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Pharmaceutical Quality Assurance of Diazepam Injection at the National Health Laboratory of Mali

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ABSTRACT

Objectives: In a world marked by the increase in chemoresistance leading to the adoption of therapeutic combinations, the advent of generic multi-source drugs, the spread of counterfeiting and substandard drugs, often without active ingredients or falsified active ingredients, a Greater vigilance by pharmaceutical regulatory authorities is needed. Drug Post-Marketing Surveillance (PMS) therefore plays an important role in detecting poor quality products on the market.

Methods: The survey covered certain regions and certain points of sale. It aimed to assess the quality of Diazepam injection available on the market. The selection of drugs and geographic areas was made using risk-based sampling using the Drug Risk Assessment Tool (MedRS) developed by USP / PQM +.

Results: A total of 44 samples were analyzed according to a risk-based protocol, of which 32 were compliant with a rate of 91% against 12 non-compliant or 9% (P≤0,05). Non-compliant drugs were mainly from the public sector. We also found that all samples were unregistered.

Conclusion: The results clearly raise the issue of registration of drugs before their market authorization and the importance of continuous quality control and post-marketing drug analysis to ensure health and guarantee access to quality medicines for the health and well-being of populations.

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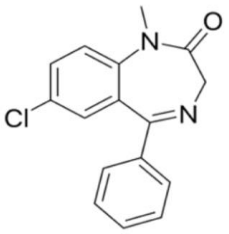
INTRODUCTION

Diazepam is a drug belonging to benzodiazepine group (7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepine-2-one] known for its depression activity on the central nervous system with anticonvulsant, anxiolytic, sedative and muscle relaxant properties [1]. It is also used in the treatment of alcoholic withdrawal syndrome [2] and in the treatment of organophosphorus poisoning [3, 4]. Diazepam is one of the most widely prescribed benzodiazepine for a variety of conditions particularly for anxiety, depression, epilepsy and insomnia. Diazepam was first synthesized in 1955 by Leo Sterbatch and marketed by Hoffmann-La Roche in 1963 in the brand name as Valium. [5, 6]



Several methods for the qualitative and quantitative analysis of diazepam in pharmaceutical dosage forms have been reported, among them, UV spectrophotometry is at the forefront of the most sensitive and widely used analytical techniques. In recent years it has found wide applications for the determination of many important drugs. [7–9]

Diazepam is a powerful sedative-hypnotic, and it is one of the most prescribed drugs in the world. It is also one of the five most widely used benzodiazepines, and misuse can lead to

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both psychological dependence and/or physical dependence. Its strong use can be a source of falsification and counterfeiting. Therefore, post-marketing follow-up is essential to monitor likely changes that may affect the performance of Diazepam.

The proliferation of counterfeit and poor quality medicines is a major public health problem; especially in developing countries that do not have sufficient resources to effectively monitor their prevalence. Currently, there are no reliable statistics on the level of incidence of counterfeit medicines in Mali. The WHO estimates that one in ten medicines in circulation in low- and middle-income countries are either substandard or falsified. Counterfeiting can concern both branded and generic products; and counterfeit products may include products with the right ingredients or the wrong ingredients, no active ingredients, with insufficient active ingredients, or with counterfeit packaging. [10, 11]

From a public health perspective, counterfeit/substandard drugs have eroded public confidence in the health care delivery system. Adverse effects may include treatment failures, organ dysfunction or damage, worsening of chronic diseases, and death. When drugs with little or no active ingredients, whether counterfeit or off-label, are used for the treatment of common diseases with high untreated mortality, morbidity and mortality are likely to increase. There is also the problem of financial losses for the pharmaceutical industry. [11, 12]

This study is being carried out to assess the pharmaceutical quality of injectable Diazepam used in health facilities in Mali in an attempt to determine the prevalence of counterfeit and poor quality products.

MATERIAL AND METHODS

Material

The pure standard Diazepam sample was obtained from United States Pharmacopeial Convention, USA, while the Diazepam Injection samples were purchased from licensed pharmacies and outlets in Mali. These samples were stored at a temperature < 25°C, in a cool place, without direct access to light, and then tested within the expiry times. Table 1 provides a brief description of the Diazepam samples collected. Others include: chloroform, anhydrous sodium sulfate, methanolic sulfuric acid, pH 7 phosphate buffer, filter papers (Whatman), glass test tubes (Pyrex), Agilent UV/Vis spectrophotometer (Cary 60), a pH meter (METTLER TOLEDO).

