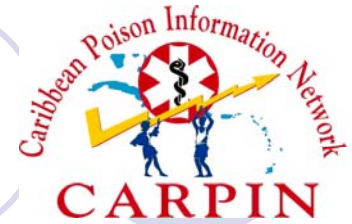


CARIBBEAN POISON INFORMATION NETWORK



**THIRD ANNUAL SCIENTIFIC CONFERENCE
UHWI KINGSTON, JAMAICA
MAY 31-JUNE 1, 2008**

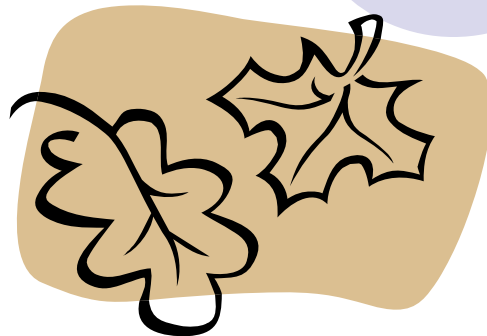


Contribution of Counterfeit Medicine to Toxicity



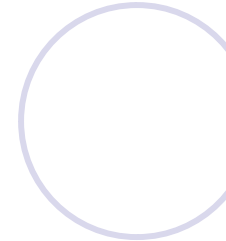
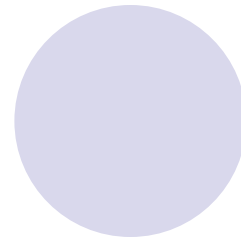
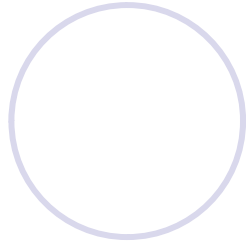
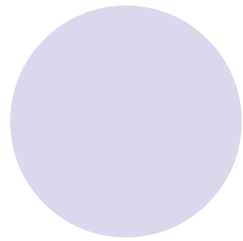
By

*Sarafadeen Adebayo, Ph.D.
MFIP, MAPV*



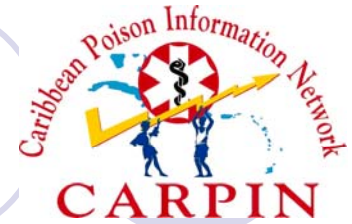
Tuesday, June 03, 2008





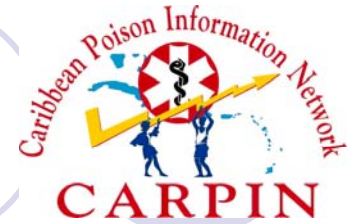
“The most useful drugs are poisons at low Doses, the most dangerous poisons are drugs at High Doses”

Objectives of this presentation



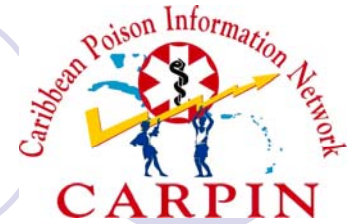
- At the end of this presentation, participants shall be able to:
- Review the various processes that modulate API release from dosage form
- Identify the impact of dosage form on the ability of API to reach the general circulation after administration.
- Identify the relationship between drug product ineffectiveness, effectiveness and toxicity.
- Establish the impact of counterfeiting on drug product ineffectiveness, effectiveness and toxicity.

Objectives ..cont.

