Review

Impurities in Pharmaceutical Products: Review on Qc Practices in DRCongo

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Abstract: Background: The World Health Organization estimates that more than 10% of the medications in use in developing nations are fake. False active ingredients or contaminants that pose a risk to public health can be found in counterfeit medications. **Objective:** The aim of this research was to evaluate the applicability of the quality control procedures that Kinshasa's reference laboratories employ. **Methods:** The analysis managers of three approved laboratories were chosen, and they were questioned regarding the kinds of analyses they performed, the tools they had, and the experience of their staff. **Results:** It was discovered that all of these labs could identify and measure active substances. However, only the majority active ingredient is quantified in medications containing many active compounds. Furthermore, none of the labs look into and measure contaminants, leftover solvents, or distinguish between enantiomers in final goods. These laboratories have been determined to possess the qualified personnel and up-to-date equipment necessary to perform all the tests necessary to identify and quantify contaminants ; yet, all of this potential is still underutilized. **Conclusion:** To guarantee the population receives the high-quality medications it is important to ensure that public health authorities aware of international quality control requirements commitment from those laboratories and are rigorously adhered to and implemented.

Keywords: Counterfeit drugs; impurities; Residual solvents; Potential genotoxic impurities; Human carcinogens

Introduction

Counterfeit, falsified, or fraudulent drugs are those that have faults caused by a deliberate act of fraud during manufacturing and/or distribution. The offenders' purpose is to defraud everyone (distributors, authorities, prescribers, patients, etc.) in order to make money [1]. Falsified medicines can be obtained through both informal and formal channels [2], and they can contain both generic and reference compounds. The falsification could involve the active ingredient (drugs with questionable quality and quantity), the packaging (extension of the expiration date), or the drug's presentation and composition being identical to those of the reference drug (drugs with a lack of traceability) [3,4].

Substandard pharmaceuticals are traceable drugs that have accidental faults caused by negligence or technical inadequacy (lack of modern equipment) during the manufacture or distribution process. These pharmaceutical goods may have dosage issues (under- or overdosage),

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active component instability, bioavailability, contamination with other chemicals in the manufacturing environment, lack of sterility, poor labeling, and so on [2]. Counterfeit and substandard drugs are currently a major public health issue, claiming thousands of lives each year, with Africa bearing the brunt of the cost. Statistics reveal that around one-third of all drugs circulating on the continent are counterfeit [3]. Several factors contribute to the prevalence of inferior and fraudulent medicines on the African market. Studies have shown that the risk of finding these medicines in the distribution chain is high, due to : the absence or weakness of National Regulatory Authorities in the health system, weak or outdated legislation, lack of effective quality control of medicines, lack of modern technical capacity, and even conflicts of interest and corruption [3,4].

Poor(lower)-quality drugs can induce negative effects that may have major consequences:

- Fake ingredients (false API) that can result in treatment failure.
- Under-dosed medications which can worsen the patient's health, increase the likelihood of antibiotic resistance, with direct impact on life which can possibly cause death.
- Active component overdosage can result in patient intoxication, erode patient trust in the healthcare system, and cause established treatment regimens to fail.
- Companies that manufacture illegally duplicated pharmaceuticals may face significant financial losses, potentially hindering future research and production of new drugs.
- And finally, substandard drugs can cause the manufacturer's reputation to suffer, potentially driving away many of its customers and reducing sales.

Several tragedies in Africa show the terrible consequences of counterfeit and substandard medicines:

- In Cameroon in 2019, an antidiabetic (glibenclamide) was used as an antihypertensive together with hydrochlorothiazide. Victims of this false medicine experienced hypoglycemia episodes, which could lead to death. During the immunization campaign in Niger that year, huge batches of a fake meningitis A vaccine (Mencevax ACWY) were discovered [5].
- As if that weren't enough, the World Health Organization (WHO) warned in October 2022 that cough syrups manufactured by the Indian company Maiden Pharmaceuticals Limited were linked to the deaths of 66 Gambian children. Subsequent quality testing on these samples indicated that they were contaminated with substantial amounts of ethylene glycol and diethylene glycol, both hazardous and potentially lethal compounds [6].

Another risk of poor or falsified drugs is that they may include contaminants that might harm health by causing teratogenic, mutagenic, or carcinogenic effects [7].

- In April 2021, the European Directorate for the Quality of Medicines and Healthcare (EDQM) notified the potential existence of mutagenic azido contaminants in several Sartan-class medications used to treat hypertension and heart failure [8].
- In May 2021, Health Canada issued a warning to the public about specific batches of irbesartan, losartan, and valsartan after testing confirmed the presence of azido contaminants at levels over the permitted limit. Long-term exposure to these azido impurities that above the permissible level may raise the risk of cancer and mutation [4].

Pharmaceutical impurities are chemicals that coexist with the active pharmaceutical ingredient (API) or can arise during the API's manufacture or aging and formulation. Even small amounts of these contaminants can have an impact on the drug's efficacy and safety. Drug safety is determined by both the toxicological qualities of the active substance and the impurities it contains. Because impurities in APIs can have an impact on the safety and quality of pharmaceutical products, investigating and quantifying API impurities must be a top priority in medication quality control [9].

