

WHO PREQUALIFICATION OF FINISHED PHARMACEUTICAL PRODUCTS (FPPs)

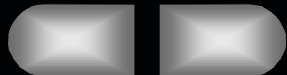
used in the treatment of HIV/AIDS, MALARIA
and TUBERCULOSIS

- Nairobi, Kenya - 13 April 2004
- János Pogány, Univ. D. Pharm. Sci., Consultant to WHO
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SUBJECTS FOR DISCUSSION

1. WHO MINIMUM REQUIREMENTS
FOR QUALITY OF FPPs
2. PREQUALIFICATION PROJECT
3. MAJOR CONCLUSIONS

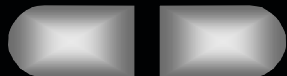


WHO'S MINIMUM REQUIREMENTS

(FOR WELL-ESTABLISHED, MULTISOURCE FPPs)

1. INTERCHANGEABILITY WITH PHARMACEUTICAL EQUIVALENTS ON THE SAME MARKET
2. CONSISTENT AND ACCEPTABLE QUALITY
3. ACCURATE AND LOCALLY USEFUL PRODUCT INFORMATION

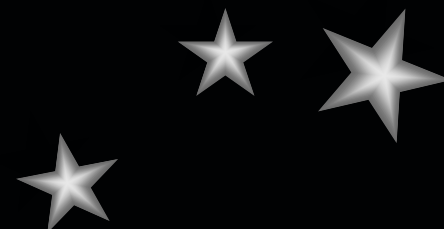
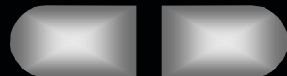
TOGETHER THESE AMOUNT TO ASSURANCE OF
QUALITY, SAFETY AND EFFICACY



INTERCHANGEABILITY

INTERCHANGEABILITY (IC) =
(ESSENTIAL SIMILARITY) =
PHARMACEUTICAL EQUIVALENCE (PE) +
+ BIOEQUIVALENCE (BE)

$$IC = PE + BE$$



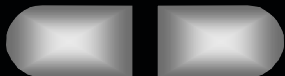


CONSISTENT AND
ACCEPTABLE QUALITY

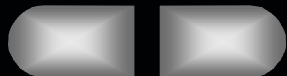
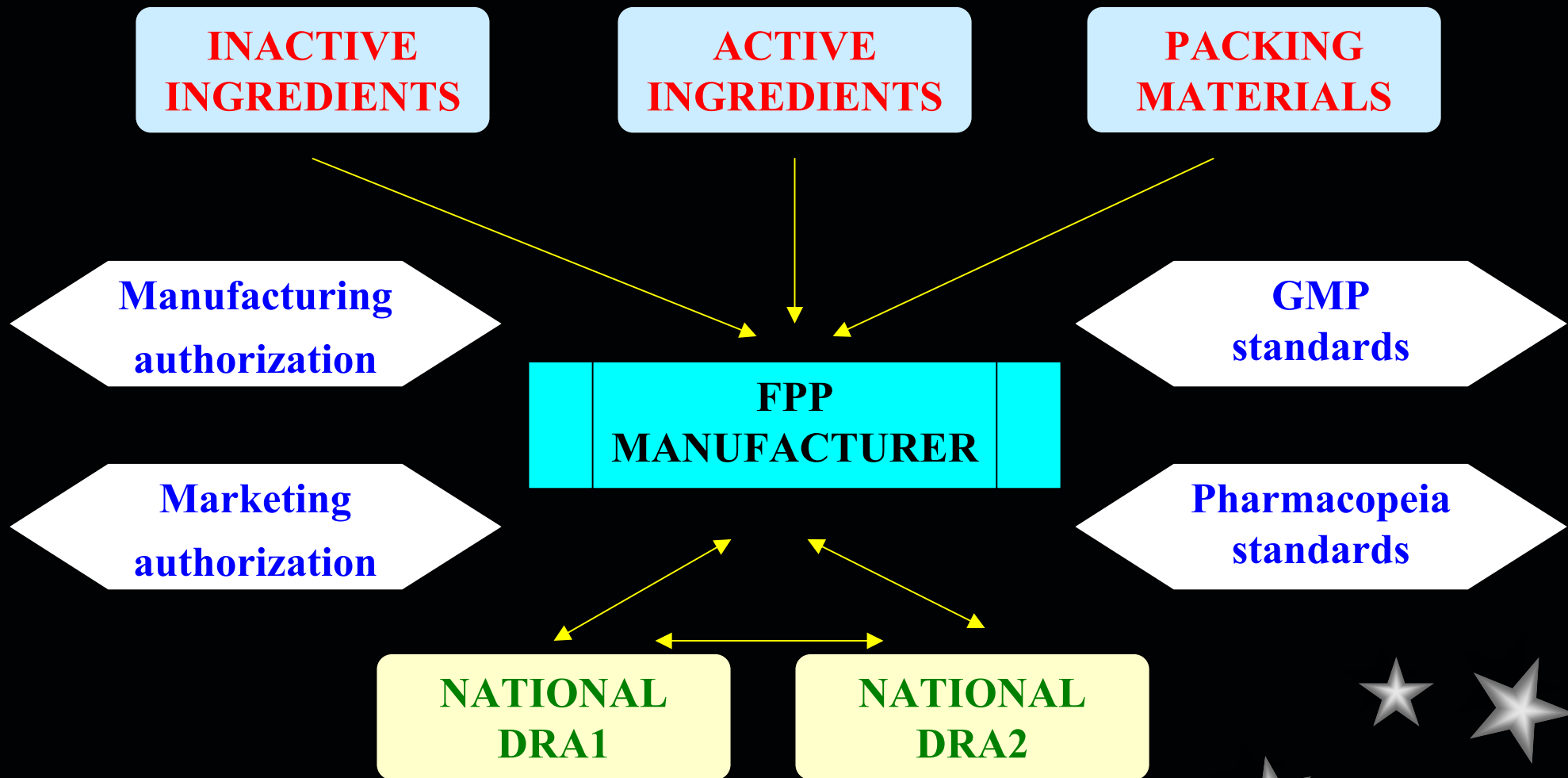