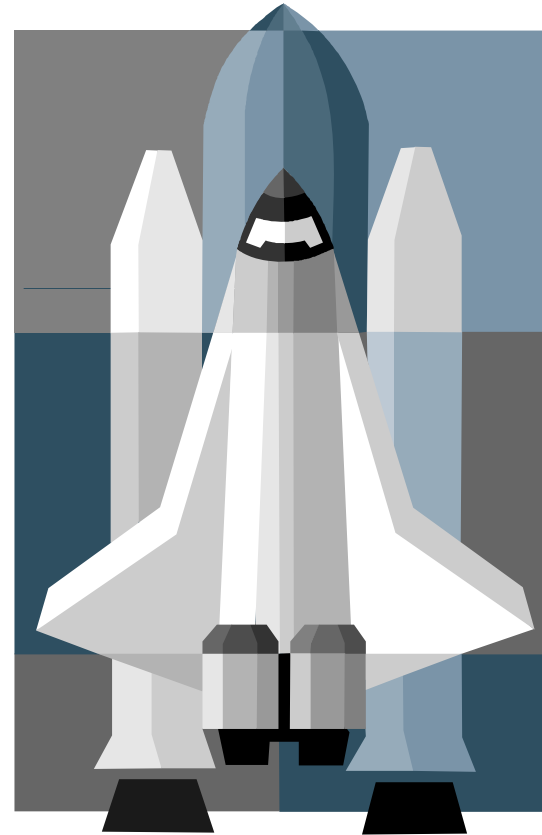


- Given a product on the shelf, apply some simple basic and semi-quantitative tests to determine its medicinal quality.
- Optimize drug product selection for safety, efficacy, stability and acceptability requirements of the patient or users.
- Articulate the main features of a counterfeit medicine and employ these features to avoid medication error and safeguard the health of the society.
- Establish the protocol for reporting the toxic effects of counterfeit medicines and medicinal products.

Introduction – Scope to this Presentation



- Drug products are vital components of therapeutic plans.
- Therapeutic effect depends on drug's ability to appear in adequate amounts at the site of action and remain for sufficient duration of time.
- Drug products must be of very high quality in design and in performance.
- Counterfeit drug products are those prepared, accidentally or deliberately, to contain no API or low level of API, low quality of API and /or excipients or those products manufactured under poor standards of GMP compliance.

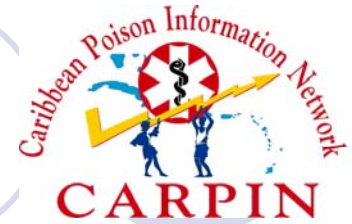


Introduction – Scope of this Presentation...



- Complete absence or low levels of API would result in therapeutic failure
- ***Wrong type or poor quality of API (which invariably would imply high levels of contaminants or degradation products) may result in toxicity.***
- In this presentation, distinctive features of counterfeit medicines and how they can be identified on the shelf will be discussed.
- In addition, some cheap, effective and available distinguishing qualitative and semi-quantitative tests, available in the developing countries, for counterfeit medicinal products identification will be discussed.

Dosage Form Design



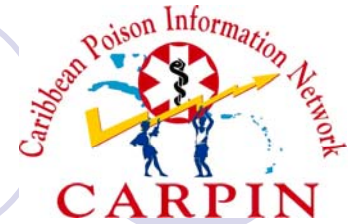
- Drugs are usually given as formulated preparations or medicines.
- Drug + Additives = Medicine
- Formulations can vary from relatively simple solutions to complex drug delivery systems.

Dosage Forms for Different Route of Administration



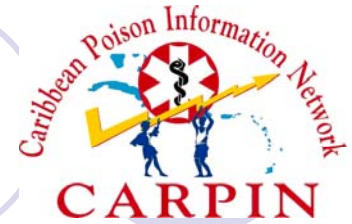
<i>Route of Administration</i>	<i>Dosage Forms</i>
Oral	Solutions, syrups, suspension, emulsion, gels, powders, granules, capsules, tablets
Rectal	Suppositories, ointment, cream, powder, solution (enema)
Topical	Ointments, creams, paste, lotions, gels, solutions, topical aerosols

Dosage Forms for Different Route of Administration (Cont.)



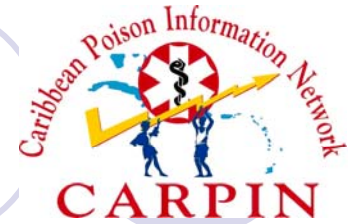
Parenteral	Injections (as solutions, suspensions, emulsions), implants, irrigation and dialysis solutions
Respiratory	Aerosols (solutions, suspensions, emulsion, powder forms), inhalations, sprays and gases
Nasal	Solutions, ointments, creams
Aural (Ear)	Solutions, suspensions, ointment and cream

Need for Dosage Form Design



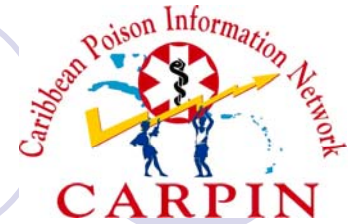
- Convenience for administration
- Protection & product stability
- Enhance dissolution rate & bioavailability
- Apply extended, controlled or targeted release
- Economy of scale in manufacturing
- Improved compliance/concordance

Major Objectives of Dosage Form Design



- **Safety**
- Effectiveness
- Predictable therapeutic response
- Stability
- Acceptability
- Amenable to large scale manufacturing with reproducible product quality

