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SOUTHERN AFRICAN PHARMACEUTICAL REGULATORY AFFAIRS ASSOCIATION

A Review of the Common GMP Non-conformances during Regulatory Inspections

Lubowa Nasser

Lead GMP Inspector-Uganda

About me!

Training

- Bachelor of Pharmacy - **Makerere University, Uganda**
- Postgraduate- Project Planning and Management- **Uganda Management Institute, Uganda**
- Post Graduate Course in Clinical Pharmacology, Drug Development and Regulation- **Tufts Center for the Study of Drug Development, Tufts University, Boston, Massachusetts, U.S.A**
- Masters of Science- Biotechnology Innovation and Regulatory Science (BIRS) and currently PhD Student at **Purdue University, West Lafayette, USA**

Experience

- **Pharmacist with 12 years experience** in Regulation of Pharmaceuticals
- Currently **Lead GMP Inspector** and **Manager Post Market Surveillance-** National Medicine Regulatory Authority – Uganda
- GMP inspections –Over **120 pharmaceutical companies across 5 Continents**

Publication

Pharmaceutical Industry in Uganda: A Review of the Common GMP Non-conformances during Regulatory Inspections

https://docs.lib.purdue.edu/cgi/viewcontent.cgi?article=1009&context=birsafricatr

Contacts

- Tel: **+256772025544**;
- Email: nlubowa@nda.or.ug; nlubowa@purdue.edu; nasqo2018@gmail.com;
- Linkedin: https://www.linkedin.com/in/nasser-lubowa-86291571/

01

Outline

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- Opportunities/Way Forward

Background

Medicine Sources

Africa relies mainly on imports to meet their medicines needs- over 80% importations for some countries

Manufacturing Capacity

Local Pharmaceutical Industry in Africa cannot meet the market demands.

Quality Assurance

Some manufacturers operate at unacceptable standards due to the lack of robust quality assurance systems and lack of quality culture among local manufacturers.

Market Bias

Medicines manufactured locally are perceived as of low-quality products and substandard compared to imported ones. The medicines are claimed not to be efficacious and safe and sometimes cause ADRs.

CONSEQUENCES

WHO

10% of the medications of the global medicine market are SFs, and more than 25% in LMICs

GAMBIA AND INDONESIA

Over 100 children have died due to adulterated cough syrups with Diethylene Glycol

UNDER 5

120,000 deaths of children under-five, annually, due to poor-quality antimalarials in sub-Saharan Africa

SOUTH AFRICA

7 of 10 Rifampicin formulations found not to be bioequivalent to the reference drugs

(Ref. Pillai G, Fourie PB, Padayatchi N et al. Recent bioequivalence studies on fixed-dose combination anti-tuberculosis drug formulations available on the global market)

Why GMP

01 Patients

- Poor quality, inefficacious and unsafe medicines
- Poor treatment out comes
- Antimicrobial Resistance
- Adverse Drug Reactions
- Increased treatment costs/medical insurance
- Decreased economic productivity.

02 Pharma

- Noncompliance leads to substandard medicines
- Avoid mix up and Cross contamination
- Affects company Reputation
- Increased customer complaints
- Recalls
- Increased Production Waste
- Regulatory Penalties
- Decreased Profitability and loss of market share