Impurity profiling in pharmaceuticals is currently required, as the presence of impurities, even in trace amounts, can pose a risk to human health. Numerous pharmacopoeias, including the European (EU) [10], American (USP) [11], Indian (IP) [12], and British (BP) [13] Pharmacopoeias, have developed monographs outlining the minimal levels of permitted contaminants in pharmaceutical products for human consumption. Compliance with the monographs included in pharmacopoeias

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on impurity profiling is becoming a responsibility that regulatory bodies must prioritize, as this issue affects national interests [14,15]. The methods described by these monographs for identifying and quantifying these impurities must be exceedingly sensitive, as impurities are frequently detected in trace amounts in pharmaceutical goods. These cutting-edge techniques include: High-Performance Liquid Chromatography (HPLC), Ultra High-Performance Liquid Chromatography (UHPLC), Liquid Chromatography Mass Spectrometry/Mass Spectrometry (LCMS/MS), or Gas Chromatography Mass Spectrometry (GCMS)...Nuclear Magnetic Resonance (NMR), High-Performance Liquid Chromatography (HPLC), Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (FTICR-MS).

This modern technology remains prohibitively expensive, making it inaccessible to many scientists, particularly those in underdeveloped nations. Furthermore, these new techniques still require skilled staff for efficient use, which might drive up the cost of analysis and render medicines inaccessible to Africa's poor population.

Obtaining chemical substances in their completely pure condition is nearly impossible. Indeed, even reference substances contain minute amounts of contaminants. It is possible to acquire chemicals of appropriate purity if proper precautions are taken at various stages of production [16]. Thus, reaching an acceptable level of purity for pharmaceutical compounds is heavily reliant on the cost-effectiveness of the process, the efficacy of the purification method, and the stability of the finished product. Obtaining high-purity, pharmacologically safe pharmaceutical products would necessitate a significant investment in capital, modern technology, and skilled labor. Purification of chemical components is thus a very expensive process that will raise the price of the drug [17].

The pharmaceutical industry is especially vulnerable to fraud and corruption due to the high market value of pharmaceutical products. Because the objective of individuals who produce low-quality pharmaceuticals is to make more money, they will undoubtedly not invest the money required to achieve an acceptable level of purity in the drugs they give to the public, resulting in a significant chance of detecting contaminants in low-quality drugs [17].

The Democratic Republic of Congo (DRC) remains a destitute country that has been at war for 30 years. Its healthcare system has yet to receive a big budget, while the war effort and institutional lifestyles absorb a significant portion of the national budget. For example, the draft finance law for the fiscal year 2024 allocates only 9.2% of the national budget to health [18].

This study was initiated in this context, with the goal of assessing the relevance of quality control testing of pharmaceutical products performed by approved laboratories in the city and province of Kinshasa, and, if necessary, drawing the attention of regulatory authorities to potential flaws in our quality control system and the risks posed to the population.

Materials and Method

A survey of approved laboratories in the city of Kinshasa Province was conducted to determine the adequacy of their procedures for assessing pharmaceutical items. A total of three approved laboratories (Lab01, Lab02, and Lab03) were chosen, and their pharmacists in charge of drug analysis and quality control were interviewed using a prepared questionnaire.

The study took place over two months, from September 3 to November 3, 2023. During this time, we were able to conduct in-depth interviews with pharmacists and staff members from participating laboratories. These interviews were semi-structured, which allowed us greater freedom in the questions asked and a more tailored approach to each participant.

Additionally, we took care to protect the participants' confidentiality and anonymity by gaining their prior approval for the recording and use of the information they provided.

Our methodological approach allowed us to obtain accurate data, which served as a solid foundation for analyzing our findings.

Furthermore, a review of the literature on contaminants was conducted on some medicinal goods regularly consumed and available in Congolese marketplaces. In fact, the research focused on identifying the contaminants that these medications may contain and their potential effects on human

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health. Finally, a final investigation was conducted on the reappearance of specific chronic diseases that are likely to be caused by contaminants in certain pharmaceutical items, as well as a cause-and-effect analysis.

Results

I. Physico-chemical testing of medicinal products

Identifying and measuring the active ingredients in the medications to be tested is a critical step in pharmaceutical quality assurance. This phase ensures that prescribers and patients are dealing with the correct products and quantities. This ensures disease treatment as long as the patient follows the dosage prescribed by his or her doctor.

The identification and measurement of contaminants, degradation products, and residual solvents in pharmaceuticals has become vital, following the scandals already documented globally due to their harmful nature [10–12]. Today, global organizations and reference books are establishing criteria to minimize the percentage of contaminants in medicines. Another key problem is differentiating the enantiomers of certain medications, which may exist as racemic mixes or have the active enantiomer replaced by the non-active enantiomer. This can pose a serious risk, as one of the enantiomers may be more harmful than the other (as in the case of thalidomide). Table 1 displays the results of physicochemical tests, as well as impurity and enantiomer analysis.

Table 1. Physico-chemical tests and impurity analysis.

Questions for assessment	Lab01	Lab02	Lab03
Identification and quantification of the active ingredient	Yes	Yes	Yes
Identification and quantification of impurities	No	Yes	No
Identification and quantification of residual solvents	No	No	No
Identification and quantification of all active ingredients present in the medicine	No	No	No
Identification of enantiomers in raw materials	No	Yes	No
Identification of enantiomers in finished products	No	No	No

II. Identification of available modern equipment

The presence of impurities in pharmaceutical products is a severe issue not only for human health but also for medication stability. The search for contaminants and their characterisation are thus critical tasks in medicine quality management. Impurities are detected in trace amounts, Hence, there are limits above which they must be reported, identified, or quantified. All of this is only possible if laboratories have access to cutting-edge, specialized equipment. The Table 2 presents the results for the equipment available in Kinshasa's reference laboratories.