Dosage forms, Sales Volume & Propensity for counterfeiting



- Which dosage forms are most commonly counterfeited??***

- Which dosage forms have the largest volume of sales??***

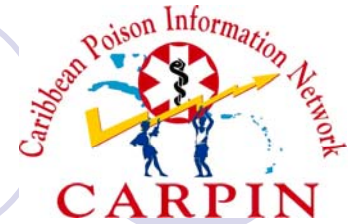
- Does correlation exist between volume of sale and potential for counterfeiting??***

Primary Dosage Forms

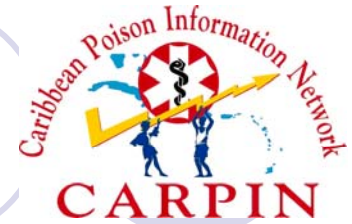


- The main target dosage forms are tablets and/or capsules.
- Although < 25 % of the tablets are marketed as injection, IV route is always required during the early toxicity, metabolic, bioavailability and clinical studies for precise drug and dose deposition.
- Other dosage forms are usually drug-specific and depend on successful development of tablets, capsules and injections.

Role of Excipients: Contribution to toxicity



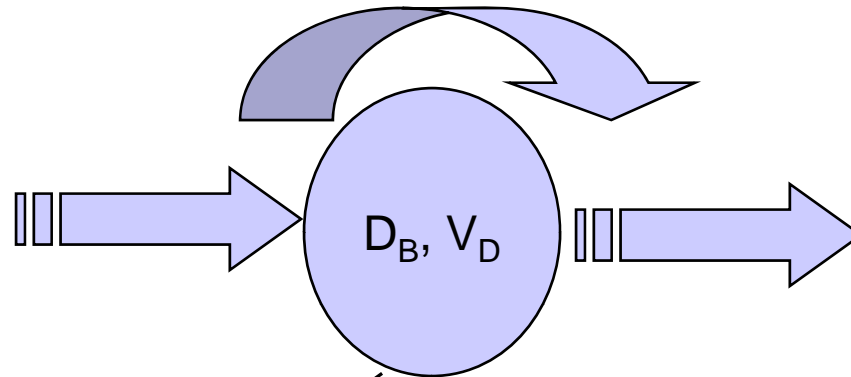
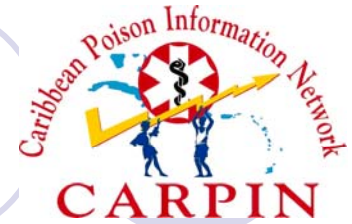
- **Co-solvents**
- Solubilizing agents
- Suspending agents
- Thickening agents
- Preservative
- Emulsifying agents.
- Others may be used to improve drug dissolution from dosage forms, improve fluidity and compressibility or add to organolepsis (elegance) as in colour, flavour and sweeteners



Major Assumptions on Drug appearance in the Plasma and activity

- Drug transportation is by blood/plasma
- Conc. in plasma represents the conc. in any other part of the body
- Any factor that affect drug conc. so as to be outside the TW will affect its activity
- Drugs of narrow therapeutic indices are the most critical