PHARMACEUTICAL EQUIVALENCE

- FPPs MEET THE **SAME OR COMPARABLE** STANDARDS
 - **SAME** API (CHEMICAL EQUIVALENCE)
 - **SAME** DOSAGE FORM (EU CPMP/QWP/1401/98 applies to different oral forms: tablets \approx capsules)
 - **SAME** STRENGTH
 - **COMPARABLE** LABELING
- GMP, BATCH-TO-BATCH CONSISTENCY
- STABILITY EQUIVALENCE



CONSISTENT AND ACCEPTABLE QUALITY



PILLARS OF REGULATORY QA

**MANUFACTURING
AUTHORIZATION**

DESIGN

CONSTRUCTION

MAINTENANCE

**AUTHORIZED
PERSON,**

ETC.

GMP, INSPECTION

IPC ADJUSTMENT

CONCURRENT
VALIDATION

RETROSPECTIVE
VALIDATION

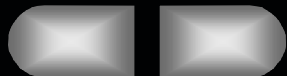
REQUALIFICATION,
ETC.

**MARKETING
AUTHORIZATION**

DEVELOPMENT
PHARMACEUTICS

ACCELERATED
STABILITY
SCREENING

PROSPECTIVE
VALIDATION, ETC



PILLARS OF REGULATORY QA

MANUFACTURING
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GMP, INSPECTION

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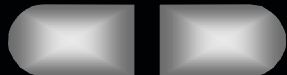
RETROSPECTIVE
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MARKETING
AUTHORIZATION
DEVELOPMENT
PHARMACEUTICS

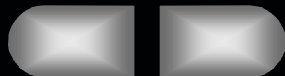
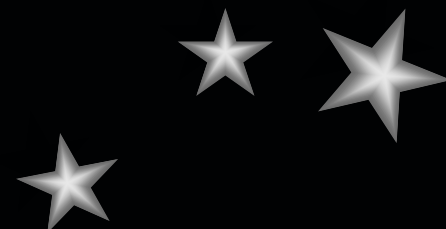
ACCELERATED
STABILITY
SCREENING

PROSPECTIVE
VALIDATION, ETC



Domestically manufactured products

- If the product has been locally developed and manufactured, the DRA **must** evaluate the data set itself (p. 23).
- If an **evaluation report** —critical summary and interpretation of the data, with conclusions— **is not available it is not possible to seek a WHO-type certificate** (p. 23).