The Methods

Sample Collection

The survey covered selected regions and outlets identified by the National Technical Working Group on Post-marketing Drug Surveillance. Samples were collected from public, private and other healthcare facilities that store the affected drugs. These may be manufacturers, import and wholesale establishments, hospitals, health centers, pharmacies and private depots. Sample collection was carried out from September to December 2021.

Packaging and labeling inspection

The primary and secondary packaging of different brands will be carefully examined to verify the required information, such as product name, manufacturer's address, dates of manufacture, batch numbers, expiry date, quantity of principles assets, registration number.

Physicochemical Analysis

Organoleptic Property Test

The organoleptic properties of the different samples, e.g. appearance, color, smell of the medicine will be determined by inspection. These properties are directly related to the chemistry of the drug and as such can serve as a non-specific drug identification test.

Average Volume Determination

The American Pharmacopoeia [13] clarifies that the average volume is used to provide assurance that oral liquids, when transferred from the original container, will deliver the dosage form volume declared on the label. The average volume of liquid obtained from the 10 containers is not less than 100%, and the volume of any container is less than 95% of the volume declared in the labeling.

pH determination

The pH meter will be calibrated with standard buffer solutions of pH 2.0, 4.0, 7.0. The contents of 5 vials were emptied into a beaker. The pH will be measured by inserting the electrode of the pH meter into the drug solution and the reading will be taken after stabilization. This will be done in duplicate and the procedure will be repeated for each sample.

Quality assurance testing

Thin Layer Chromatography (TLC) GPHF

Enabling routine medicine quality control in resource-limited settings has been piloted by inventing and implementing simple, stand-alone mobile testing kits such as the GPHF Minilab®. The spot obtained from the test solution must correspond in terms of color, size, intensity, shape and distance to that of the chromatogram obtained with the standard solution according to the formula : %Rf =(RfStd-RfEch) /RfStd*100 ≤ 5%. [14, 15]

Spectro UV-Vis

The active ingredient content of each sample will be determined using an ultraviolet spectrophotometer (UV Agilent Cary 60), according to the method described by the British Pharmacopoeia [16]. To a volume containing 10 mg of Diazepam add 20 mL of mixed phosphate buffer pH 7.0 and extract with four 20 mL quantities of chloroform, passing each extract through the same 5 g of anhydrous sodium sulfate. Combine the chloroform extracts, dilute to 100 mL with chloroform and mix. Evaporate 10 mL to dryness in a current of nitrogen, dissolve the residue in 25 mL of 0.05m methanolic sulfuric acid, mix and measure the absorbance of

the resulting solution at the maximum at 368 nm, Appendix II B. Calculate the content of $C_{16}H_{13}ClN_2O$ taking 151 as the value of A(1%, 1 cm) at the maximum at 368 nm.

DATA ANALYSIS AND STATISTICS

Data were analyzed using SPSS with P≤0.05 considered statistically significant.

RESULTS

Situation of the samples taken

A total of 44 samples were taken from 4 geographical regions (Table 3) at the 4 levels of the drug distribution chain described in the methodology.

Table 1. Situation of samples taken by region

Region	Effectifs	Percentage (%)
BAMAKO	7	15,9
KAYES	15	34,1
SEGOU	8	18,2
SIKASSO	14	31,8
Total	**44**	**100,0**

MANUFACTURERS AND PRODUCTS COLLECTED

A large majority of products came from India (73%) followed by China (20%).

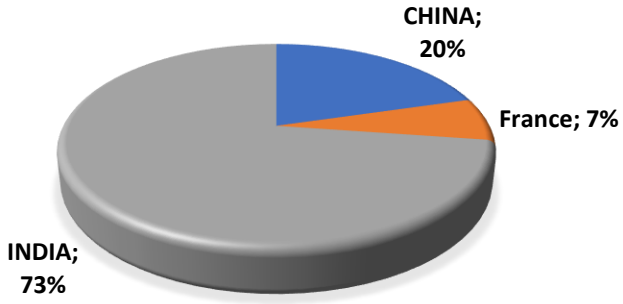

Figure 1. Situation of products by origin.