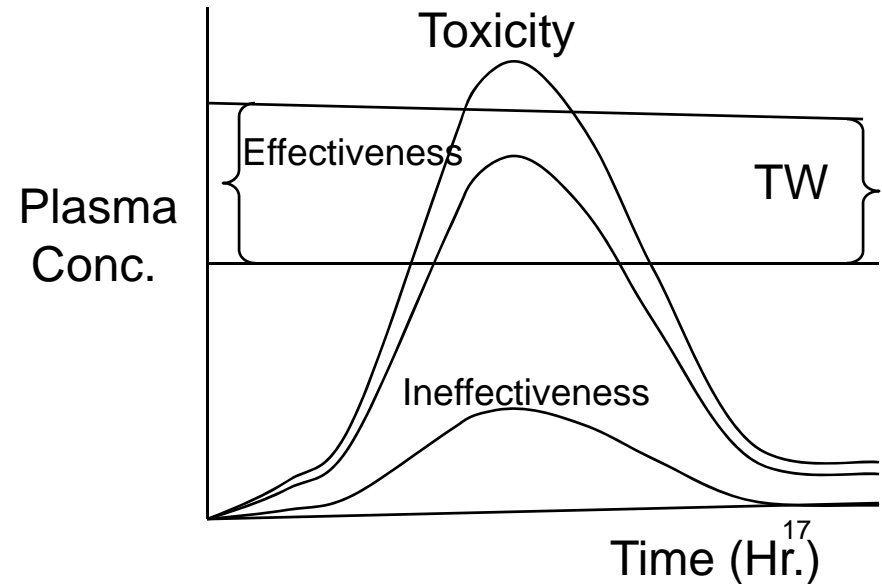
Drug Concentration and Movement



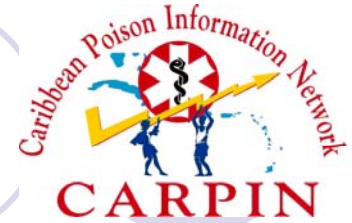
$$Conc. = \frac{Dose}{Volume}$$

**Obtaining this on consistent basis
requires robust DF design, validated
mfr process and QC programmes**

Tuesday, June 03, 2008



Causes of product defect



○ Raw material

- Purity – presence & proportion of contaminants: levels in mesylate salts of methyl & ethyl esters of methane sulphuric acid
- Potency – Presence of contaminants/degradation or loss of API
- Stability

○ Mfg process

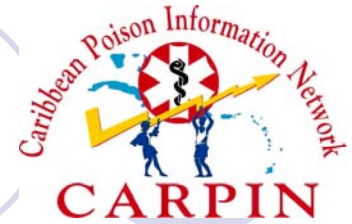
- May generate different form of API
- Packaging may also promote instability and cause toxicity

Salt Selection



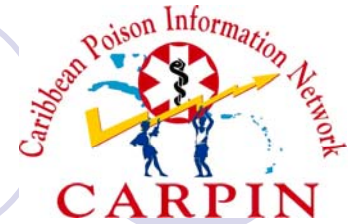
- A good salt should possess the following desirable characteristics:
 - Acceptable organoleptic properties
 - Easy to synthesize
 - Good flow and compaction properties
 - Minimal hydration
 - Non-toxic
 - Reproducible particle size & size distribution
 - Stable
 - Suitable aqueous solubility & intrinsic dissolution characteristics
 - Suitable bulk density
 - Suitable & sharp melting point.
 - Non-irritating to veins
 - Non-hygroscopic

Counterfeiting



- A product that is deliberately & fraudulently mislabelled with respect to its identity and/or source – WHO.
- Counterfeiting of medicinal products, API or product labels are criminal offences which may endanger patient health

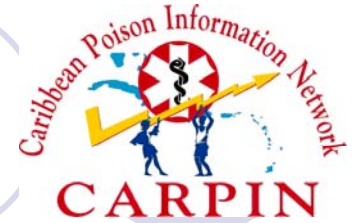
Counterfeit Medicines



- ***Counterfeit medicinal product may:***

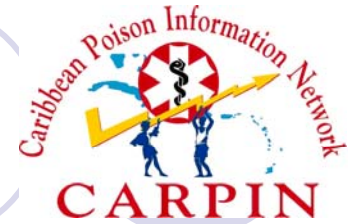
- Contain no API
- Contain the wrong API (cheap antibiotic instead of expensive one)
- Contain an incorrect (usually) low quantity of the API
- Be in low quality packaging
- Be manufactured with ***low-quality API or excipients***
- Manufactured under poor standards of GMP compliance

COUNTERFEIT MEDICINES



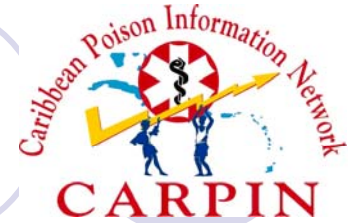
- Counterfeit medicines are part of the broader phenomenon of substandard pharmaceuticals – medicines manufactured below established standards of quality
- Dangerous to patients' health
- Ineffective for the treatment of diseases.
- Counterfeits are deliberately and fraudulently mislabeled with respect to identity or source.
- Counterfeiting occurs both with branded and generic products

Challenges presented by CM



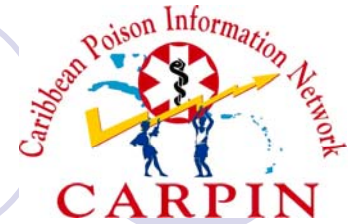
- Counterfeit medicines represent an enormous public health challenge.
- Anyone, anywhere in the world, can come across medicines seemingly packaged in the right way, in the form of tablets or capsules that look right, but which ***do not contain the correct ingredients and, in the worst case scenario, may be filled with highly toxic substances.***
- In some countries, this is a rare occurrence, in others, it is an everyday reality.

