference 25.	% of patients consuming medicine, by API and dose	2018
Detailed distribution or dispensing data	Secondary data provided by facilities	Volumes distributed or dispensed by API, dose, brand and month: district warehouse; two primary health centres; one private distributor; two pharmacies	April - October 2020
National aggregate sales volume	IQVIA public health	Sales volume by API and dose, by INN status and outlet sector (hospital or retail).	April - October 2020
Listing of pharmacies	District health office, verified by research team	Location of pharmacies and medicine shops in 8 study villages and 4 neighbouring market centres*; private health care providers in 8 study villages	2019 data received March 2020, verified October 2020
Listing of health care providers and medicine shops	Internet search and public directories, verified by research team	Location of private health care providers and medicine shops in 8 study villages	October – November 2020
Rapid survey of pharmacies and medicine shops	Primary data	Estimate of patients served per day with any study medicine	October – November 2020
Rapid survey of health care providers	Primary data	Estimate of patients served per day with any study medicine, medicines sold, source of medicines	November – December 2020

266 * These bordering locations are frequent shopping destinations for residents of the 8 villages
 267 The public health division of health information science company IQVIA provided data on
 268 sales volumes of study medicines in Indonesia, disaggregated by INN/branded status. These
 269 data are collected on a quarterly basis from a nationally representative panel of >1000
 270 pharmacies, 175 medicine shops, and 250 hospitals in both the private and public sectors.
 271 We obtained listings and contacts of pharmacies, medicine shops and health care providers
 272 from sources shown in Table 1. All were contacted in person, and the purpose of the study
 273 was explained. From pharmacies, we asked for consent to collect two pieces of information:
 274 the estimated number of customers served each day, and the estimated number who were
 275 buying medicines for blood pressure, cholesterol, or diabetes. Health care providers gave
 276 written consent for brief interviews around medicines provision and procurement. If they
 277 reported selling study medicines, we asked for details of dosages, brands, estimated monthly
 278 volume and source of medicines, and requested permission to recontact them for possible
 279 sampling (see below). Medicine shops were visited to ascertain if they sold study medicines.
 280 Most health care providers stated that they sourced their medicines from one of five
 281 pharmacies in the two cities nearest to the study area; we added these pharmacies to our
 282 sampling list.

283 **Construction of the sample frame**

284 We constructed a sample frame that reflects the risk that a patient will take any given
285 medicine, by active ingredient, source and brand. For all five study medicines (and eight
286 dosage forms), we triangulated detailed distribution or dispensing data from different sources,
287 dividing volumes by the average number of tablets taken by a patient each month to get an
288 estimated distribution of patients taking each medicine and dose, by branded status. The
289 maximum sample size of 200 was distributed across medicines and dosages to reflect the
290 percent of patients exposed to each medicine and dose.

291 The overall target was then distributed by sector and outlet type as shown in Figure 1. A
292 detailed explanation of how the same frame was constructed to reflect estimated exposure is
293 provided in the supplementary material, <https://doi.org/10.7910/DVN/EBQYUB>, File 02.