Table 2. Available and operational peak equipment.

Questions for assessment	Lab01	Lab02	Lab03
Do you have an HPLC available and operational ?	Yes	Yes	Yes
Do you have a CE available and operational ?	Yes	Yes	Yes
Do you have a GC available and operational ?	No	No	No
Do you have a LC-MS available and operational ?	No	No	No
Do you have people qualified to handle them?	Yes	Yes	Yes
Do you use this equipment for routine analyses as recommended by pharmacopoeias?	No	No	No

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III. Impurities found in some medicines commonly used in Kinshasa

Impurities or pollutants in pharmaceutical products, even in trace amounts, might undermine their stability and efficacy, posing a risk to public health. The International Conference on Harmonization's (ICH) rules provide for the control of contaminants in final pharmaceutical compounds [19]. Because it is not always possible to entirely eliminate contaminants from pharmacological compounds during synthesis, producers frequently attempt to reduce their presence after synthesis is completed. Nonetheless, it is difficult to remove structurally bound contaminants from the final product, and doing so incurs significant costs. As a result, pharmaceutical companies are dedicating an increasing amount of effort and money to developing new, effective procedures for minimizing contaminants in the final product [20].

1. Paracetamol

Acetaminophen, or paracetamol, is the most commonly used painkiller. It is used to treat a variety of pains (headaches, toothaches, joint discomfort, illness, menstrual cramps, ...). It is also effective in treating fever related to other sickness such as malaria, etc. However, Paracetamol contains a variety of impurities :

1.1. p-aminophenol or 4-aminophenol (PAP)

The 4-aminophenol, also known as p-aminophenol (PAP), is a significant impurity of paracetamol that can occur during the production process or as a result of poor storage conditions [21]. PAP is a nephrotoxic and teratogenic metabolite of paracetamol that can cause methemoglobinemia even at low levels [22]. Because of its high toxicological profile, drug regulatory organizations such as the European Medicines Agency (EMEA) and the Food and Drug Administration (FDA) have set a limit of 50 ppm (0.005% w/w) for PAP impurities in drugs [23,24].

1.2. p-Chloro-acetanilide

Another acetaminophen impurity is p-chloro-acetanilide (PCA). Numerous investigations have found that certain chloro-acetanilide derivatives are carcinogenic and can damage genetic material [14].

1.3. 4-nitrophenol

It is a precursor of 4-aminophenol, and is regarded as a possible contaminant in paracetamol. Given the documented toxicity of 4-aminophenol, the British Pharmacopoeia limits the maximum concentrations of 4-aminophenol and 4-nitrophenol to fewer than 0.1% and 0.05% (w/w) [25].

2. Drugs of the Sartan class [26–28]

2.1. Azido impurities

Azido impurities are pollutants that can be generated and integrated into drug substances or drug products by using catalysts, reagents, raw materials, or solvents during the drug substance manufacturing process. They belong to the Sartan class of medications (irbesartan, azilsartan, losartan, valsartan, olmesartan, candesartan, telmisartan, etc.) and are known mutagens and carcinogens.

2.2. N-nitrosoalkylamine

Among them we can cite N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosoethylisopropylamine, N-nitrosodibutylamine, and N-nitroso-N-methyl-4-aminobutyric acid that are all known as carcinogenic compounds and which are commonly considered like impurities found in generic drug substances and drug products belonging to the Sartan-class drugs.

2.3. Potential genotoxic impurities

Methyl N-((2′-(1H-tetrazol-5-yl) -[1,1′-biphenyl]-4-yl)-N-nitroso-L-valinate and methyl N-nitroso are two potentially genotoxic impurities found in Valsartan.

3. Metronidazole benzoate [29,30]

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Metronidazole is a basic medicine used to treat anaerobic bacterial and protozoal diseases. Metronidazole is now a widely established antibacterial that is used to treat a variety of illnesses, including amoebiasis and bacterial septicemia.

3.1. Benzoic acid

Benzoic acid serves as a starting ingredient in the production of metronidazole benzoate. The breakdown of metronidazole benzoate yields benzoic acid. When the residual content of respirable suspended particles surpasses the tolerable level of 0.1%, it causes toxicity in the lungs, neurological system, and mucosal membranes. Repeated or extended exposure to the chemical may cause organ damage.

3.2. Nickel

When used as a catalyst in the manufacture of metronidazole, the residual respirable suspended particle content can surpass 20 ppm, causing hazardous consequences such as dyspnea, asthma, acute pulmonary edema, and pulmonary fibrosis [31].

4. Metformin and Ranitidine

These three medicines also include N-nitrosodimethylamine (NDMA), which is classified as a probable carcinogen and genotoxic in vivo and in vitro by the International Agency for Research on Cancer (IARC) [32].

4.1. Metformin

Metformin is the most often given pharmacological treatment for type 2 diabetes, either alone or in combination with insulin or other hypoglycemic agents [32]. In December 2019, NDMA was found in metformin pharmaceuticals in Singapore, prompting a voluntary recall of the drug product; by January 2023, 17 separate medication manufacturers in the United States had recalled a total of 283 batches of metformin for the same reason. Nitrites in excipients, nitrites in manufacturing water, and nitrocellulose in packing materials may all operate as nitrosating agents [33]. Unfortunately, metformin is still freely available in the DRC.