Nature: Inactive or Toxic



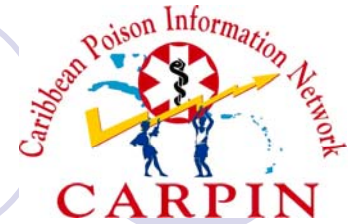
- Counterfeit medicines range from random mixtures of harmful toxic substances to inactive, useless preparations.
- Occasionally, there can be “high quality” fakes that do contain the declared active ingredient.
- In all cases, contents of counterfeits are unreliable because:
 - ***their source is unknown or vague and always illegal.***
 - ***Fake drugs can cause harm to patients and sometimes lead to death.***

Popular Products counterfeited



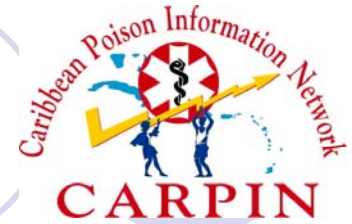
- Any kind of product can be and has been counterfeited:
 - expensive lifestyle and anti-cancer medicines
 - antibiotics
 - medicines for hypertension
 - cholesterol lowering drugs, hormones, steroids
 - inexpensive generic versions of simple pain killers and antihistamines.
 - medicines for the treatment of life-threatening conditions such as malaria, tuberculosis and HIV/AIDS.
 - Life saving drugs like adrenaline & hydrocortisone injections

Why are products counterfeited??



- Counterfeit Medicine is a Big Business
- The US based Centre for Medicines in the Public Interest predicts that counterfeit drug sales will reach **US\$ 75 billion globally in 2010, an increase of more than 90% from 2005.**
- Although precise and detailed data on counterfeit medicines is difficult to obtain, estimates range from around **1% of sales in developed countries to over 10% in developing countries**, depending on the geographical area.

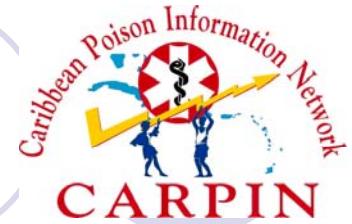
Potential toxic effects of Counterfeit Medicines: Case scenarios



- **A case in Argentina: In 2004, fake medicine led to a trail of death in Argentina.**

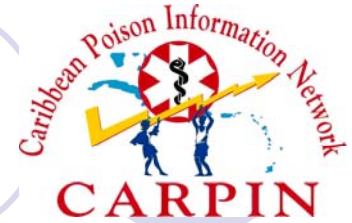
Veronica Diaz was a healthy 22 year old woman, living in Viedma, Argentina, who had mild anaemia caused by insufficient iron in her blood and required her to receive iron injections. In December of 2004, she became very sick and died of liver failure after receiving the 7th of a 10 injection treatment. The medicines authority of Argentina, ANMAT, determined that she had been given a highly toxic counterfeit. Authorities were unable to determine the source of the counterfeit product due to falsified paper work. While most of the counterfeit production throughout Argentina was recovered and four persons were prosecuted, the highly fragmented distribution system prevented the recall from being 100% successful. In May of 2005 another woman died and a 22 year old pregnant woman was injected with the same counterfeit. She survived but gave birth to a 26 week premature baby. To date, Argentinean law does not consider counterfeiting medicines a crime.

Cases of toxicity with Counterfeit Medicines



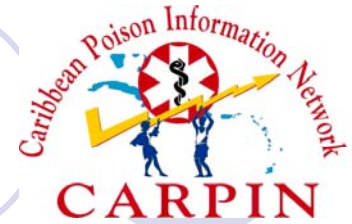
- During a meningitis epidemic in Niger in 1995, more than 50 000 people were inoculated with **fake vaccines** resulting in 2 500 deaths.
- The vaccines were received as a gift from a country which thought they were safe.
- 89 children died in Haiti in 1995 and 30 infants died in India in 1998 due to the consumption of paracetamol cough syrup prepared with diethylene glycol (a toxic chemical used in antifreeze).
- In 2001, in South-East Asia, a Wellcome Trust study revealed that 38% of 104 anti-malarial drugs on sale in pharmacies did not contain any active ingredients.
- In Cambodia, in 1999, at least 30 people died after taking counterfeit anti-malarials prepared with sulphadoxine-pyrimethamine (an older, less effective anti-malarial) which were sold as artesunate.

Prevalence



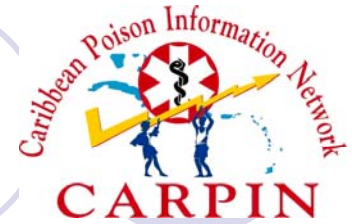
- Counterfeiting is greatest in those regions where the regulatory and legal oversight is weakest.
- Most industrialized countries with effective regulatory systems and market control (e.g. USA, most of EU, Australia, Canada, Japan, New Zealand) have a low proportion, i.e. less than 1% of market value
- Medicines purchased over the Internet from **sites that conceal their physical address** are counterfeit in over 50% of cases.