294 **Sample collection**

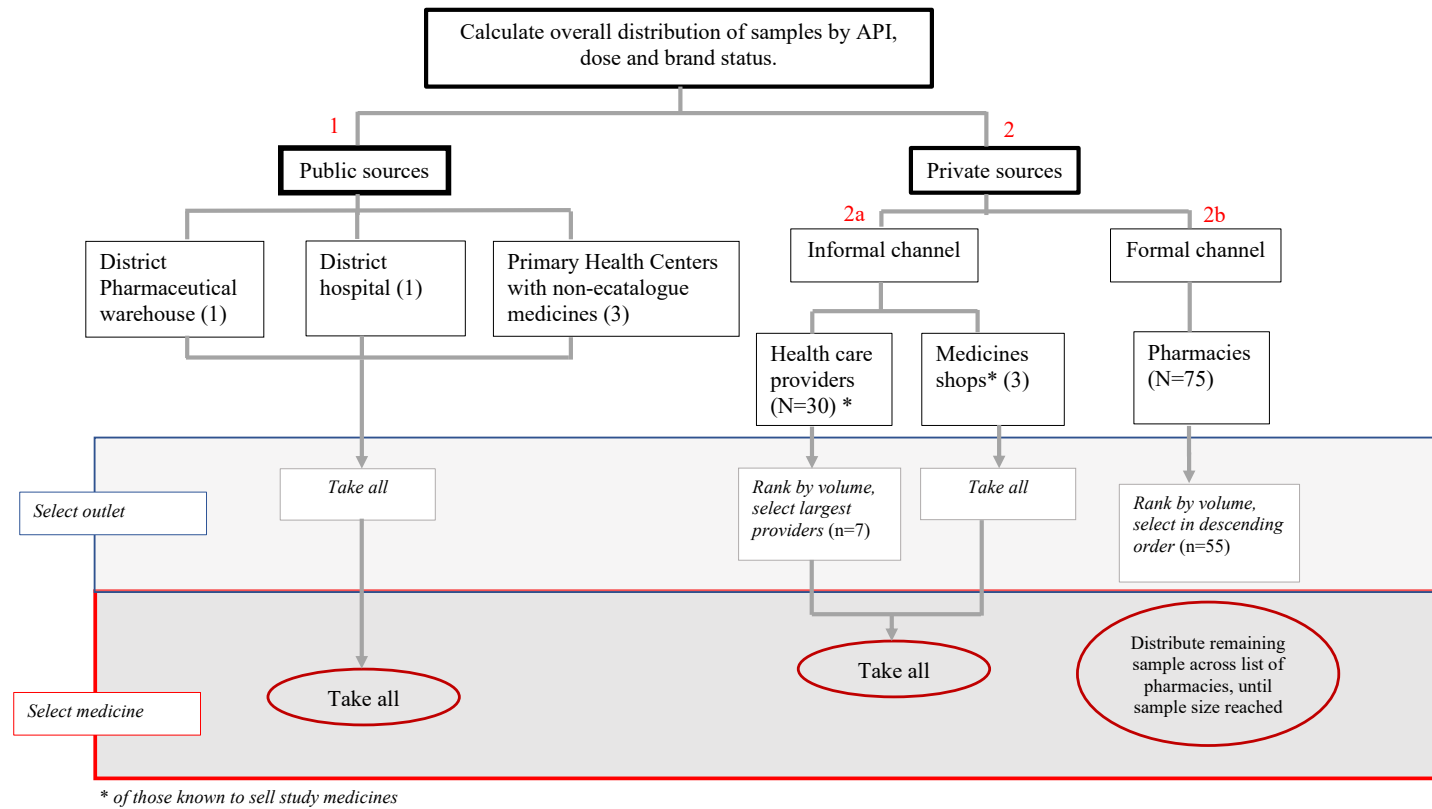
295 Samples were collected between February 3 – May 6 2021. Table 2 summarises sampling
296 methods by facility. Prescriptions were provided by a doctor collaborating with Brawijaya
297 University and were only presented if requested by pharmacists.

298 **Table 2. Sampling method by facility**

Facility	Sampling Method	Acquire by
District Medicine Warehouse	Overt, with letter from district health authorities	Replacement
Primary health centres	Overt, with letter from district health authorities	Replacement
District hospital	Overt, with letter from hospital director and formal request letter from university of Brawijaya	Purchase
Health care providers	Overt, with letter from district health authorities and formal request letter from university of Brawijaya	Purchase
Pharmacies and medicine shops	Mystery shopper, with prescription if requested	Purchase

299
300 For the mystery shopper approach, samples were collected by sample collectors trained using
301 role-play and common vignettes, such as buying medicines for an elderly relative. At each
302 outlet, they requested a single medicine, or a combination consistent with common clinical
303 needs. In order to approximate likely exposure, mystery shoppers did not ask for a specific
304 brand or manufacturer, but rather accepted pharmacists' suggestions. They did, however,
305 target either branded or unbranded medicines using signalling phrases such as "I'm looking
306 for something affordable" (for INN generics) or mention specifically that they want to buy
307 generic medicines. For the premium/branded, the mystery shoppers will mention that they
308 want a "patent" product, the term commonly used in Indonesia to signify a premium product.

309 If the sample frame called for clinically incompatible combinations, or repetitions (for
310 example an INN and a branded version of the same product) from a single outlet, different
311 mystery shoppers were used.