SECTOR OF FACILITY

70% of the samples were from the public sector against 30% for the private sector

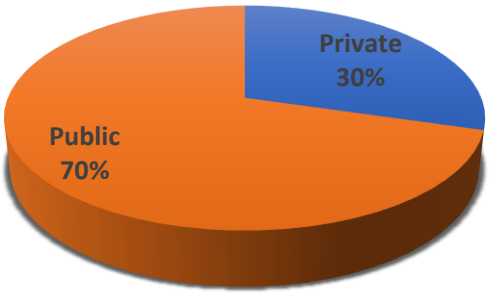

Figure 2. Situation of products by sector.

COMPLIANCE WITH SPECIFICATIONS

Global Results

Out of 44 samples tested, 32 were compliant, i.e. a rate of 91% and 12 non-compliant, corresponding to a rate of 9%.

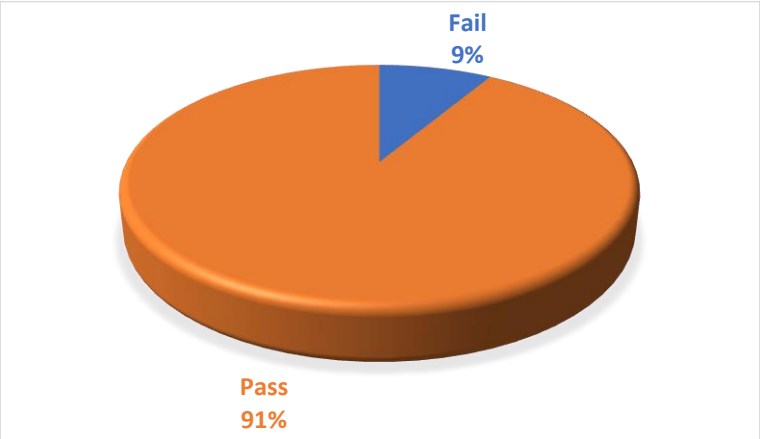

Figure 3. Global situation of products according to compliance

pH AND COMPLIANCE

All compliant samples had good pH. On the other hand, among the non-compliant samples, some had a good pH.

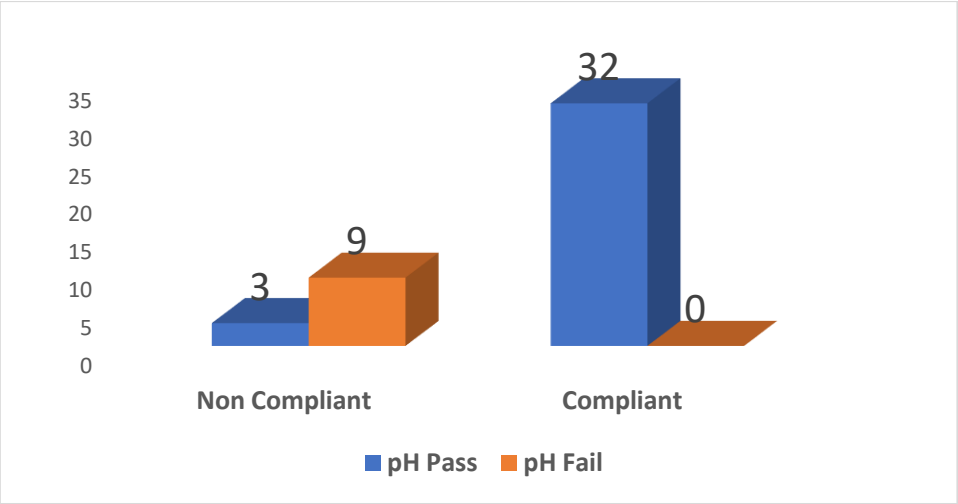

Figure 4. Product compliance by pH.

TLC AND COMPLIANCE

All compliant samples had a good TLC result and in contrast, all non-compliant samples had a poor TLC result.