4.2. Ranitidine

Ranitidine is a histamine H2-receptor antagonist used to treat peptic ulcers. It was one of the most commonly given medications in the 1980s. Proton pump inhibitors have gradually supplanted it, yet it still ranks among the top 15 prescription medications in some European nations [34].

In 2020, ranitidine, better known under the brand name Zantac, virtually disappeared from the world market after several regulatory bodies, including the US Food and Drug Administration, recommended its withdrawal following contamination by NDMA, a known animal carcinogen [35]. And Ranitidine has just been withdrawn from the Congolese market on February 19, 2024.

5. Enantiomers

The presence of one (or more) asymmetrical carbon(s), which create chiral center(s), can provide a variety of medicinal or poisonous effects. In many cases, one of the isomers is employed to treat a specific ailment, whilst the other may have adverse effects. Examples include:

5.1. Levo-dopa

Levo-dopa is a dopamine precursor used to treat Parkinson's disease, and the medicine exclusively contains the (S)- (-) enantiomer. The opposite enantiomer, dextrorotatory (R)-(+), is poisonous and can cause agranulocytosis. As a result, it must not be present in the final medicine, or at least in trace amounts that do not exceed tolerable levels [36].

5.2. Bupivacaine

Bupivacaine, which is utilized as an anesthetic due to its (S)- (-) isomer, is sold as levobupivacaine. The (R)- (+) enantiomer poses a risk to the heart and central nervous system.

5.3. Thalidomide

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The drug is utilized as a sedative and hypnotic during pregnancy because of its (R)-(+) enantiomer, while the (S)-(-) enantiomer has a teratogenic impact via its hydroxylated metabolite [37].

5.4. Dexambutol

Dexambutol, also known as (S, S) -(+) -ethambutol, is the only isomer employed as an antituberculosis medication because the other isomers, (R, R)-(-)-ethambutol and meso (R,S) isomers, are considered too toxic [36].

5.5. Quinin

Quinin is one of the medicines suggested by the National Malaria Control Program to treat malaria, which is endemic in the Democratic Republic of the Congo. It is derived from cinchona bark and is accompanied by the enantiomer quinidin [38].

5.5.1. Quinidin as an impurity of Quinin

Quinidin is a drug prescribed to treat irregular or fast heartbeats. It operates by regulating the heartbeat and electrical impulses. It is also used to treat specific forms of malaria.

However, it is becoming less popular due to its negative effects and the availability of more effective medications to face up that issue as new therapeutic alternatives for treating cardiac arrhythmias [39].

In a quinin-based preparation, quinidin is regarded an undesirable contaminant since it can impair product purity and induce significant side effects such as heart abnormalities and severe allergic reactions.

IV. Inorganic impurities

Inorganic impurities include substances like chemical reaction catalysts, which are a common source of non metals, metals and heavy metals such as chlorides, sulfates and so on.

These elements' probable presence must be thoroughly investigated, as they are frequently employed during synthesis and pose a risk to public health.

Heavy metals are a type of impurity that must be studied in order to confirm the conformance of the regulated substance [40].

Metals are examined based on their potential danger to human health and are classified as :

- Class 1 (that includes all the metals of high safety concern) : chromium, iridium, molybdenum, nickel, platinum, rhubium, and vanadium.
- Class 2 (metals with low safety concerns) : copper, manganese, and vanadium.
- Class 3 (metal with minimum safety issues), which includes iron and zinc.

V. Residual solvents

Residual solvents are volatile organic contaminants that may persist in active substances, excipients, intermediary products or finished products following processing.

Proper solvent selection may be motivated by a desire to increase synthesis yield or to determine properties such as crystal shape, purity, and solubility of a medication. In this case, the solvent can play a critical role in the synthesis process. However, because residual solvents have no therapeutic value, they must be removed whenever possible in order to comply with safety restrictions, ingredient and product standards, Good Manufacturing Practices, and other quality-based requirements [41].

V.1. Classification of residual solvents according to health risks [41]

Residual solvents are classified as follow :

- Class 1 solvents : should be avoided during drug manufacture as they are considered hazardous to human health.
- Class 2 solvents : are of limited use, as their toxicity is less severe.
- Class 3 solvents : are the most widely used, as they present less risk to human health than class 1 or class 2 solvents.

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Table 3. Classification of residual solvents and assessment of their health effects.

Classes of residual solvents	Assessment
Class 1 : Benzene, Carbon tetrachloride, 1,2-Dichloroethane 1,1-Dichloroethene and 1,1,1-Trichloroethane (solvents to be avoided)	✓ Known human carcinogens ✓ Strongly suspected human carcinogens ✓ Solvents particularly known to have ozone-depleting properties.
Class 2 : Acetonitrile, Chlorobenzene, Chlorobenzene, Cyclohexane 1,2-Dichloroethene, 1,2-Dimethoxyethane N,N-Dimethylacetamide... (solvents to be limited)	✓ Non-genotoxic animal carcinogens or agents possibly responsible for other irreversible toxicities, such as neurotoxicity or teratogenicity. ✓ Solvents suspected of other significant but reversible toxicities
Class 3 : Acetic acid, acetone, anisole 1-Butanol, 2-Butanol, butyl acetate, ethanol... (solvents with low toxic potential)	✓ Solvents with low toxic potential for humans; no health-based exposure limits required

Discussion

Identification and quantification of the active ingredient

Given the documented circulation of low-quality medicines around the world, particularly in poor nations like the Democratic Republic of the Congo, identifying and quantifying active components in pharmaceutical products is a vital aspect of the quality control process. This step is important for various reasons :

- Safety

Correct identification ensures that the appropriate medicine is administered to the correct patient. Indeed, a number of incidences involving inaccurate active ingredient identification have been documented all around the world [42].

