QUALITY OF MEDICINES: EVERYONE A STAKEHOLDER?

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IT LOOKS LIKE WE'LL RELEASE OUR NEW PRODUCT ON TIME, DESPITE ITS MANY DEFECTS.

WE'VE MINIMIZED THE ECONOMIC IMPACT OF THE DEFECTS VIA AN ADVANCED BUSINESS PROCESS CALLED "HOPING NOBODY NOTICES."

AND WE'VE DOUBLED OUR PROJECTED INCOME BY MODIFYING OUR ASSUMPTIONS!

A LOT OF THIS JOB IS MENTAL.
What is quality?
- State of excellence
- State of zero defects
- Features and characteristics
  - Having ability to satisfy implied needs
EVOLUTION OF QUALITY

From Craftsmen
Masters of arts and crafts
Training and supervision

To Civilization
Demand of mass production
Repetition of crafts

http://www.ancient-egypt.info/2012/02/crafts-in-ancient-egypt-for-kids-craft.html
http://en.wikipedia.org/wiki/Tool
Customers’ Satisfaction ratings

- Quality
- Durability
- Efficiency
- Warranty
- Usability
- Experience

Top 3
- Quality
- Durability
- Efficiency

Top 10
- Good
- Fair
- Poor

Top 5
- Very Good
- Good
- Fair
- Poor

Excellence

Like
MANAGEMENT OF QUALITY

Methods

- Quality loss function
- Quality robustness
- Quality cycle
- Kansei Engineering
- Design of Experiments
- PDCA cycle
- Six Sigma
PDCA CYCLE OF QUALITY MANAGEMENT
QUALITY IMPROVEMENT WITH PDCA

Plan → Do → Check → Act → Standard → Continuous improvement

Consolidation through standardization

Time → Quality improvement

fppt.com
### Sigma Quality Level

<table>
<thead>
<tr>
<th>Sigma Level</th>
<th>Yield % (Long Term)</th>
<th>Defects, DPMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 σ</td>
<td>99.9997</td>
<td>3.4</td>
</tr>
<tr>
<td>5 σ</td>
<td>99.98</td>
<td>233</td>
</tr>
<tr>
<td>4 σ</td>
<td>99.38</td>
<td>6210</td>
</tr>
<tr>
<td>3 σ</td>
<td>93.32</td>
<td>66807</td>
</tr>
<tr>
<td>2 σ</td>
<td>69.13</td>
<td>308538</td>
</tr>
<tr>
<td>1 σ</td>
<td>30.23</td>
<td>697700</td>
</tr>
</tbody>
</table>

DPMO = Defects Per Million Opportunities

An introduction to design for six sigma by Simon Barnard; [https://www.youtube.com/watch?v=f9LJhUNktZI](https://www.youtube.com/watch?v=f9LJhUNktZI)
BENCHMARKING

7σ  Airline Flight Fatality rate
6σ  Wrong Site Surgery
5σ  Airline baggage handling
4σ  England football team taking penalties in major tournament
3σ
2σ
1σ

Adapted from An introduction to design for six sigma by Simon Barnard; https://www.youtube.com/watch?v=f9LJhUNktZI
BENEFITS OF QUALITY

- Cost savings
- Enhanced customer satisfaction
- Access to new markets
- Increased market share

100% Satisfaction Guaranteed
SIX VALUES OF QUALITY CULTURE

Values 1 & 2
- We’re all in this together: company, suppliers, customers.
- No subordinates or superiors allowed.

Values 3 & 4
- Open, honest communication is vital.
- Everyone has access to all information on all operations.