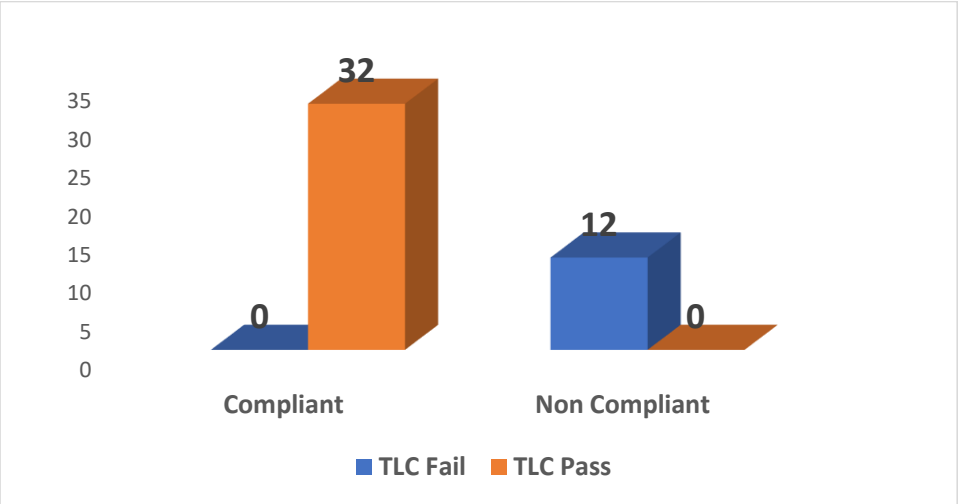

Figure 5. Product compliance by TLC.

COMPLIANCE BY SECTOR

Of the compliant samples, 23 were from the public sector and 9 from the private sector. Also, among the non-compliant samples, 8 were from the public sector against 4 from the private sector.

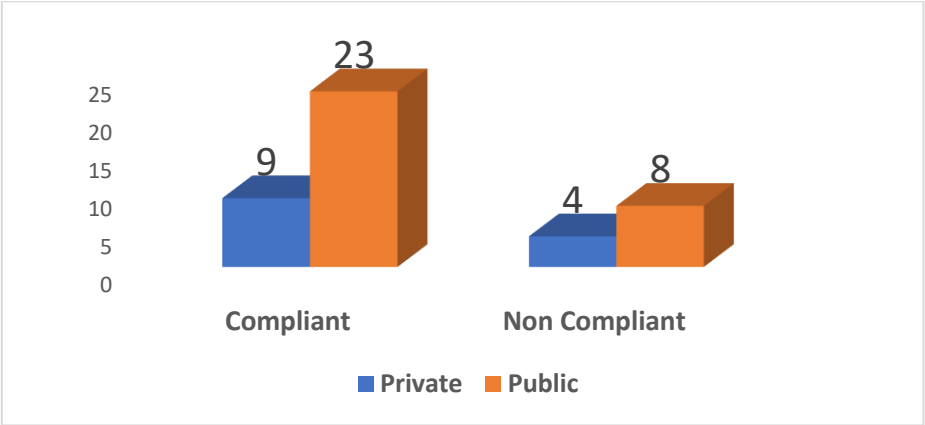

Figure 6. Product compliance by sector.

COMPLIANCE BY ORIGIN

All the products came from China (75%) was non compliants and the rest (25%) from India.

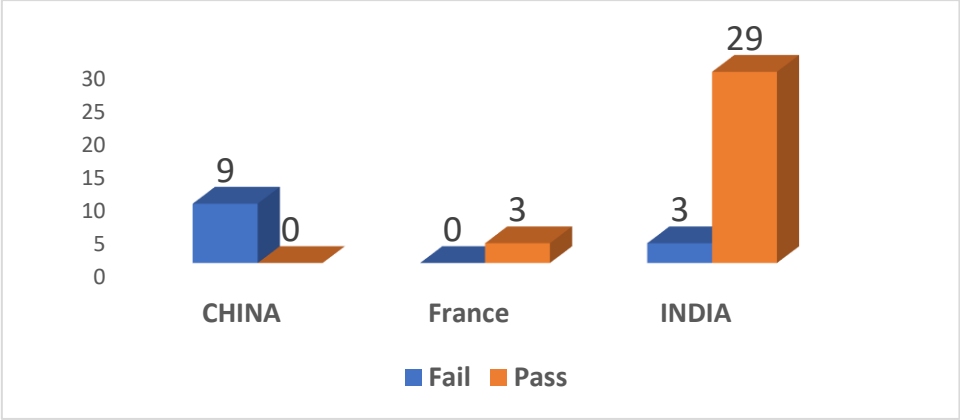

Figure 7. Product compliance by origin.

COMPLIANCE BY REGION

The Kayes region had the highest number of non-compliances with 6 samples. On the other hand, we encountered non-compliance in each region.