312
313

Figure 1. Steps undertaken in construction of sample frame

314 All the study medicines are normally packaged in strips/blisters of 10 tablets. We collected
315 40 tablets per sample; if 40 tablets were not available, we accepted a minimum of 30 tablets.
316 On exiting the outlet, sample collectors put each sample in a sealable plastic bag marked with
317 a pre-printed barcode. The barcode was scanned and field-related data were entered into a
318 form pre-loaded onto the shoppers' mobile phones, using open-source KoboCollect software
319 [30]. Further data entry, including product photographs and details of market authorisation
320 holder, manufacturer, registration number and expiry date took place at the end of the day,
321 using a second form linked by the same barcode. The ODK-format data collection forms are
322 available at <https://doi.org/10.7910/DVN/EBQYUB> Files 03 and 04.

323 Research team members inspected packaging visually. No reference packaging was available
324 for comparison, so visual inspection, using a magnifying glass as necessary, was limited to
325 checking for anomalies such as mis-spellings, and discrepancies in formatting of batch
326 numbers and expiry dates.

327 **Sample handling and testing**

328 Samples were stored in a temperature-controlled environment for an average of 21 days,
329 batched and sent (with a temperature logger) for testing to PT Equilab International, an
330 ISO/IEC 17025-certified private laboratory in Jakarta, according to USP 42 NF 37
331 monograph and using USP reference standards. Methods were validated for all APIs before
332 testing. The full protocols for each molecule are available at
333 <https://doi.org/10.7910/DVN/EBQYUB>, Files 09-14.

334 Briefly: laboratory staff inspected tablets visually, noting shape, colour, lettering and other
335 defining characteristics. Chemical analysis was performed for determination of identity, assay
336 (% of labelled active ingredient) and dissolution (% of labelled active ingredient in the tablet
337 dissolved over time). For all APIs, assay testing was by high-performance liquid
338 chromatography, (HPLC -UV; Waters, Alliance 2695 with UV Detector 2489 for amlodipine,
339 glibenclamide, furosemide and simvastatin; Waters, Alliance 2695 with Photodiode Array
340 Detector 2996 for captopril), while dissolution was by Spectrophotometer-UV/VIS
341 (Shimadzu UV-1800) with the exception of glibenclamide, where dissolution was tested by
342 HPLC (Waters, Alliance 2695 with UV Detector 2489).

343 No testing was performed for uniformity or impurities.

344 Staff conducting the tests differed from those handling the packaged product, but could see
345 any defining marks on tablets or capsules. Testing took place April – August 2021, an
346 average of 95 days after sample collection.

347 Results from the certificate of analysis were entered into a database by study staff, using the
348 sample barcode as identifier. Raw dissolution data were added to the database at a later date,
349 delaying stage 2 dissolution. Where necessary, this was undertaken in March 2022.

350 **Analysis**

351 The KoboCollect field data form, product data form and the laboratory data were merged on
352 barcode number using Stata 17. Stata 17 was also used for reproducible cleaning and coding,
353 and to generate simple descriptive statistics and graphs. The merge and analysis code in Stata
354 format are provided at <https://doi.org/10.7910/DVN/EBQYUB>, Files 05 and 06.

355 **Table 3. Limits of compliance, United States Pharmacopeia 42 [% of declared content],**
356 **and average tablets per month used in sample frame calculations**

API	Assay (%)	Dissolution [Q] (%)	Stage 1 dissolution [Q+5] (%)	Tablets per month
-----	-----------	---------------------	-------------------------------	-------------------

Amlodipine	90-110	75	80	30
Captopril	90-110	80	85	60
Furosemide	90-110	80	85	30
Glibenclamide	90-110	70	75	90
Simvastatin	90-110	75	80	30

357

358 Table 3 shows the definitions used for compliance with specifications, following USP 42 NF
359 37 limits, along with the average number of tablets taken by a patient in a month.

360 If any one of six pills included in stage 1 dissolution fell below the Stage 1 threshold of Q+5,
361 we continued to stage 2 testing using additional 6 tablets. The sample was considered out of
362 specification if:

- 363 • The assay fell outside the stated limits OR
- 364 • Any single tablet fell below the Q threshold -25 in dissolution testing OR
- 365 • Any 2 tablets fell below Q threshold -15 in dissolution testing OR
- 366 • The average of 12 tablets fell below the Q threshold in stage 2 dissolution testing

367 Results

368 Details of sample frame construction following an exposure-based approach and more
369 detailed information about target sample numbers by medicine, dose and branded status are
370 reported at <https://doi.org/10.7910/DVN/EBQYUB>, File 02.