PILLARS OF REGULATORY QA

MANUFACTURING
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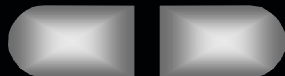
GMP, INSPECTION
IPC ADJUSTMENT
**CONCURRENT
VALIDATION**
**RETROSPECTIVE
VALIDATION**
**REQUALIFICATION,
ETC.**

MARKETING
AUTHORIZATION

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PHARMACEUTICS

ACCELERATED
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SCREENING

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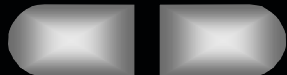
ACCURATE AND
LOCALLY USEFUL
PRODUCT INFORMATION



WHO MINIMUM REQUIREMENTS

- Summary of Product Characteristics (SmPC)
- Package insert
- Labels

Preferably approved by the NDRA.





PREQUALIFICATION PROJECT

WHO'S ROLE



WHAT ARE THE PROBLEMS?

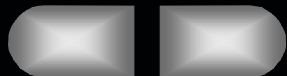
1. Sub-standard drugs purchased

- weakness or absence of quality assurance systems

2. Duplication of work in procurement

- no harmonized quality assurance system available for procurement organizations
- lack of harmonized GMP inspections

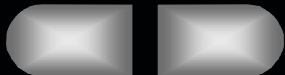
3. Risk: Sourcing sub-standard drugs is a waste of money and health risks to patients.



SUB-STANDARD FPPs

ORIGINATE „LEGALLY” FROM COUNTRIES WHERE:

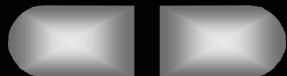
- Manufacture of APIs is not regulated
- Pharmaceutical exports/imports are not regulated
- Marketing Authorization (MA) of FPPs is issued without evaluation by the NDRA
- Stability studies are not required for MA
- Biostudies are not required for MA
- cGMP do not comply with WHO-GMP



PREQUALIFICATION PROJECT

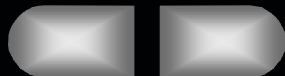
- **HIV/AIDS** FPPs and manufacturers on behalf of the United Nations partners including **WHO, UNICEF, UNAIDS** and **UNFPA**¹; **June 2001**
- **Malaria** FPPs and manufacturers on behalf of **WHO, Roll Back Malaria** and **Malaria Directorate**. **July 2002**
- **Tuberculosis** FPPs and manufacturers on behalf of **WHO**, the **Global Drug Facility** and **Stop TB partnership**; **September 2002**

¹The **World Bank** supports, in principle, prequalification of FPPs and manufacturers



BASIC PRINCIPLES (1)

- **VOLUNTARY** for participating manufacturers
- **LEGITIMATE** - General procedure and standards approved through WHO Expert Committee system involving all WHO Member States and WHO Governing bodies
- **WIDELY DISCUSSED** in many fora
 - FIP Congress, Nice 2002
 - Many meetings in Africa, Asia and Latin America
 - Supported by ICDRA in 2002 and 2004, representing more than 100 national drug regulatory authorities

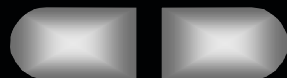


BASIC PRINCIPLES (2)

- **TRANSPARENT** (all information available on the web site):

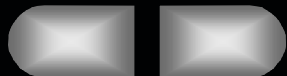
<http://mednet3.who.int/prequal/default.shtml>

- **OPEN** to both innovators and multisource/generic manufacturers
- **NO COST** for applicants during pilot phase



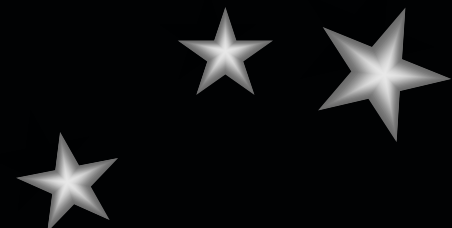
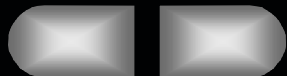
ROLE OF WHO

Technical assistance based on **WHO** quality specifications (monographs of the International Pharmacopoeia) and guidelines, plus **ICH** and other standards, where applicable



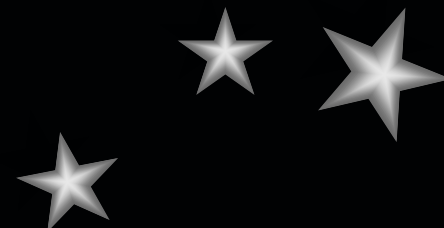
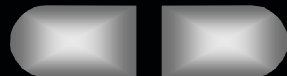
BASIC QUALITY STANDARDS