- Efficacy

Quantification ensures that medications contain an adequate amount of active chemicals to treat the ailment for which they are prescribed. Accurate measurement ensures that doses are sufficient to maintain therapeutic efficacy. In this approach, the measurement of active components contributes to the prevention of medication resistance caused by the population's use of underdosed products [43].

- Quality

Precise quantification and identification of active components helps to ensure the quality of pharmaceutical goods. This includes meeting drug manufacturing criteria. Finally, in pharmaceutical laboratories, physicochemical evaluations are critical for ensuring drug quality and regulatory compliance.

Our study revealed that the approved laboratories in Kinshasa all identify the active ingredients present in the final products to be analyzed. As for the quantification of all the active ingredients present in medicines composed of several active ingredients, all admitted to quantifying only the majority active ingredients. Analyzing only the majority active ingredient does not provide complete safety for the population, as the unquantified minority product may well be under- or over-dosed, hence the importance of systematic quantification [44].

Research and quantification of impurities

It goes without saying that pharmaceutical items meant for human consumption must be extensively tested, as the safety of a medicine is determined by the degree of purity of the final

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product [45]. The process of synthesizing active pharmaceutical ingredients (APIs) involves using raw materials and reagents to produce the final medication substance after going through many synthesis intermediates. Some of these intermediates, or byproducts of the synthesis process, may be harmful and coexist at low concentrations as contaminants in the active ingredient or final drug product [46].

Toxic contaminants, if present in high enough proportions, would be harmful to human health. As a result, pharmaceutical sponsors and regulatory bodies emphasize the necessity of impurity profiling in medicinal compounds [46].

The recent discovery of nitrosamine impurities, which are likely human carcinogens, in drugs such as angiotensin II receptor antagonists (ARBs), ranitidine, nizatidine, and metformin has highlighted the importance of developing a strategy to assess the risks associated with the potential presence of nitrosamines in all pharmaceutical products.

Our investigation revealed that, despite the availability of contemporary technology and competent staff in the DRC, the detection and quantification of contaminants in pharmaceutical goods is not yet included in the studies performed by accredited laboratories. The concern for the population's health and compliance with medication analysis requirements should push them to reconsider their quality control priorities.

This is why, on February 19, 2024, in a circular note in response to the pharmacovigilance commission's numerous reports and recommendations, the Congolese Pharmaceutical Regulatory Authority (ACOREP) decided to require all drugs in the SARTAN family (valsartan, losartan, telmisartan, libersartan, candersartan, and olmesartan) to be tested for incriminating impurities before registration. Applicants must submit risk management strategies and reports for marketing authorization (MA) renewals. ACOREP also mandates enterprises to produce a benefit-risk assessment report along with analytical results. Finally, ACOREP has decided to withdraw a variety of items from the market, including all types of ranitidine, due to their nitrosamine content. Toxic metals like As, Pb, Pt, Pd, Cd, Hg, Se, Cr, Al, Ni, Cu, and U enter the human body through alimentary diets, air, water, and pharmaceuticals.

Metals such as Pt and Pd are good catalysts and are thus commonly employed in drug production. As a result, they may be present in the final product as catalyst residues [45]. Hence the need of regulating the presence of heavy metals in finished pharmaceutical products.

Identification and determination of residual solvents

Because of the possible hazards to public health, analyzing residual solvents in pharmaceutical preparations is a critical aspect of drug quality control.

For toxicological reasons, producers must adhere to the limits outlined in the various pharmacopoeias and guidelines. Aside from having little medicinal use, they can be poisonous and hasten the disintegration of the completed product. Our survey results revealed that none of the approved laboratories conduct residual solvent research or quantification, putting the entire population at risk of contracting cancer, as most organic solvents are carcinogenic.

Differentiation of enantiomers

Today, pure enantiomers are preferred over racemic combinations. Indeed, multiple studies have revealed that the two enantiomers of a medication frequently have opposite pharmacological effects on the body. They can interact differently with biological proteins, enzymes, and receptors, resulting in therapeutic effects for one and deleterious effects for the other, as in the instance of thalidomide, where one of its enantiomers is an anti-vomiting medication and the other is teratogenic [47].

In the case of levodopa, the levorotatory enantiomer of dopa, the precursor of dopamine, used to treat Parkinson's disease, only the levorotatory (S)-(-) isomer is preserved because the (R)-(+) isomer increases the risk of agranulocytosis [48].

(R)-(+) bupivacaine and (R)-(+) ropivacaine are two similar synthetic local anesthetics. While the former was utilized in a racemic mixture, proof of the (R)-(+) enantiomer's toxicity to the heart and brain led to the marketing of only the (S)-(-) bupivacaine isomer. The same is true with ropivacaine,

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where the (S)-(-) enantiomer is chosen for its higher anesthetic activity and longer duration of action, whereas the (R)-(+) isomer has only a little arrhythmogenic effect on the heart due to its low affinity for sodium channels in cardiac muscles [49].