371 Table 4 summarises the number of samples collected from different sources, by INN-branded
372 status

373 **Table 4. Sources of samples collection, by INN or branded status**

Source	Sector	Outlets	INN samples	Branded samples	Total samples
District warehouse	Public	1	6	0	6 (2.9%)
District hospital	Public	1	8	5	13 (6.4%)
Primary health centres	Public	2	3	0	3 (1.5%)
Doctor	Unregulated	4	7*	12	19 (9.3%)
Midwife	Unregulated	3	3	5	8 (3.9%)
OTC medicine shop	Unregulated	2	6	0	6 (2.9%)
Wholesale pharmacy	Private	5	18	8	26 (12.7%)
Other pharmacy	Private	55	71	52	123 (60.3%)
Total		73	122 (59.8%)	82 (40.2%)	204 (100%)

374 OTC: Over-the-counter

375 *Six samples collected, but one sample contained one strip with different package printing, which was tested
376 separately.

377

378 In the private sector, we collected a total of 42 unique INN products, and 32 different branded
379 products. Including the public sector, we collected 83 different products (API, dose and
380 brand/market-authorisation holder). All the medicines collected were manufactured in

381 Indonesia, and all had valid national market authorisations. Thirty-five samples were
382 packaged in blisters (of which 4 had secondary packaging), the remaining 186 (82.9%) in foil
383 strips.

384 Mean time to expiry from the date of collection was 674 days in the public sector, 712 days
385 in pharmacies, and 773 days from unregulated sources (private health care providers and
386 medicines shops, who are not technically permitted to sell prescription medicines to patients
387 in Indonesia), with a minimum of 162, 185 and 54 respectively. All samples were tested
388 before expiry.

389 Retail prices varied by over 100-fold between brands for some medicines, and even the
390 identical product saw up to 10-fold differences in price between retail outlets. Analysis of
391 these data will be reported in detail elsewhere.

392 **Observations from the field**

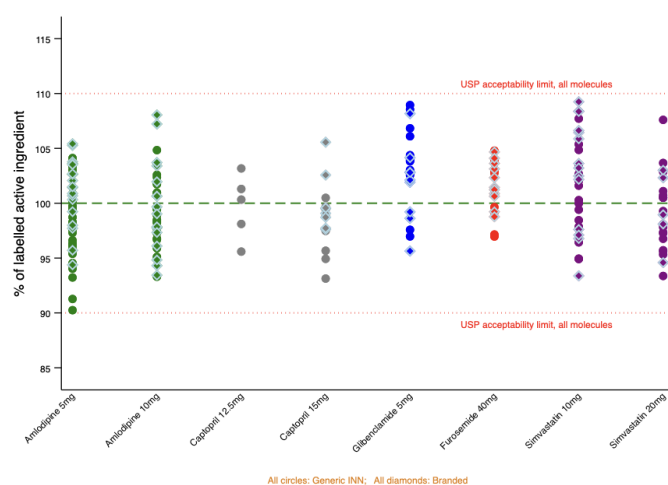
393 We found fewer branded generics than expected on the basis of the national market data we
394 used to construct the sample frame (details at <https://doi.org/10.7910/DVN/EBQYUB>, File
395 02). Prescriptions are technically required for all study medicines, but sample collectors were
396 instructed to present prescriptions only if requested. None of the 55 retail pharmacies we
397 bought medicines from asked to see a prescription for any medicine.

398 Daytime temperatures in the study area at the time of data collection ranges between 28 and
399 30 degrees centigrade, bordering on the unsafe range for storage of medicines. Packaging for
400 all study medicines stipulated that the product should be stored below 30°C. Only 2 of 60
401 pharmacies (one wholesale and one other) were airconditioned at the time of our visits.
402 In basic visual inspection, we found a few anomalies, such as strips with two to three tablets
403 in a one-tablet pocket, expiry dates that easily rubbed off, and one medicine with identical
404 batch numbers but with variations in printing techniques for batch number and other
405 information.

406 **Pharmacopeial testing results**

407 The entire dataset including laboratory results, with brand names masked according to the
408 terms of the ethics approval, is available in xlsx format at
409 <https://doi.org/10.7910/DVN/EBQYUB>, File 07.

410 All samples contained the labelled active ingredient. Figure 2 shows the results of assay
411 testing, by API and dosage. Generic INN products are represented by circles, and branded
412 products by diamonds.