1. <http://www.who.int/medicines/library/qsm/manual-on-marketing/who-dmp-rgs-985.doc>
2. <http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpcover.html>
3. International Conference on Harmonization (ICH) guidelines



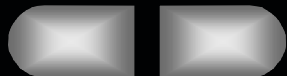
INTERNATIONAL PHARMACOPOEIA

- ABACAVIR – draft stage
- DIDANOSINE – draft stage
- EFAVIRENZ – draft stage
- INDINAVIR SULFATE – draft stage
- NELFINAVIR MESILATE – draft stage
- NEVIRAPINE – draft stage
- STAVUDINE – draft stage
- ZIDOVUDINE – draft stage



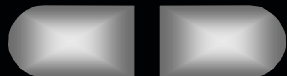
INTERNATIONAL PHARMACOPOEIA

- ARTEMETHER
- ARTEMISININ
- ARTEMOTIL
- ARTENIMOL
- ARTESUNATE
- MEFLOROQUINE HYDROCHLORIDE
- PROGUANIL HYDROCHLORIDE



MAJOR ACTIVITIES

1. **ASSESSMENT OF PRODUCTS DOSSIERS:** teams of professionals from national drug regulatory authorities *Brazil, Canada, China, Denmark, Estonia, Finland, France, Germany, Hungary, Indonesia, Malaysia, Philippines, Spain, South-Africa, Sweden, Switzerland, Tanzania, Zimbabwe ...*
2. **MANUFACTURING SITE INSPECTIONS:** teamwork of inspectors: chief inspector from well-established inspectorates (Pharmaceutical Inspection Convention Scheme countries) **WHO representative** (qualified GMP inspector) and **national inspector(s):** *Canada, France, Italy, Switzerland, The Netherlands ...*

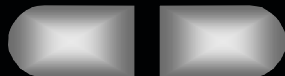


CURRENT STATUS

Evaluation of applications for the Marketing Authorization of FPPs used in treatment of:

- HIV/AIDS (270 – 97 as at January 2004)
- Malaria (37 - 2 as at January 2004)
- Tuberculosis (138 - 6 as at January 2004)

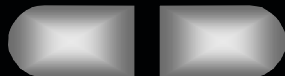
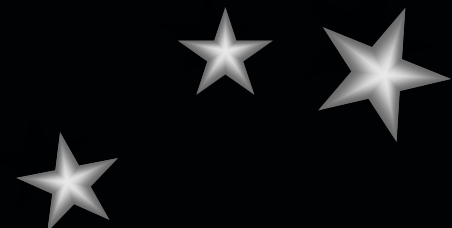
+ WHO-GMP inspection of the manufacturing sites of the applicants.



FPP DOSSIER ASSESSMENT

WHO evaluation criteria differ for a:

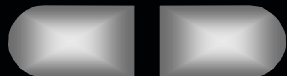
- Product **licensed**/registered in the ICH region and associated countries
- Product **not licensed**/registered in the ICH region and associated countries
 - Originator FPP exists
 - Originator FPP does not exist



NO ORIGINATOR AND GENERIC FPP NOT LICENSED IN THE ICH REGION

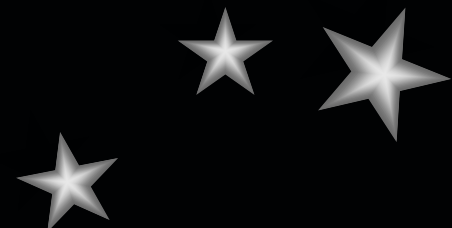
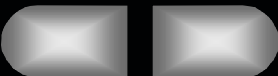
Examples have been/are:

- Artemisinin-type antimalarial FPPs
- 4-FDC antituberculous FPPs
- 3-FDC antiretroviral FPPs



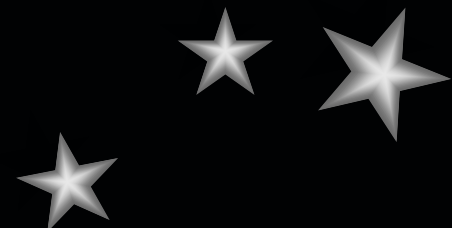
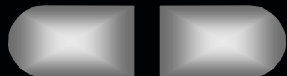
What will be required for generic drugs (1) ?