A Review of the Common GMP Non-conformances during Regulatory Inspections

01 Methodology

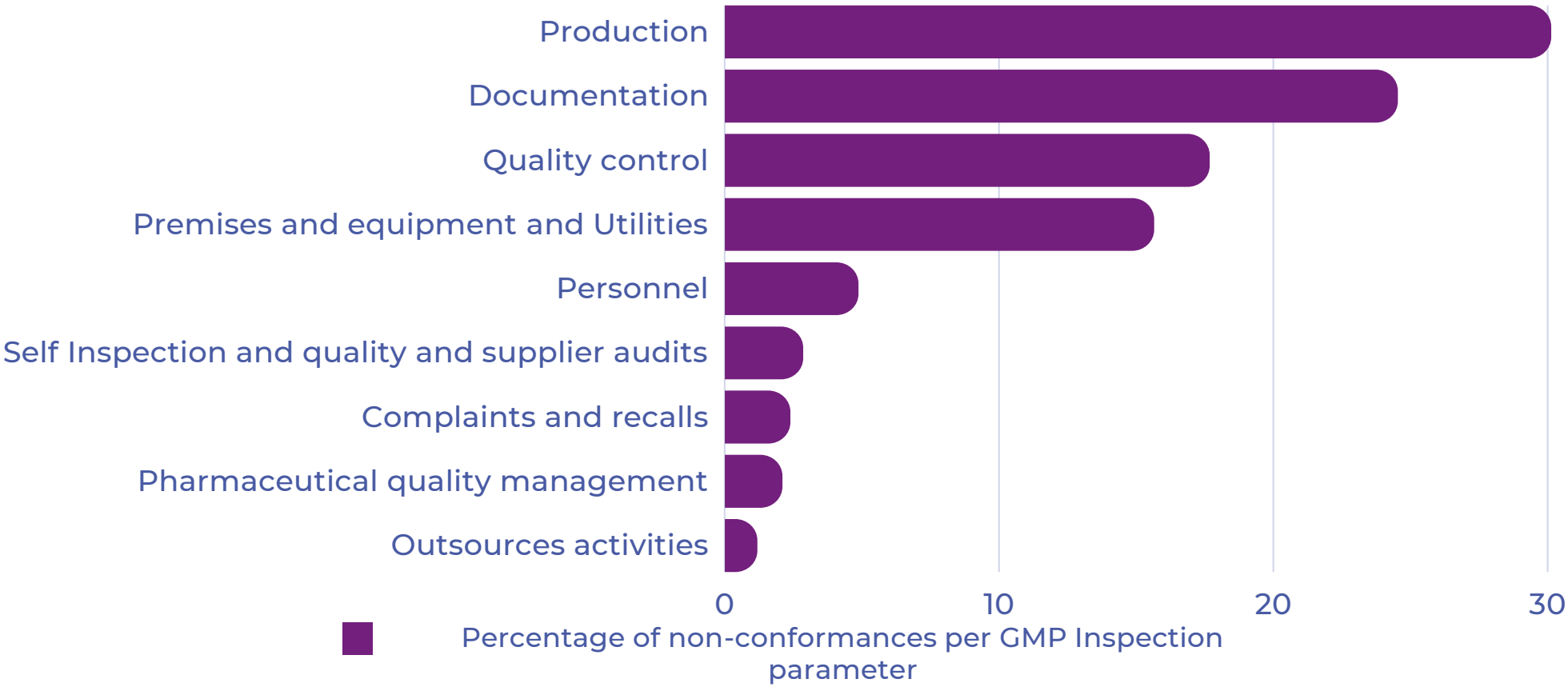
This study adopted a **quantitative study design** with categorization and quantification of the non-conformances obtained from a review of the available 50 GMP inspection reports for 21 local pharmaceutical companies in Uganda

- Binary logistic generalized estimating equations (GEE) model was applied to estimate the association between **odds of a company failing to comply with** GMP **requirements and non-conformances under each GMP inspection parameter.**

- Dummy estimation to linear regression was used to analyze the **relationship that existed between the selected** variables **(GMP inspection parameters) and the** production **capacity of the local pharmaceutical industry.**

- GMP parameters considered: pharmaceutical quality management; product market complaints and recalls; self-inspection, quality and supplier audits; personnel; premises, equipment and utilities; documentation; production, outsourced activities and quality control.

02 Results



Results contrast to a similar study carried out in Brazil by Geyer et al., 2019, where the most common areas of deficiency were qualification and validation (35.1%), documentation (32.2%), premises (26.4%), and quality control (23.5%).

2 Results–Statistical Analysis (1)

- Regression results using dummy estimations comparing pharmaceutical production capacity and non-conformances per given GMP inspection parameter
- Non-conformances relating to premises, equipment, and utilities were significantly higher in small-scale (B=2.29, P=0.04) and medium-scale industries (B=2.02, P=0.045) compared to large-scale industries.
- Large-scale industries had significantly more non-conformances relating to quality control as compared to small scale (B=-1.41, P=0.03) and the medium scale industries (B=1.89, P=0.008). The quality control laboratories in large-scale facilities were not in tandem with the testing requirements for manufactured products. However, for some medium and small-scale industries, quality control activities can be considered non-existent.

Variable/GMP inspection parameter	D_large	D_small	P-Value	D_medium	P-value
Pharmaceutical quality management	1.0	0.43	0.52	0.49	0.879
Personnel	1.0	1.16	0.38	0.70	0.208
Premises and equipment and utilities	1.0	2.29	0.04	2.02	0.045
Documentation	1.0	0.99	0.26	-0.31	0.729
Production	1.0	2.83	0.84	3.22	0.428
Quality control	1.0	-1.41	0.03	1.89	0.008
Outsources activities	1.0	-0.92		-1.17	0.005
Complaints and recalls	1.0	0.22	0.20	0.81	0.162
Self-inspection and quality and supplier audits	1.0	0.57	0.318	0.10	0.219