Values 5 & 6
- Focus on processes.
- There are no successes or failures, just learning experiences.
QUALITY OF MEDICINES

Described by:

- Suitability for use
- Efficacy and safety
- Conformity to standard specifications
- Identity, strength and purity
Three broad categories:

- Counterfeit medicines
- Substandard medicines
- Degraded Medicines
WHO Definition of counterfeit:

A drug is said to be counterfeit when there is a false representation in relation to its identity and/or source. This applies to the product, its container or other packaging or labeling information.
Medicines formulated by legitimate manufacturers that do not attain the pharmacopoeial standards because of errors in the quality or quantity of raw materials or in manufacturing.
Degraded Drugs

Exhibit chemical and biological instabilities due to unfavourable storage especially in tropical climates.
1. Avoidable illnesses
2. Avoidable deaths
3. Treatment failure
4. Drug resistance
I MARRIED FOR HER BEAUTY

ALL THAT SHINES IS NOT QUALITY
CHALLENGES TO QUALITY OF MEDICINES

1. Poor regulatory control at ports of entry
2. Weak enforcement of regulations
3. Inadequate quality control
4. Irrational use
5. Poor storage
EVOLUTION OF QUALITY IN PHARMACEUTICALS

1820/1864
- The first edition of United States Pharmacopoeia
- The first edition of British Pharmacopoeia

1902
- Unification of formula for potent drugs

1962
- Concept of efficacy with safety - toxicity testing
- Subsequently compliance to GMP and GLP

1967
- Int. Pharmacopoeia specifying quality control

1990s
- Establishment of the registration of pharmaceuticals for human use
- Quality assurance and quality control approach

2010s
- Quality Management System
- Six Sigma
- Lean Six Sigma
Quality Assurance vs Quality Control

**QA**
- Process
- Proactive
- Staff Function
- Prevent defects

**QC**
- Product
- Reactive
- Product line function
- Find defects

**QA focuses on product as well as equipment and procedures**

**QC focuses on product testing; daily assessment of all operations**
QA-QC Program was an attempt to provide a wholesome approach to quality of medicines.
Quality Management System

- Quality by testing (QbT)
- Quality by design (QbD)

QbT promotes testing of product to find defects.

QbD promotes “the building in of quality and not testing it.”
QUALITY BY DESIGN
Benefits of QbD for pharma Ind

- Better quality design of products
- Less # of manufacturing supplements
- Quick uptake of new technologies
- Better understanding and mitigation of risk
- Efficient review and quicker drug approvals
- Improvements in products and manufacturing
- An improved overall business model
THE SIX SYSTEM MODEL

Product

Quality system

Production system

Facilities & Equipment system

Laboratory control system

Materials System

Packaging & Labeling system
ASSURING QUALITY OF MEDICINES

Participants in assuring quality

How to test for quality
PARTICIPANTS IN ASSURING QUALITY

- Government leaders and policymakers
- Drug Regulatory Agencies
- Pharmaceutical Manufacturers
- Donors & NGOs
PARTICIPANTS IN QUALITY

- Procurement organizations, wholesalers and distributors
- Healthcare Providers
- Dispensers
- Patients and other consumers
PARTICIPANTS’ RESPONSIBILITIES

Governments
- Major keyplayers

Donors, NGOs
- Multi-roles reaching all key players

Regulate
- Producers
  - Build in Quality
- Sellers of medicines

License & Guide
- Healthcare providers and dispensers
  - Maintain Quality

Educate
- Patients and other consumers
  - Guide & Educate
HOW TO TEST FOR QUALITY OF MEDICINES

Analytical Tests:
- Description
- Identity test
- Assay
- Purity test
- Microbiological testing
- In-process tests
  - Uniformity of weight
  - Hardness
  - Friability
  - Disintegration
  - Dissolution
HOW HAVE WE ASSURED QUALITY?

DRUGS
BUILDING IN QUALITY
Counterfeit, Substandard And Genuine Medicines In Nigerian Market

Fake packaging
- wrong ingredient
- no active ingredient
- correct qty of ingredient
- incorrect qty of ingredient

Genuine packaging
- wrong ingredient (deliberate)
- no active ingredient
- incorrect qty of ingredient (deliberate)
GLOBAL SITUATION OF BAD QUALITY MEDICINES

WHO data base

- No API: 32.1%
- Incorrect Qty of API: 21.4%
- Wrong APIs: 20.2%
- Correct qties of API but fake packaging: 15.6%
- Copies of an original product: 8.5%
- High levels of impurities: 1%
CATEGORIES OF MEDICINES TESTED