- 1. Details of the product
- 2. Regulatory situation in other countries
- 3. Active pharmaceutical ingredient(s) (API)
 - 3.1 Properties of the active pharmaceutical ingredient(s)
 - 3.2 Sites of manufacture of API(s)
 - 3.3 Route(s) of synthesis
 - 3.4 Specifications
 - API described in a pharmacopoeia
 - API not described in a pharmacopoeia
 - 3.5 Stability testing



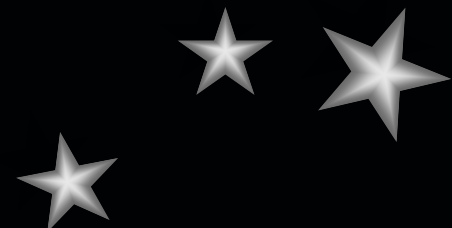
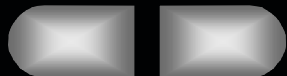
What will be required for generic drugs (2) ?

- Finished pharmaceutical product
- 4.1. **Formulation**
- 4.2. Sites of manufacture
- 4.4. **Manufacturing procedure**
- 4.5 Specifications for excipients
- 4.6 Specifications for the finished product
- 4.7 Container/closure system(s) and other packaging
- 4.8 **Stability testing**



What will be required for generic drugs (3) ?

- 4.9 Container labelling
- 4.10 **Product information**
- 4.11 **Patient information and package inserts**
- 4.12 Justification for any differences to the product in the country or countries issuing the submitted WHO-type certificate(s)
- 4.13 **Interchangeability (bioequivalence studies)**
- 4.14 Summary of pharmacology, toxicology and efficacy of the product



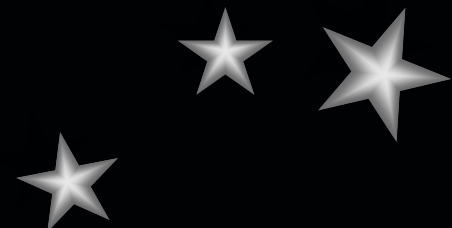
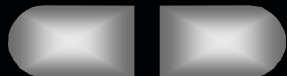
EXPANSION TO COVER OTHER AREAS

Prequalification of QC laboratories

- Standards and procedure ready
- Two laboratories assessed, one approved

Prequalification of procurement agencies

- Standards and procedure ready
- Model Quality Assurance System created, under finalization



4-FDC antituberculosis FPP

Originator FPP in ICH region

None

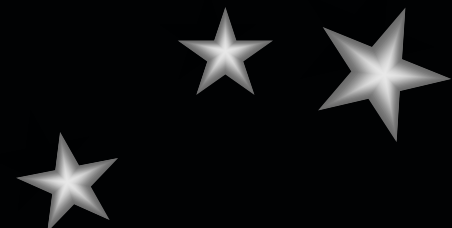
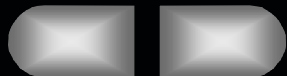
FPP in current Essential Drug List

Rifampicin 150 mg

Isoniazid 75 mg

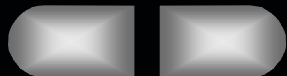
Pyrazinamide 400 mg

Ethambutol 275 mg



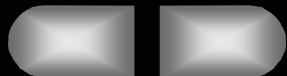
DEVELOPMENT PHARMACEUTICS (1)

1. Aluminium-strip packed products were stable, blister packed products showed both physical and chemical changes under accelerated test conditions.
2. Rifampicin is incompatible with isoniazid, in particular under acidic conditions.
3. Tablets in unpacked conditions showed severe (~60%) decomposition of rifampicin and also extensive physical changes.

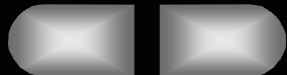


DEVELOPMENT PHARMACEUTICS (2)

4. The major decomposition product was isonicotinyl hydrazone.
5. The 4-FDC is sensitive to light.
6. Bioequivalence/dissolution time correlate with each other and deterioration on storage is formulation specific.