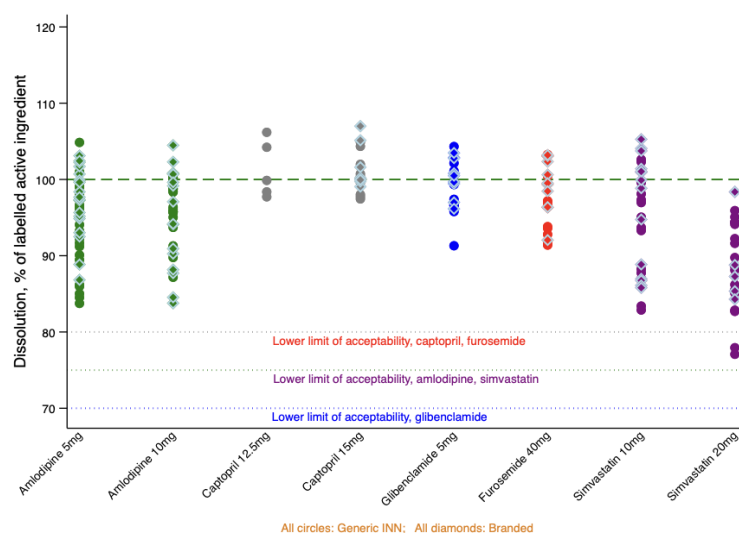


413
414
415

Figure 2: Results of assay testing, by API, dose and INN status

416 Assay values ranged from 90.3 to 109.3%, meaning that all samples fell within the USP 42
417 NF 37 (and Farmakope Indonesia VI) criteria for acceptability which is 90-110%.

418 Dissolution testing was performed on 203/204 samples. Dissolution parameters differ for
419 different study medicines, as shown in Table 3. While the certificate of analysis showed that
420 average dissolution of the first 6 pills exceeded the required value for all samples, a later
421 review of raw data showed that for 16 samples, not every individual met the overall
422 acceptability threshold plus 5%. Twelve of these samples passed at second dissolution,
423 meaning that a total of 199 samples were considered acceptable by USP 42 NF 37 and
424 Farmakope Indonesia VI standards. Limited remaining tablets meant we were not able to
425 perform Stage 2 dissolution for the remaining four samples. One had a "twin" sample of the
426 same batch which passed at Stage 1 dissolution. Two more were of a single batch of
427 simvastatin which averaged 81.1% at Stage 1 dissolution, well above the acceptability limit
428 of 75%. For the fourth sample, also simvastatin, the average dissolution value for stage one
429 testing was 87.7. Figure 3 shows the final dissolution results by API and dose.



430
431 **Figure 3: Results of dissolution testing, by API, dose and INN status**

432 Results were shared with the national and provincial offices of BPOM within a month of the
433 completion of assay and stage 1 dissolution testing.

434 Discussion

435 In our study of 204 samples of 5 common CVD medicines sampled from public, private and
436 informal sources, all were registered; within their expiry dates; all met USP 42 and
437 Farmakope Indonesia VI specifications for assay; and 199 met specifications for dissolution.
438 We were unable to complete dissolution testing for the remaining 5 samples but there were
439 no grounds to expect extreme deviations.

440 The use of mystery shoppers reduced the likelihood that retail sales staff would selectively
441 provide better quality products, while our take-all approach for medicines provided free in
442 public facilities prevented sampling bias there, despite overt sample collection. However,
443 study limitations mean we cannot conclude that the risk of exposure to poor quality CVD
444 medicines for patients in the study area is zero. We did not test for impurities. Sample
445 collection from doctors and midwives was overt, so although we bought a sample of every

446 variety of study medicine they offered, it is possible that they held back medicines they
447 suspected were of poor quality. However, mystery shoppers also obtained samples of
448 medicines from the pharmacies that doctors and midwives reported buying from, with similar
449 results, suggesting that if bias did exist, it was not considerable.

450 We did not sample from the internet, or from any of the five private general hospitals in the
451 study area. We do not have data allowing us to estimate the volume of study medicines sold
452 through these channels. However, the additional per-visit consultation fee would likely
453 prevent many patients from choosing to buy medicines for a chronic condition from private
454 hospitals.