2 Results–Statistical Analysis (2)

Variable/GMP inspection parameter	Average	cOR	P-Value	aOR	P-Value
Pharmaceutical quality management	0.72	2.21	0.013	3.26	0.003
Personnel	1.68	3.86	0.016	5.73	0.001
Premises and equipment and utilities	5.42	4.20	0.034	6.81	0.001
Documentation	8.50	1.11	0.399	-	-
Production	10.44	1.06	0.213	-	-
Quality control	6.12	3.14	0.021	5.32	0.003
Outsources activities	0.40	0.85	0.74	-	-
Complaints and recalls	0.82	2.23	0.019	3.82	0.023
Self-inspection and quality and supplier audits	0.98	2.26	0.029	5.97	0.001

cOR= Crude Odds Ratio, aOR= adjusted Odds Ratio

- Logistic regression model showing likelihood of failure to comply with GMP due to non-conformances per given GMP parameter
- For every non-conformance under premises, equipment, and utilities, there was a 7-fold likelihood of failing to comply with the GMP requirements (aOR=6.81, P=0.001);
- For every non-conformance under Self inspection and quality and supplier audits, there was a 6-fold likelihood of failing to comply with the GMP requirements (aOR=5.97, P=0.001);
- There was also a five times likelihood that a firm was unable to conform to GMP, for any non-conformance related to quality control (aOR=5.32, P=0.003).

03 Common GMP Non-Conformances

- **Lack of adequate pharmaceutical manufacturing environments**- No HVAC facilities in some factories
- **Poor facility designs**- Unidirectional flow of materials and personnel not followed and poor maintenance- old facilities not upgraded. Inadequate Classification of critical areas/clean rooms as per ISO 14644-1 2015.
- **Poor equipment maintenance, cleaning, old technologies** –Incomplete maintenance schedules; Non-validated cleaning methods- Worst case determination, swabs /recovery studies; consideration of cleaning agent residues; MACO; Microbial limits; SIP and CIP systems, New products.
- **Struggles in the establishment of sterility assurance systems** – Inadequate environmental monitoring, cleaning deficiencies, No simulations, Inadequate personnel training….

03 Common GMP Non-Conformances

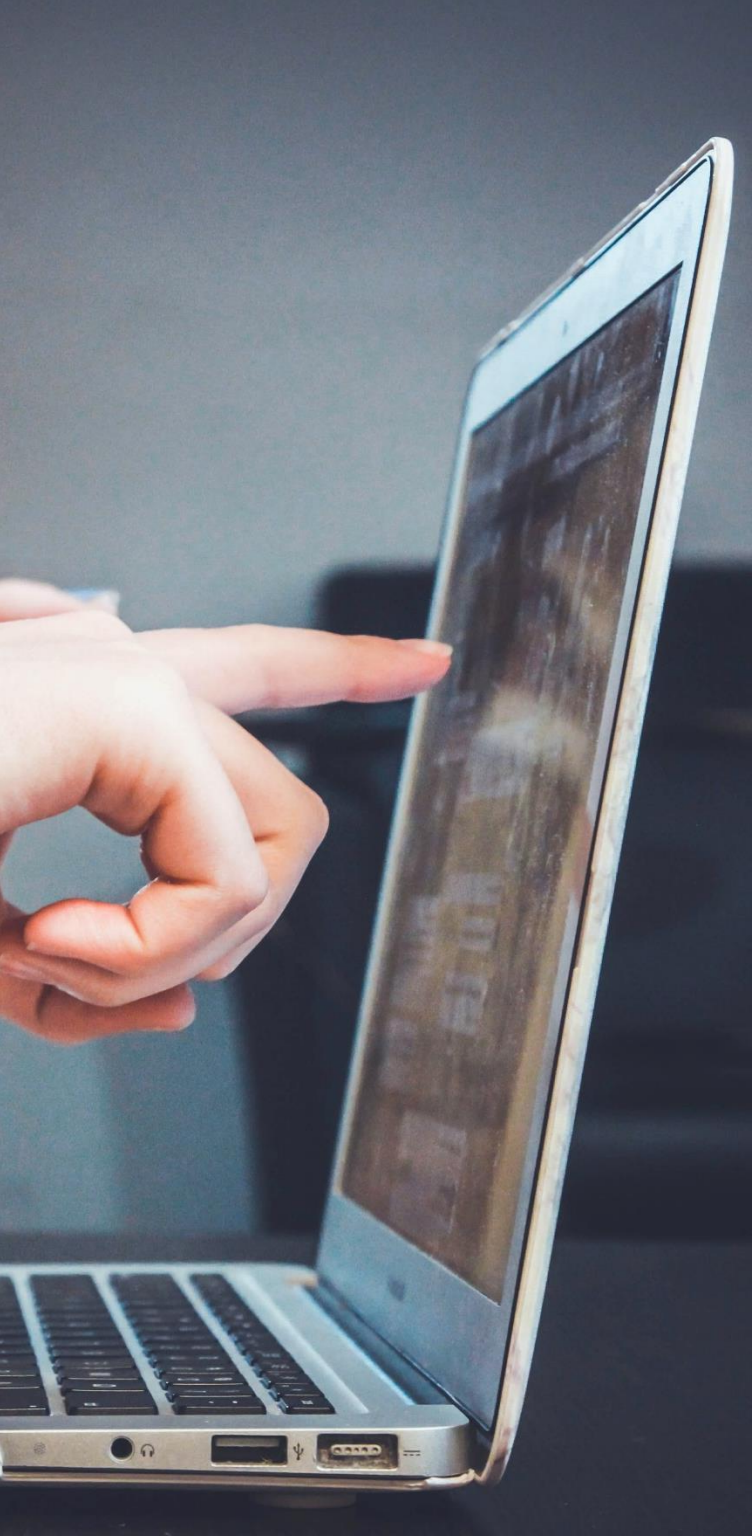
- **Struggles in the establishment of sterility assurance systems cont'd** – Utility defects including filtration challenges - WFI, HVAC, Pure Steam, Compressed Air, Nitrogen, poor aseptic techniques; No determination of House isolates; Disinfectant validation; sterilization controls- worst case scenarios; sterility indicators; filter integrity tests; bioburden testing; holding times for sterilized equipment and garments, filling time; un validated loading of lyophilizers; visual inspection breaks/fatigue and poor illumination.
- **Data Integrity** – Not following ALCOA+; No Audit trails, No system for authorization of changes, management of passwords; Equipment with out printers; No defined access controls and user levels; No Back up and Archive systems, Review of da not systematically done.