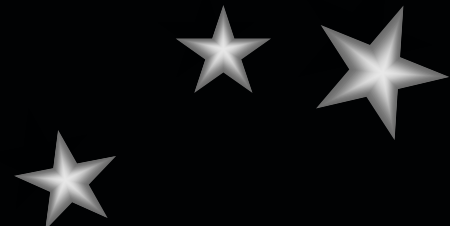
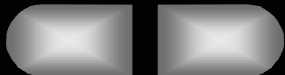


*40°C/75%RH (left) and
40°C/75%RH/Light (right)*



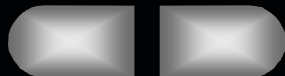
GOOD NEWS

- An **evidence-based**, unique **knowledge** has been obtained about generic FPPs used in the treatment of HIV/AIDS, malaria and TB
- Many potential manufacturers appreciate feedback and are willing to improve
- **QUALITY GENERIC FPPs DO EXIST**

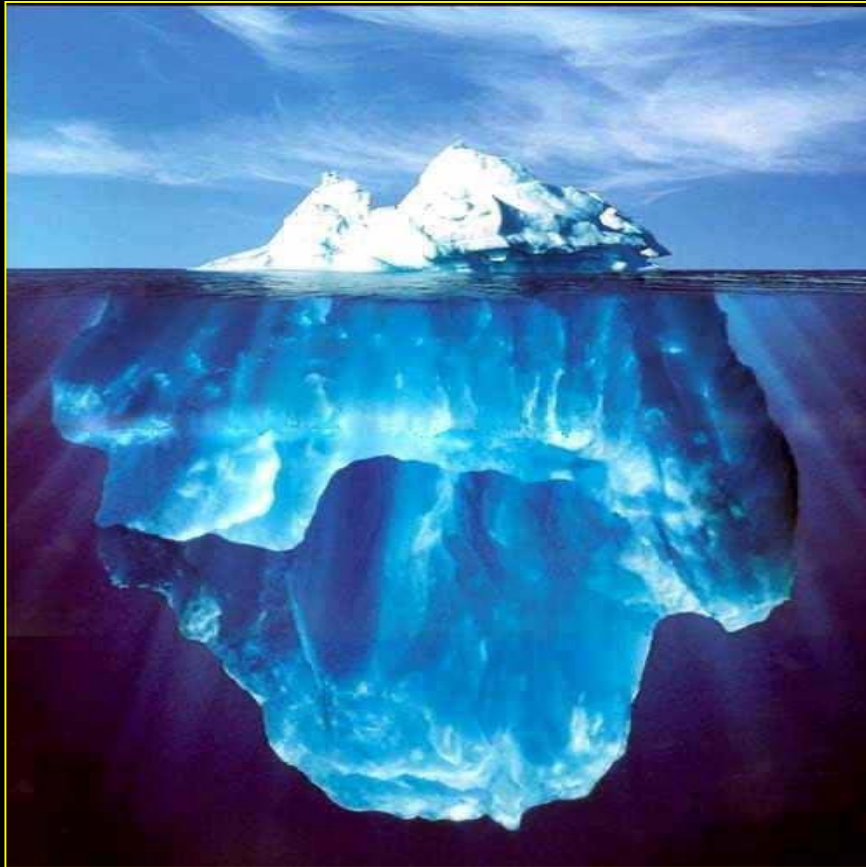


BAD NEWS

- Only **limited number of FPPs** have met the required standards
- **Takes time to get into compliance**
 - Data to be generated, tests carried out
 - GMP upgrade needed
- **QUALITY ASSURANCE COSTS MONEY AT THE INITIAL STAGE**

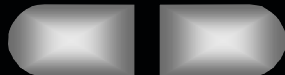


QUALITY COSTS



Visible costs

Hidden costs, e.g., changes after registration, non-competitive manufacturing process, low yield, waste, rework, etc.



THE KEY POINTS AGAIN

1. WHO GUIDELINES –ENDORSED BY THE MEMBER STATES- FOR MARKETING AUTHORIZATION AND GMP ARE FOLLOWED
2. PHARMACEUTICAL EQUIVALENCE
 - DEVELOPMENT PHARMACEUTICS
 - CRITICAL ASPECTS OF MANUFACTURING ARE IDENTIFIED FOR VALIDATION AND MONITORED THROUGH IPC TESTS AND SOPs
 - STABILITY
3. BIOEQUIVALENCE
4. NDRA_s SHOULD STRENGTHEN IMPLEMENTATION of MA and GMP REQUIREMENTS