NAFDAC/WHO/DFID

- Genuine: 47.5%
- Substandard: 35.6%
- Counterfeit: 16.9%
WHO STUDY 2010

Failure rates in QC laboratory testing

Cameroon (n=41)  Ethiopia (n=39)  Ghana (n=38)  Kenya (n=43)  Nigeria (n=61)  Tanzania (n=45)

37%  0%  39%  5%  64%  11%

Overall failure rate

Domestic
Imported
Drug product A is said to be bioequivalent to product B if it has the same:

- Ingredient
- Molar dose
- Route of administration
- Rate of availability
- Safety and efficacy
- Extent of absorption
BENEFITS OF BIOEQUIVALENCE STUDIES

- Acceptable and unacceptable drug products
- Generic substitution
- Aid price regulation
- Limit no of registered brands
- Guide regulatory decisions
- Good clinical decisions
- Reduce scarcity of drug products
- Effective tool for post-market surveillance
IN VITRO BIOEQUIVALENT STUDIES
BENEFITS OF DISSOLUTION TESTING AS IN VITRO BIOEQUIVALENCE TESTING

- A surrogate marker
- Economic approach
- Bioavailability problems
- Predict *in vivo* performance
- Assess if *in vivo* study is required
- Minimal ethical issues
Comparative dissolution profiles of i) lamivudine in 0.1N HCl and; ii) Zidovudine in 0.1N HCl (Ochekpe et al., 2006)
Comparative dissolution profiles of i) lamivudine in pH 4.5 and; ii) Zidovudine in pH 4.5 (Ochekpe et al., 2006)
Comparative dissolution profiles of i) lamivudine in pH 6.8 and; ii) Zidovudine in pH 6.8 (Ochekpe et al., 2006)
**SIMILARITY OF DISSOLUTION PROFILES OF ANTI-RETROVIRALS**

**Table 1:** Similarity of dissolution profiles of the drug products determined by similarity factor $f_2$

<table>
<thead>
<tr>
<th>Lamivudine</th>
<th>Zidovudine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand</strong></td>
<td><strong>$f_2$</strong></td>
</tr>
<tr>
<td>Ref - Combivir</td>
<td></td>
</tr>
<tr>
<td>Lazid</td>
<td>39.31</td>
</tr>
<tr>
<td>Virex-LZ</td>
<td>48.84</td>
</tr>
</tbody>
</table>

**Table 2:** Similarity of dissolution profiles of lazid and virex-LZ

<table>
<thead>
<tr>
<th>Lamivudine</th>
<th>Zidovudine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand</strong></td>
<td><strong>$f_2$</strong></td>
</tr>
<tr>
<td>Lazid vz Virex-LZ</td>
<td>59.31</td>
</tr>
</tbody>
</table>
DISSOLUTION TESTING FOR ANTIMALARIALS (SP) IN 0.1N HCl

Comparative dissolution profiles of i) Sulphadoxine drug products and sulphadoxine reference and; ii) Pyrimethamine drug products and pyrimethamine reference in 0.1N HCl (Ochekpe et al., 2012)
Comparative dissolution profiles of i) Sulphadoxine drug products and sulphadoxine reference and; ii) Pyrimethamine drug products and pyrimethamine reference in pH 4.5 (Ochekpe et al., 2012)
Comparative dissolution profiles of i) Sulphadoxine drug products and sulphadoxine reference and; ii) Pyrimethamine drug products and pyrimethamine reference in pH 6.8 (Ochekpe et al., 2012)
## Similarity of Dissolution Profiles of SP