03 Common GMP Non-conformances

- **Inadequate containment systems for sensitive products** e.g. Beta-Lactam medicines, Oncology products which posed a potential threat of cross-contamination.
- **Lack of adequate quality control facilities**- Inadequate QC equipment; failure to comply to specifications- pharmacopeia vs In house; Unvalidated methods of analysis; stability study failures; Impurity testing not done; No Reference standards used and no data for qualification of working standards.
- **Lack of quality management systems**- No quality risk assessments, inadequate product quality reviews-statistical analysis, poor management of deviations and change controls, No CAPA systems, No independence of Quality Control and Production.
- **No or inadequate validations or qualifications done**- equipment, facility, utility qualifications; cleaning, process, analytical , computerized systems validations; Media Fills and Transport Validation.

03 Specific non-conformances

- **Poor documentation practices**- Inadequate SOPs or failure to comply to procedures; No following ALCOA+; Not following BMRs; Validation/qualification reports with no protocols
- **Poor Sourcing of raw materials and packaging materials**- No Vendor qualification systems, Preference to cheaper low quality raw/packaging materials, No due diligence done on vendors.
- **Poor investigation of complaints, OOS results and causes of recalls**- No risk assessment and root cause identified.
- **Inadequate control of outsourced activities**- No systems for outsourcing activities, No raw data reviewed before batch release.
- **Poor control of utilities**- Regarding PW and WFI -No continuous monitoring of TOC/Conductivity/ Temperature at Return points, No defined sampling schedules/ trending / sanitization programs; Poor designs-dead legs; No testing



04 Opportunities/Way Forward

- **Quality risk assessment of critical production and quality control of pharmaceuticals**. Investigations-Deviations, complaints, OOS should include root cause analysis with adequate supportive data would be conducted to guide development of the CAPA plan which has to be verified for its effectiveness.
- **Strengthen internal audits(with honesty)** including identification of the non-conformances with trend analysis followed by evaluation of the potential impact using risk assessment tools on the quality of the product.
- **Introduce Post market surveillance and Pharmacovigilance systems** for your drugs in liaison with NMRA in addition to stability studies done. Always work in consultation with the regulator.

04 Opportunities/Way Forward

- **Refresher and tailored GMP training** for the local pharmaceutical manufacturers need to be conducted more frequently based on the findings on GMP non-conformances during regulatory inspections and internal audits.
- **Compliance and Certification to ISO standards**- ISO 90001-Quality Management Systems and ISO 17025-Competencies in Laboratory Testing to augment GMP and Creation of a Quality Culture
- **Updating knowledge**- Following current Good Manufacturing Practices; Attending Technical international meetings; Review current publications/ regulatory guidance -FDA in the manufacturing industry. Embrace new technologies- Single use systems/ continuous manufacturing, PAT and RTRT e.t.c.
- **Participating in Regional Regulatory Harmonization activities**-SADC/ ZAZIBONA and enhance working together as the pharmaceutical industry to increase bargaining power!


"Quality means doing it right when no one is looking."
Henry Ford

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