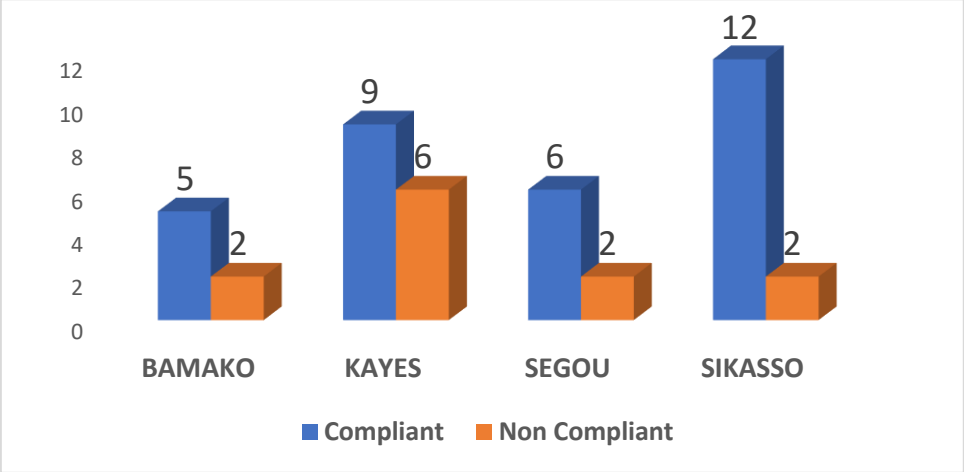

Figure 8. Product compliance by region.

RESULTS AND DISCUSSION

Physical Evaluation : Physico-Chemical Analysis

Upon inspection of the packaging and labels of the primary and secondary packaging of the various samples used for analysis, all samples complied with the BP specification [20]. Results obtained for physicochemical analysis, pH and TLC were analyzed against USP and BP specifications [16], [17]. The pH of a pharmaceutical product is a measure of its acidity/alkalinity. It is a very important factor in the formulation of pharmaceutical products because it influences the solubility, stability and palatability of the product. The pH of the product may reflect the intrinsic pH of the active

pharmaceutical ingredient. In this study all samples with pH out of specification were found to be non-compliant in the assay tests. The TLC of the different samples showed that out of 44 samples, 12 were non-compliant. The causes of non-compliance were due to a total absence of stains implying an absence of active ingredient.

Pharmaceutical Quality Analysis

The average volume of all samples tested met the BP specification [16] relative to volume uniformity of single dose preparations. They were between 90 and 110%. The active ingredient contents showed that 32 samples complied with the required specifications according to the British Pharmacopoeia standard with a range of drug content ranging from 90% to 110%. Among and 12 non-compliant samples.

DISCUSSION

Test Methods and Data Quality

Non-compliant samples were subject to OOS processing in accordance with the lab procedure which describes the management of out-of-specification results. All data has been submitted for review and approval by the laboratory's quality control functions in accordance with our procedure for the control of technical records, which describes the provisions specific to the certificate analysis and controls required before final approval.

Results Interpretation

In this study, a large majority of the products came from India (73%) followed by China (20%). These results confirm those of Sidibé et al who found 45% and 17% for India and China respectively.[18, 19]

This study found that all of the products were unregistered. This explains the high rate of non-compliance obtained.

Also in this study, 70% of the samples were from the public sector against 30% for the private sector. This is explained by the non-compliance with the master plan for the supply and distribution of essential drugs. The regions of Kayes had the highest numbers with 6 accounts for 50% of the non-conformance products. These results confirm those of Sidibé et al who found that 87.7% came from the public sector and 12.3% from the private sector.[18]

We found that all samples with out-of-specification pH and CCM also had out-of-specification active ingredient content. The causes of non-compliance were due to a total absence of active principle.

CONCLUSION

Quality assurance testing performed on samples of Diazepam Injection used in health facilities in Mali, using standard quality control tests of assay (mean volume, pH), identification (TLC, UV) and Dosage by UV-Vis spectrophotometry, in order to determine their quality revealed that out of 44 samples, 12 were non-compliant. The results clearly raise the issue of registration of drugs before their market authorization, the follow-up of the Master Plan for the Supply and Distribution of Essential Drugs (SDADME) and also the importance of continuous quality control and post-marketing drug analysis.

CONFLICTS OF INTEREST: None

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