Prevalence....



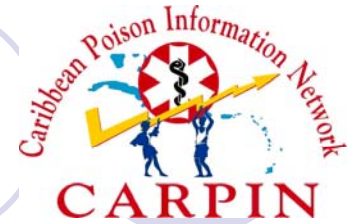
- Many countries in Africa and parts of Asia and Latin America have areas where more than 30% of the medicines on sale can be counterfeit, while other developing markets have less than 10%; overall, a reasonable range is between 10% and 30% (WHO, 2007)
- Many of the former Soviet republics have a proportion of counterfeit medicines which is above 20% of market value — this falls into the developing country range

Internet sales



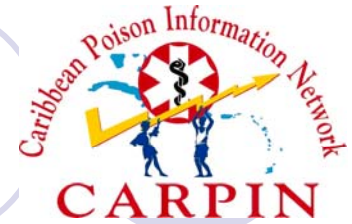
- In industrialized countries and to some extent in poorer countries, Internet-based sales of pharmaceuticals are a major source of counterfeit medicines, threatening those who seek cheaper, stigmatized or unauthorized treatments.
- Some Internet pharmacies are completely legal operations, set up to offer clients convenience and savings.
- They require patient prescriptions and deliver medications from government licensed facilities.
- Illegal Internet pharmacies sell medications without prescriptions and use unapproved or counterfeit products.
- In some cases, Internet pharmacies are operated internationally and sell products that have an unknown or vague origin.

Prevalence



- More prevalent in countries with:
 - weak drug regulation and enforcement,
 - scarcity or erratic supply of basic medicines,
 - unregulated markets and
 - unaffordable prices.

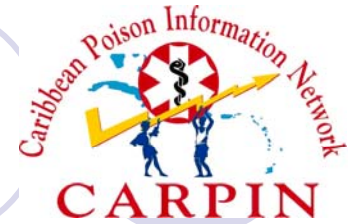
But as counterfeiting becomes more sophisticated, these products are increasingly present even in better regulated markets.



Sophistication of counterfeiting increase presence in Advanced Countries

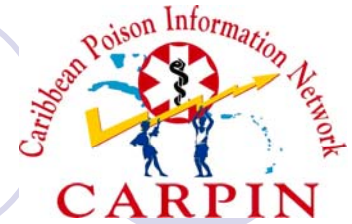
- The United States Food and Drug Administration (FDA) issued an alert about fraudulent flu remedies, including counterfeit prescription oseltamivir (Tamiflu) medication – Jan. 2006
- Counterfeit capsules of Tamiflu found in the Netherlands containing lactose and vitamin C, and no active substance - 2006 (The Dutch Healthcare Inspectorate warned consumers in early 2006 not to buy Tamiflu through the Internet)
- In the United Kingdom, officials seized 5 000 packets of counterfeit Tamiflu in early 2006, estimated to be worth £500 000.
- *The Lancet* published recently a report that up to 40% of products labeled as containing artesunate (anti-malarial) contain no API
- Studies have shown that counterfeiters' ability to reproduce holograms and other sophisticated printing techniques had dramatically improved between 2001 and 2005, making detection even more difficult.

Around the world: reports of counterfeit medicines



- Peru: estimated at US\$ 40 million in 2002 to a current US\$ 66 million, according to Peru's Association of Pharmaceutical Laboratories (ALAFARPE)
- The General Directorate of Medicines, Supplies and Drugs (DIGEMID) of the Department of Health (MINSA) seized around 460 000 adulterated and expired medicines in 2005 alone.
- In 2006, Russia's Federal Service for Health Sphere Supervision (FSHSS) reported that 10% of all drugs on the Russian market were counterfeit.

Around the world: reports of counterfeit medicines



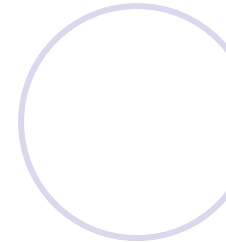
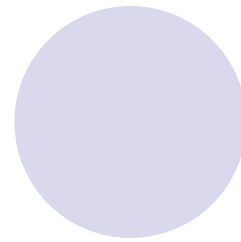
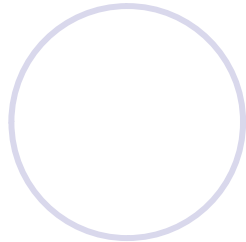
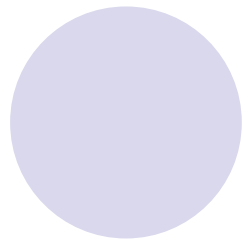
- **In 2003**
- The Philippine: 30% of drug store outlets visited by food and drug deregulation officers carry and sell counterfeit drugs.