Our survey results revealed that just one laboratory admitted to doing the essential tests to detect enantiomers on the raw material ; the rest do not do so on either the raw material or the completed product.

Enantiomer identification necessitates the use of specific but easily available techniques (polarimeter, chiral chromatography, NMR). Because health is priceless, enantiomer identification should be included in routine tests to ensure population health.

The performance of available equipment : HPLC, GC, EC

Drug quality control is a critical phase in the drug distribution process. It ensures their dependability before they are utilized and helps to combat counterfeit or low-quality drugs. Traditionally, quality control is conducted out using the procedures indicated in pharmacopoeia monographs.

Today, most pharmacopoeias and reference works recommend instrumental techniques such as infrared spectroscopy (primarily identification), UV-visible spectroscopy (identification and assay), thin-layer chromatography (identification and analysis of impurities), high-performance liquid chromatography (HPLC) (identification, assay, determination of impurities or related substances), and gas chromatography for the analysis of volatile substances and residual solvents (59). Several high-performance detectors can be used with these techniques to improve their efficiency (LC-MS, GC-MS, ...).

Our survey found that the majority of this equipment is already accessible in DRC reference laboratories, but its usage in regular analyses remains problematic. Titrimetric analyses have outlived their usefulness due to constraints in terms of the level of precision required for drug analysis and a lack of selectivity. Our laboratories must confront the facts and recognize that only cutting-edge procedures are capable of reliably identifying and measuring contaminants that can pose major health risks to the population.

Exposure to impurities: a possible cause-and-effect relationship

Chronic noncommunicable diseases such as cancer, hypertension, and kidney failure are causing increased morbidity and death in developing countries such as the Democratic Republic of the Congo. Epidemiological research on these diseases have identified a number of risk factors, most notably lifestyle-related.

Several papers indicate smoking, alcohol intake, sedentary lifestyles, low-fiber diets, and changes in reproductive behaviors, among other things [50,51]. Medicines, through their interactions with the human body or their makeup, can cause diseases in humans. Antibiotics, antidepressants, antihypertensives (calcium channel blockers, angiotensin II converting enzyme inhibitors) [52–54], and counterfeit medications may all contain genotoxic impurities or carcinogenic residual solvents [55]. More in-depth local studies are required to examine these risk variables in real terms, in order to assure the safety of the community.

Conclusion

This investigation demonstrated the need of checking for potential impurities, as the presence of contaminants reduces product quality and poses health concerns to patients.

Several drugs have been withdrawn from the global market due to the presence of contaminants that are harmful to human health, but these items continue to circulate freely in the DRC. This is true for certain drugs in the Sartan and Metformin families. Several other medicines that are believed to contain harmful impurities continue to circulate freely in the DRC, despite the fact that these impurities are never studied. This is the case with paracetamol, which may contain para-aminophenol, a nephrotoxic product, and piroxicam, which contains 2-aminopyridine, a genotoxic product.

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Finally, it was discovered that the cutting-edge equipment and professional staff available were underutilized. In truth, the Faculty of Pharmaceutical Sciences at the University of Kinshasa's drug analysis department already employs several professionals trained at Congolese state expense but who are underutilized.

The public health authorities must ensure that international quality control standards are strictly followed and applied in order to provide the population with the high-quality medicines it deserves.