455 Though we checked registration status, we did not have reference packaging, or perform
456 detailed packaging analysis. We are thus unable to rule out falsification, including extension
457 of expiry dates or repackaging of quality INN products to imitate a more expensive brand.
458 However, there were no out-of-specification products on either assay or dissolution among 83
459 unique products sampled from 73 outlets, including the district warehouse (which supplies
460 most of the public sector), all of the wholesale pharmacies mentioned as sources of medicine
461 by health-care workers who sell to patients, and 73% of retail pharmacies in the area,
462 including all of the highest volume sellers. We can thus state with confidence that the risk of
463 exposure to poor quality versions of the study medicines is very low in this semi-rural setting
464 in one of Indonesia's most populous provinces. The situation may differ in other areas of
465 Indonesia. Overall, however, our findings support reports from BPOM's post-market
466 surveillance which suggest that the overwhelming majority of medicines in the regulated
467 supply chain in Indonesia, including very low-cost unbranded generics in public facilities,
468 meet quality standards.

469 Our findings differ from those of many previous field surveys in LMICs. The five diabetes
470 prevalence surveys identified by Saraswati et al. in 2019 included 527 samples collected from
471 31 countries, 382 of them from LMICs. The failure rates in the latter group was 8.6%,
472 compared with 2.1% in high income countries. Within LMICs, failure ranged from 0 (in
473 Chile, CIS, India Pakistan, Thailand and Turkey) to 37.5% in Argentina. However, samples
474 sizes were mostly in single figures. While the failure rate reported for Indonesia was 25%, the
475 1993 study in question included just four samples from the country, all of glibenclamide. The
476 27 prevalence surveys for CVD medicines reviewed by Do et al (2021) included 1,889
477 samples collected in lower-middle income countries, including Indonesia. In this sub-set,
478 prevalence of failure was 16.5%. By country it ranges from 100% failure in Indonesia (4/4
479 samples) to 0.6% of 521 samples in India (the only other country in the list with a Maturity
480 Level 3 regulator and limited imports of generic medicines) [15,31,32]. In the lower-middle
481 income group, 63.5% of samples were from Africa, with a failure rate of 24.4%. The
482 remainder were from Asia, with a failure rate of 2.9%.

483 We thus find it difficult to agree with the conclusions of Redfern et al. in their 2019 study of
484 antihypertensive drugs in lower-middle income Nigeria, that "a representative sample from 3
485 chosen Nigerian states is highly relevant and potentially generalizable across Africa and other
486 developing countries [33]."

487 Indonesia has a large domestic pharmaceutical industry, and all authorised versions of the
488 study medicines are manufactured locally [34]. Currently, the global market for medicines
489 works on a "buyer beware" system, and national regulatory authorities are not responsible for
490 the quality of medicines made for export [35]. Unless countries that rely heavily on imported
491 medicines can police their quality at import, they may thus be exposed to substandard
492 medicines produced elsewhere without adequate regulatory oversight. We speculate that
493 Indonesia's success in securing the quality of CVD medicines may be in part related to the
494 production-to-market supervision by a single, relatively well-resourced regulator. However,
495 we also note that not all regulations or best practices are observed; we were able to buy all

496 samples without prescriptions, some from sources not permitted to sell these medicines, and
497 most from pharmacies that were not temperature-regulated.
498 Initial exploration of pricing data indicates that same company may sell a product at very
499 different price points, often producing one or more brands as well as INN versions. This
500 allows for cross-subsidisation across a company's portfolio, potentially protecting the quality
501 of very low-cost products in the Indonesian market. We plan further investigation of this
502 topic.
503 Obtaining requisite permissions to collect secondary data for the construction of the
504 exposure-based sample frame, as executed, was time-consuming but feasible. Because no
505 substandard products were found, we were unable to proceed with more detailed estimates of
506 exposure as originally planned. Schiavetti and colleagues, weighting the results of their study
507 of medicines sampled from distributors in the Democratic Republic of Congo by market size,
508 found that those with larger distributions were more likely to be of good quality [10]. We
509 suggest exposure-based sampling could be repeated in settings known to have more poor-
510 quality products, in order to better estimate the true population exposure to substandard and
511 falsified medicines.

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518 United States Pharmacopeia for providing testing standards at a discounted price for
519 academic research.

520 **Conflict of interest**

521 The authors declare that they have no conflict of interests.

522 **Data availability statement**

523 The sample level data are available at <https://doi.org/10.7910/DVN/EBQYUB>, File 07. In
524 accordance with the terms of the ethics approval, names of individual manufacturers and
525 batch numbers are masked, product registration numbers removed, and outlets grouped by
526 type. Data are provided for reuse, with the expectation that users will cite the dataset and this
527 paper.

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530 substandard and falsified medical products. Geneva, Switzerland: : WHO 2017.
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