- **In 2002**
- Cambodia: 13% of drugs on the domestic market were counterfeit or substandard, including anti-malaria drugs and antibiotics.
- China: about 8% of over-the-counter drugs sold in China are counterfeit.
- India: illegal drugs had grown from 10% to 20% of the total market.
- Nigerian: 70% of drugs in circulation in the country are either fake or adulterated.

WHO contributions to the global effort to combat counterfeit medicines

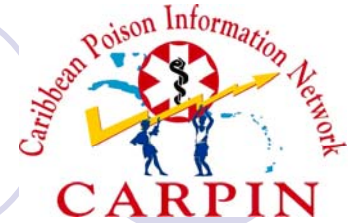


- In order to mobilize awareness and action in the fight against fake drugs, in February 2006, WHO created the first global partnership known as the International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT).
- IMPACT is comprised of all 193 WHO Member States on a voluntary basis and includes international organizations, enforcement agencies, national drug regulatory authorities, customs and police organizations, non-governmental organizations, associations representing pharmaceutical manufacturers and wholesalers, health professionals and patients' groups.
- These groups have joined to improve coordination and harmonization across and between countries so that eventually the production, trading and selling of fake medicines will cease. To accomplish this mandate, IMPACT will focus on the following five key areas:



Identification of counterfeit medicinal Products

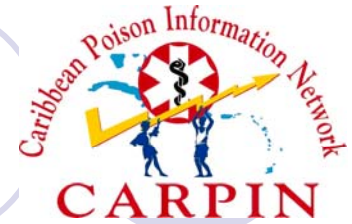
Available methods



- Verify content of API
- Make visual observations (colour, size, shape, markings, etc.)
- Examine label information about API
- Use identity tests specified in the registered product specification or pharmacopoeia specification

Identity test to distinguish glycerol from diethylene glycol became official after 100 children died in mid-1990

Specific & Non-specific Instrumental Techniques



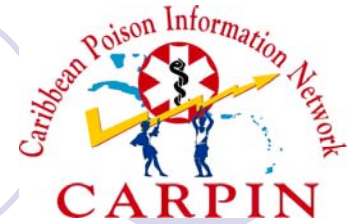
- IR Spectrum – one of the most commonly used (xteristic fingerprint spectrum) – e.g. atenolol CH₃Cl extract
- Combination of non-selective techniques – m.p., TLC & UV spectrometry e.g. atenolol drug substance identification
- Oral solution uses TLC & HPLC

ID Test ...



- Should distinguish optical isomer, different salts & polymorphic forms
- Optical rotation suffices to distinguish enantiomers
- Chiral HPLC to verify enantiometric nature of wanted & quantify enantiomeric impurities

Identification ...



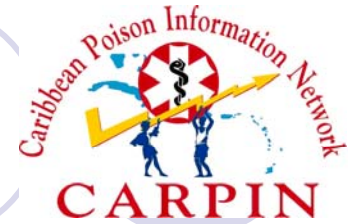
- Counter ions of acidic & basic drugs can be confirmed in bulk substances
- Std. Pharmacopoeial tests for Chloride, phosphate, citrate, sodium, calcium, aluminum etc.

Identification of solid dosage forms



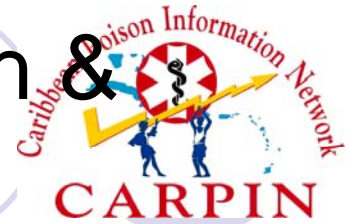
- Combination of colour, size, shape, breakmarks/scoring
- Physicochemical tests for qualitative & quantitative composition of API
- Chromatographic screening using TLC, HPLC, GC
- Identification of 'rogue' tablets in a container

Quantification of API



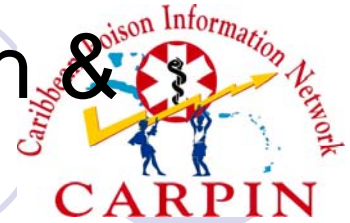
- Content of API is important quality parameter for efficacy
- With no access to assay method in market authorization or pharmacopoeia monograph, suitable assay procedure may have to be developed
- Common technique for assay include: HPLC, LC, UV, CE, NIR spectroscopy