References

1. Kaur H, Louise Allan E, Mamadu I, Hall Z, Ibe O, El Sherbiny M et al. Quality of artemisinin-based combination formulations for malaria treatment: Prevalence and risk factors for poor quality medicines in public facilities and private sector drug outlets in Enugu, Nigeria. PLoS One. 2015 May 1;10 (5):e0125577.
2. Makenga G, Menon S, Baraka V, T R Minja D, Nakato S, Delgado-Ratto C et al. Prevalence of malaria parasitaemia in school-aged children and pregnant women in endemic settings of sub-Saharan Africa: A systematic review and meta-analysis. Parasite Epidemiol Control. 2020 Nov;11:e00188.
3. OMS, rapport 2020 sur le paludisme dans le monde, 2020 nov.
4. Yamlak G, Getahun D, Sugerman D, Tongren E, Tokarz R, Wossen M et al. Adherence to national malaria clinical management and testing guidelines in selected private clinics of Gambela Town, Gambela Region, Ethiopia: a mixed method study. Malaria Journal (2022) 21:164 Page 2 of 8
5. World Health Organisation.World Malaria Report 2021. (Disponible sur : http://www.cdn.who.int/media/docs/default-source/malaria/world-Malaria-reports-2021.global-briefing ; Consulté le 31/08/2022).
6. Centres for Disease Control and Prevention (CDC). Impact of malaria [Internet]. 2016 [cited 2017 Oct 3]. Available from: https://www.cdc.gov/malaria/malaria_worldwide/i mpact.htm.
7. WHO. World malaria report 2020. Geneva: World Health Organization; 2020. https://www.who.int/publications/i/item/9789240015791.
8. Plan Strategique National de Lutte contre le Paludisme RDC, Kinshasa 2020-2023 Page 15 of 86.
9. Bardaji A, Sigauque B, Sanz S, Maixenchs M, Ordi J, J Aponte J et al. Impact of Malaria at the End of Pregnancy on Infant Mortality and Morbidity. J Infect Dis. 2011;203:691–9.
10. Tiono AB, Ouedraogo A, Bougouma CB, Diarra A, Konaté AT, Nébié I et al. Placental malaria and low birth weight in pregnant women living in a rural area of Burkina Faso following the use of three preventive treatment regimens. Malar J. 2009; 8:1-8. doi:10.1186/1475-2875-8-224.
11. Equipe de l'évaluation d'impact de la RDC. Evaluation de l'Impact des Interventions de Lutte Contre le Paludisme sur la Mortalité Toutes Causes Confondues chez les Enfants de moins de cinq ans en République Démocratique du Congo de 2005 à 2015: Synthèse des résultats préliminaires. Programe National de Lutte contre le Paludisme, 2017, Kinshasa, RDC.
12. Ciza PH, Sacré P-Y, Waffo C, Coic L, Avaohou H, Mbinze JK et al. Comparing the qualitative performances of handheld NIR and Raman spectrophotometers for the detection of falsified pharmaceutical products. Talanta. 2019 Sep 1;202:469–78.
13. Organisation Mondiale de la Santé. Lignes directrices de l'OMS sur le paludisme 16 Février 2021 http://www.apps.who.int/iris/rest/bitstreams/1363815/retrieve.
14. WHO. Guidelines for the treatment of malaria. 3rd Edn. World Health Organization, Regional Ofce for Africa. 2022. https://www.afro.who.int/ publications/guidelines-treatment-malaria-third-edition.
15. WHO. Guidelines for the treatment of malaria, 2nd ed. Geneva, World Heal Organization; 2010.
16. Batwala V, Magnussen, Hansen KS, Nuwaha F. Cost-effectiveness of malaria microscopy and rapid diagnostic tests versus presumptive diagnosis: implications for malaria control in Uganda. Malar J. 2011; 10:372.
17. D'Acremont V, Kahama-Maro J, Swai N, Mitasiwa D, Genton B, Lengeler C. Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. Malar J. 2011;10:107

 doi:10.20944/preprints202504.2017.v1

18. Salomão AC, Sacarlal J, Chilundo B, Gudo SE. Prescription practices for malaria in Mozambique: poor adherence to the national protocols for malaria treatment in 22 public health facilities Malar J (2015) 14:483 DOI 10.1186/s12936-015-0996-5.
19. Chinkhumba J, Skarbinski J, Chilima B, Campbell C, Ewing V, Joaquin SM et al. Comparative field performance and adherence to test results of four malaria rapid diagnostic tests among febrile patients more than five years of age in Blantyre, Malawi. Malaria Journal 2010;9:209.
20. WHO. World malaria report 2012. Geneva: World Health Organization; 2012. p.27–58.
21. Diggle E, Asgary R, Gore-Langton G, Nahashon E, Mungai J, Harrison R et al. Perceptions of malaria and acceptance of rapid diagnostic tests and related treatment practises among community members and health care providers in Greater Garissa, North Eastern Province, Kenya. Malaria Journal 2014;13:502.
22. Manyando C, Njunju ME, Chileshe J, Siziya S, Shiff C. Rapid diagnostic tests for malaria and health workers' adherence to test results at health facilities in Zambia. Malaria Journal 2014;13:166.
23. Mana DK, Kapepula PM, Ngombe NK. Completeness Assessment Of Handwritten Medical Prescriptions In Southeast Kinshasa Community Pharmacies. International Journal of Pharmaceutical Sciences and Research, 2021; Vol. 12(9): 5117-5124).
24. Yilma Z, Mekonnen T, Abdela Siraj E, Agmassie Z, Yehualaw A, Debasu Z et al. Assessment of Prescription Completeness and Drug Use Pattern in Tibebe-Ghion Comprehensive Specialized Hospital, Bahir Dar, Ethiopia. Biomed Res Int. 2020 Oct 19, 2020 : 8842515. Doi: 10.1155/2020/8842515. PMID : 33134391; PMC7503717
25. World Health Organization 2002. Promoting rational use of medicines : core components –WHO policy perspectives on medicines. http://apps.who.int/medicinedocs/en/d/Jh3011e/.
26. Assefa T, Abera B, Bacha T, Beedemariam G: Prescription completeness and drug use pattern in the university teaching hospital, addis ababa, ethiopia. Journal Basic and Clinical Pharmacy 2018; 9: 90-95.
27. Taiwo MO, Akinda OS. Emerging antibiotic resistance in Africa, threat to healthcare delivery. MOJ Biol. Med. 2017, 1, 114–115.
28. WHO Access, Watch, Reserve (AWaRe) Classification of Antibiotics for Evaluation and Monitoring of Use. 2021. Available online: https://www.who.int/publications/i/item/2021-aware-classification.
29. Gindola Y, Getahun D, Sugerman D, Tongren E, Tokarz R, Wossen M et al. Adherence to national malaria clinical management and testing guidelines in selected private clinics of Gambela Town, Gambela Region, Ethiopia: a mixed method study, Malaria Journal (2022) 21:164
30. Irikefe P. Obiebi; Adherence to antimalarial drug policy among doctors in Delta State, Nigeria: implications for malaria control. Ghana Medical Journal 2019; 53(2): 109-116 doi:http://dx.doi.org/10.4314/gmj.v53i2.5
31. Ampadu HH, Asante PK, Bosomprah S, Akakpo S, Hugo P, Gardarsdottir H et al. Prescribing patterns and compliance with World Health Organization recommendations for the management of severe malaria: a modified cohort event monitoring study in public health facilities in Ghana and Uganda. Malaria Journal 18, 36 (2019) https://doi.org/10.1186/s12936-019-2670-9
32. Dodoo ANO, Fogg C, Asiimwe A, Nartey TE, Kodua A, Tenkorang O et al. Pattern of drug utilization for treatment of uncomplicated malaria in urban Ghana following national treatment policy change to artemisinin-combination therapy. Malaria Journal. 2009;8:2. doi:10.1186/1475-2875-8-2
33. Mankulu JK, Mbinze JK, Mutwale PK, Liesse JMI, Longokolo MM, Wambale JM et al. Evaluation of Antibiotic Prescribing Pattern Using WHO