<table>
<thead>
<tr>
<th>Sulphadoxine</th>
<th>Pyrimethamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brands</strong></td>
<td><strong>f&lt;sub&gt;2&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Brand 1</td>
<td>35.45</td>
</tr>
<tr>
<td>Brand 2</td>
<td>96.32</td>
</tr>
<tr>
<td>Brand 3</td>
<td>99.29</td>
</tr>
<tr>
<td>Brand 4</td>
<td>96.88</td>
</tr>
<tr>
<td>Brand 5</td>
<td>98.18</td>
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<td>Brand 6</td>
<td>51.00</td>
</tr>
<tr>
<td>Brand 7</td>
<td>92.98</td>
</tr>
<tr>
<td>Brand 8</td>
<td>99.96</td>
</tr>
<tr>
<td>Brand 9</td>
<td>62.79</td>
</tr>
<tr>
<td>Brand 10</td>
<td>99.96</td>
</tr>
<tr>
<td>Brand 11</td>
<td>29.04</td>
</tr>
<tr>
<td>Brand 12</td>
<td>38.62</td>
</tr>
</tbody>
</table>
Dissolution profiles of five brands of artemether/lumefantrine combination
# SIMILARITY OF DISSOLUTION PROFILES OF ARTEMETHER/LUMEFANTRINE

<table>
<thead>
<tr>
<th>Brands vs Reference (Coartem)</th>
<th>Similarity Factor $f_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART/LUM vs Coartem</td>
<td>54.9</td>
</tr>
<tr>
<td>Artemef vs Coartem</td>
<td>43.9</td>
</tr>
<tr>
<td>Combisunat vs Coartem</td>
<td>56.4</td>
</tr>
<tr>
<td>Lumartem vs Coartem</td>
<td>56.7</td>
</tr>
</tbody>
</table>
IN VITRO BIOEQUIVALENCE STUDY FOR ANTIBIOTICS

Dissolution profiles of six brands of ciprofloxacin tablets in 0.1N HCl (Ngwuluka et al., 2009)
## SIMILARITY OF DISSOLUTION PROFILES OF ANTIBIOTICS

<table>
<thead>
<tr>
<th>Brands vs Reference (Brand B)</th>
<th>Similarity Factor $f_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand A vs Brand B</td>
<td>53.9</td>
</tr>
<tr>
<td>Brand C vs Brand B</td>
<td>25.8</td>
</tr>
<tr>
<td>Brand D vs Brand B</td>
<td>23.5</td>
</tr>
<tr>
<td>Brand E vs Brand B</td>
<td>53.3</td>
</tr>
<tr>
<td>Brand F vs Brand B</td>
<td>17.6</td>
</tr>
</tbody>
</table>
PREDICTION: IN VIVO ABSORPTION FROM IN VITRO DISSOLUTION

- Assists in ascertaining that the predicted $C_{\text{max}}$ will be within the therapeutic range.
- Reduces the number of in vivo studies.
- Gives insight on the need for reformulation.
- Provides information on the rate of release.
- Gives insight into liberation of drug from dosage form and absorption patterns.
- Connects absorption, dissolution, efficacy, and safety.
PREDICTION: IN VIVO ABSORPTION FROM IN VITRO DISSOLUTION…

a) Comparative dissolution profiles of Ciprofloxacin in 0.1N HCl and; b) Comparative predicted plasma concentration profiles of ciprofloxacin.
a) Comparative predicted plasma concentration profiles of ciprofloxacin (6 hours) and; b) Comparative predicted plasma concentration profiles of ciprofloxacin (24 hours)
Plasma-concentration time profiles and whole blood concentration time profiles of proguanil and its metabolites, cycloguanil (CG) and 4-chlorophenylbiguanide (CPB) (Wattanagoon et al., 1987)
ANTI-MALARIAL ACTION OF CHLOROQUINE

International Conference on Harmonization (ICH) Q3A 2008 limits of impurities

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Reporting Threshold</th>
<th>Identification Threshold</th>
<th>Qualification Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2g/day</td>
<td>0.05%</td>
<td>0.10% or 1.0mg per day intake (whichever is lower)</td>
<td>0.15% or 1.0mg per day intake (whichever is lower)</td>
</tr>
<tr>
<td>&gt; 2g/day</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