General tests for uniformity of batch & Fitness for use



- Uniformity of mass & uniformity of content of solid dosage form
- In vitro disintegration & dissolution testing of tablets & capsules
- Particle size testing of medicines such as powders/granules in sachets, dry syrup & powder for suspension

General tests for uniformity of batch & Fitness for use



- Viscosity test on creams & ointments
- Sterility test for parenteral & ophthalmic products
- Test for microbiology quality of non-sterile products
- Friability testing of tablets
- Aerodynamic assessment of fine particles in inhalation products

Defective samples & Low potency samples



- Products may show physical, chemical or microbiological defects
- These may affect safety and efficacy
- Low potency should be confirmed by assay & dissolution tests using 'good' sample as reference
- Investigate polymorphism, uniformity of AI & particle size of AI

Contamination



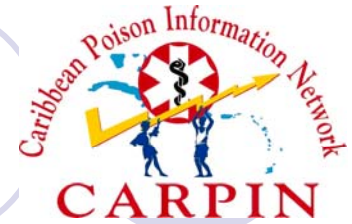
- Content of AI & impurities should be checked in products with high incidence of unwanted side-effect.
- Impurities (related substances) can be detected with HPLC, GC, CE or TLC.
- A comparison of chromatographic profiles of complaint sample should be made with that of a 'good' batch of product.

Contaminants – residual solvents



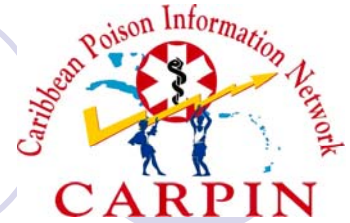
- Isopropyl ether may impart unpleasant taste or odour to the product
- Some solvents are toxic even at very low levels – Benzene & other ICH Class 1 solvents
- These should be avoided in Pharmaceutical manufacturing

ICH Class 1 solvents



- If use is unavoidable, must be controlled to very low levels in drug substances
 - Benzene – 2 ppm
 - Carbon tetrachloride – 4 ppm
 - 1,1-dichloromethane – 8 ppm
- Even less toxic Class 2 & and Low toxicity potential Class 3 ICH solvents should be controlled to permitted daily exposure levels.

Identification of Unrelated Organic impurities



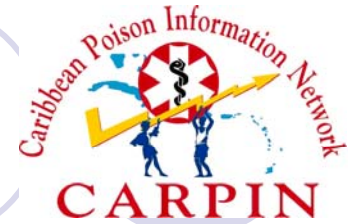
- More difficult as they are present in low levels & are unrelated to Ai or synthetic routes
- May arise from accidental cross-contamination with substances or products manufactured at the same site
- A full screenig programme with chromatographic & spectrometric instrumentation is required (e.g. HPLC-MS)

Mineral Impurities



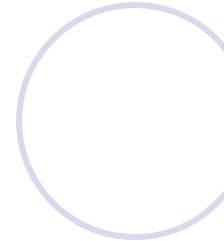
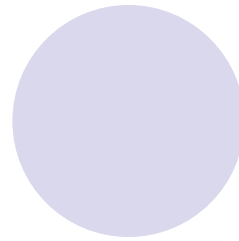
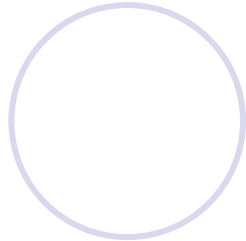
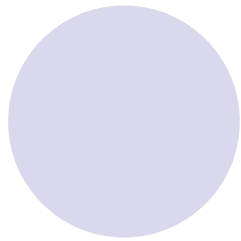
- Simple inorganic ions & heavy metals may give problems of safety & quality
- Heavy metals & ions such as Al, Ni may be toxic when administered in high doses or over long periods
- Metallic ions – Fe^{3+} , Cu^{2+} , Co^{2+} may catalyze oxidative decomposition reaction of AI e.g. (adrenaline, morphine, phenothiazines) causing formation of toxic or coloured impurities
- They can be determined by flame atomic emission or atomic absorption spectrometry
- Typical limit is 0.1 - 0.5 % for individual & 0.2 - 1% for total impurities

Biological & Biotechnology Products



- These are usually characterized by:
 - Determination of amino acid sequence
 - Determination of aa composition
 - Peptide mapping
 - Number & position of sulfydryl groups & disulphide bridges
 - Carbohydrate structure

These require special instrumentation & analytical expertise



THANK YOU