Access, Watch and Reserve Classification in Kinshasa, Democratic Republic of Congo. Antibiotics 2023, 12, 1239 https://doi.org/10.3390/antibiotics 12081239

34. Roux Le R, Gallard H, Croué JP, Papot S, Deborde M. NDMA formation by chloramination of ranitidine: Kinetics and mechanism. Environ Sci Technol. 2012;46(20):11095–103.
35. Gold SA, Margulis V. Carcinogenic Effects of Nitrosodimethylamine Contamination in Ranitidine: Defining the Relationship with Renal Malignancies. JU Open Plus. 2023;1(11):1–8.
36. Kirkiacharian S. Chimie médicinale - Structure et activité du médicament Chimie médicinale Structure et activité du médicament. 2015;33(0).
37. Knoche B, Blaschke. Stereoselectivity of the in vitro metabolism of thalidomide. Chirality. 1994;6(4):221–4.

 doi:10.20944/preprints202504.2017.v1

38. Huston M, Levinson M. Are one or two dangerous? Quinine and quinidine exposure in toddlers. J Emerg Med. 2006;31(4):395–401.
39. Natural small molecule drug from plants chapter: Quinidine. guan-hua. novenber 2018.
40. Poojashree P, Pramila T, Manoj Kumar S, Senthil kumar GP. A Review on Pharmaceutical Impurities and its Importance in Pharmacy. Am J PharmTech Res. 2019;9(5):76–87.
41. 〈467〉 Residual Solvents.pdf.
42. Matmour D. Establishment of Interest of Impurities Control. 2023;(October).
43. Hoellein L, Kaale E, Mwalwisi YH, Schulze MH, Vetye-Maler C, Holzgrabe U. Emerging Antimicrobial Drug Resistance in Africa and Latin America: Search for Reasons. Risk Manag Healthc Policy. 2022;15:827–43.
44. Achille YL, Engelbert AJ, Gabin AA, Pauline A, Parfait D, Habib G et al, quality control of Paracetamol generic tablet marketed in Benin and search of its two impurities P-aminophenol and P-nitrophenol by HPLC-UV/Visible. American journal of analytical chemistry, 13, 449-460.
45. Balaram V. Recent advances in the determination of elemental impurities in pharmaceuticals - Status, challenges and moving frontiers. TrAC - Trends Anal Chem [Internet]. 2016;80:83–95. Available from: http://dx.doi.org/10.1016/j.trac.2016.02.001.
46. Bercu JP, Dobo KL, Gocke E, Mcgovern TJ. Overview of genotoxic impurities in pharmaceutical development. Int J Toxicol. 2009;28(6):468–78.
47. Shealy YF, Opliger CE, Montgomery JA. Synthesis of D- and L-thalidomide and related studies. J Pharm Sci. 1968;57(5):757–64.
48. Scott AK. Stereoisomers and Drug Toxicity: The Value of Single Stereoisomer Therapy. Drug Saf. 1993;8(2):149–59.
49. Ekatrodamis G, Borgeat A. The enantiomers: revolution or evolution. Curr. Top. Med. Chem., (2001), 1, 205-6.
50. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: Systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 2016, 354, i3857.
51. Zeinomar N, Knight JA, Genkinger JM, Phillips KA, Darly MB, Milne RL et al. Alcohol consumption, cigarette smoking, and familial breast cancer risk: Findings from the Prospective Family Study Cohort (ProF-SC). Breast Cancer Res. 2019, 21, 128.
52. Velicer CM, Lampe JW, Heckbert SR, Potter JD, Taplin SH et Al. Hypothesis: Is antibiotic use associated with breast cancer? Cancer Causes Control 2003, 14, 739–747.
53. Brandes LJ, Arron RJ, Bogdanovic RP, Tong J, Zaborniak CL, Hogg GR et al. Labella, F.S. Stimulation of malignant growth in rodents by antidepressant drugs at clinically relevant doses. Cancer Res. 1992, 52, 3796–3800.
54. Olsen JH, Sørensen HT, Friis S, McLaughlin JK, Steffensen FH, Nielsen GL et al. Cancer risk in users of calcium channel blockers. Hypertension 1997, 29, 1091–1094.
55. Leso V, Ercolano ML, Cioffi DL, Iavicoli I. Occupational Chemical Exposure and Breast Cancer Risk According to Hormone Receptor Status: A Systematic Review. Cancers (Basel) 2019, 11, 1882.