Ten (10) brands of artesunate

Twenty-five (25) brands of paracetamol

Techniques - Accelerated Gradient Chromatography (AGC), Thin-Layer Chromatography and Gas Chromatograph-Mass spectroscopy (GC-MS)
<table>
<thead>
<tr>
<th>Code of PCM</th>
<th>Manufacture Date</th>
<th>Expiry Date</th>
<th>% of aniline per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand 1</td>
<td>Nov 2012</td>
<td>Oct 2017</td>
<td>0.59</td>
</tr>
<tr>
<td>Brand 4</td>
<td>-</td>
<td>Dec 2014</td>
<td>1.2</td>
</tr>
<tr>
<td>Brand 8</td>
<td>-</td>
<td>-</td>
<td>1.2</td>
</tr>
<tr>
<td>Brand 9</td>
<td>Aug 2009</td>
<td>Aug 2015</td>
<td>0.99</td>
</tr>
<tr>
<td>Brand 10</td>
<td>Oct 2012</td>
<td>Oct 2018</td>
<td>0.51</td>
</tr>
</tbody>
</table>

QUANTITY OF ANILINE IN PARACETAMOL SAMPLES
DIGITAL IMAGES OF DEGRADED PRODUCTS

Paracetamol

4-aminophenol
SYNTHESIS OF PARACETAMOL FROM PHENOL

Phenol → O-nitrophenol (dil. H₂SO₄, NaNO₃) + P-nitrophenol

Phenol → P-aminophenol (NaBH₄)

P-aminophenol + Acetic anhydride → Paracetamol
TLC PLATE OF ARTESUNATE INDICATING IMPURITY SPOTS AND SYNTHESIS OF ARTESUNATE
### QUANTIFICATION OF SUCCINATE IN ARTESUNATE SAMPLES

<table>
<thead>
<tr>
<th>Samples</th>
<th>Peak intensity of Dimethylsuccinate ($X10^6$)</th>
<th>Peak Intensity of other peaks ($X10^6$)</th>
<th>Total peak intensity ($X10^6$)</th>
<th>% concentration of dimethylsuccinate in sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.4</td>
<td>10.12</td>
<td>10.52</td>
<td>3.80</td>
</tr>
<tr>
<td>B</td>
<td>7.27</td>
<td>20.25</td>
<td>27.52</td>
<td>26.42</td>
</tr>
<tr>
<td>G</td>
<td>6.14</td>
<td>15.50</td>
<td>21.64</td>
<td>28.37</td>
</tr>
</tbody>
</table>
BUILDING IN QUALITY
THE NIGERIAN PHARMACEUTICAL SECTOR

Pharm sector scan (UNIDO)

- 120 Pharm industries
- 40% capacity
- Technical skills
- Improved basic infrastructure
- Upgrading of facilities
- WHO pre-qual (SWIPHA)
STABILITY OF VACCINES

Challenges:
- Cold chain
- Unstable at ambient temp
- Power supply

Possible solution:
- Stabilization of vaccines
STUDY ON NEWCASTLE DISEASE VACCINE

Method
- Stabilizers
- Blended with vaccine
- Freeze dried
- Subjected to 25°C and 37°C
- Activity determined

Outcome
- Stability maintained for 2 months
- In the absence of refrigeration
DEVELOPMENT OF NATURAL MATERIALS

- Novel excipients
- Improve the rate and extent of absorption of some drugs
- Locally source starch was modified using various techniques
- Dextrinization, hydrolysis, gelatinization and xerogelization
- Modified starches were characterized for tablet attributes
STUDY OF MODIFIED STARCHES

- Modified starches exhibited better flow properties
- Increase in disintegration times
- Can be explored for sustained release dosage forms

Time taken to release 50% ($T_{50}$) of chloroquine from tablets formulated with the various modified starches as binders (Ochekpe et al, 2013)
QUALITY OF MEDICINES: EVERYONE A STAKEHOLDER?
EVERYONE IS A STAKEHOLDER

YES!!!
References

“Fake drugs are more deadly than terrorism. Forty years of terrorism, has killed 65,000 people globally, compared with 200,000 in one year alone in China from counterfeit medicines.”

Ronald Noble, Interpol’s Secretary-General
Opening Remark to an Anti-Counterfeiting Conference in Africa