Drug Quality in Generics, Substandard Drugs & Copies

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Preamble

• Health expectations must be matched with available resources
• Not here to dismiss generic formulations
  - Many are of excellent quality
  - Can be substituted for the original product
• But immediate monetary gains, if any, may be offset by additional healthcare costs
Generic Products

• Assumptions
  - Generics save money
  - Therapeutically equivalent to branded product
• Not true for poor quality formulations
• Stakeholders concerned by drug quality
  - Patients, Prescribers and pharmacists, HMOs and Governments & Pharmaceutical companies

Substandard and Counterfeit Drugs Defined by WHO

- Substandard drug
  - A “genuine” drug product
  - Does not meet quality specifications
- Counterfeit drug
  - Deliberately and fraudulently mislabeled
  - Can apply to branded or generic drugs
  - Includes products with correct or wrong ingredients, without active ingredients, with insufficient active ingredients, with fake packaging

Streptokinase Activity

“Same” formulation!

Distributor / Manufacturer


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Known Problems with Generic Drugs

- Excipients
- Poor quality drugs
  - Content
    - Drug, isoforms, isomers & impurities
- Lack of therapeutic equivalence
- Dishonesty
  - Fake drugs
  - False registration data
What are Pharmaceutical Excipients?

Substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form.
Excipients

- Binders
- Disintegrants
- Fillers (diluents)
- Lubricants
- Glidants (flow enhancers)
- Compression aids
- Colours
- Sweeteners
- Bittering agents
- Preservatives
- Suspension/dispersing agents
- Film formers/coatings
- Flavours
- Printing inks
Pharmaceutical Equivalence

**CONSTANT**
- Strength
- Dose form
- Active ingredient
- Route of administration

**VARIABLE**
- “Inert” ingredients
  - Fillers
  - Binders
  - Excipients
- Shape
- Colour
- Flavour
- Packaging
- Shelf life
• **Clopidogrel**
  • Hydrogenated castor oil
  • Hydroxypropylcellulose
  • Mannitol
  • Microcrystalline cellulose
  • Polyethylene glycol 6000
    - Ferric oxide
    - Hypromellose 2910
    - Lactose monohydrate
    - Titanium dioxide
    - Triacetin.
  • Polished with Carnauba wax.
Problems with Excipients

- Hypersensitivity reactions
- Peripheral neurotoxicity
- Dyslipidaemia
- Inhibition of
  - P-glycoprotein
  - Cyp3A4
Poor Quality Drugs
Content
Drug, Isoforms, Isomers & Impurities
Clopidogrel

- Has an asymmetric carbon atom
- Therefore exists in R & S forms
- S-form has anti-platelet activity
- R-form does not
• **S-clopidogrel**
  - R-clopidogrel is an impurity
    • Inactive against platelet aggregation
    • Gives rise to neurological side effects
    • Should be < 0.5%

• **Other impurities**
  - Hydrolysis product < 0.4%
  - Overall < 2%
Generic Clopidogrel

Analysis of purity in 19 drug product tablets containing clopidogrel: 18 copies versus the original brand

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Gomez Y et al. Journal of Pharmaceutical and Biomedical Analysis 34, 341–348, 2004
Generic Clopidogrel

- 19 Formulations
  - 18 generic and 1 original brand
- Tested for
  - Total content
  - Impurities
    - R-isomer
    - Hydrolysis product
    - Other impurities
  - Dissolution

Gomez Y et al. Journal of Pharmaceutical and Biomedical Analysis 34, 341-348, 2004
Generic Clopidogrel Content

50%, 9/18, < 95%

Gomez Y et al. Journal of Pharmaceutical and Biomedical Analysis 34, 341–348, 2004
Generic Clopidogrel R-Isomer

100%, 18/18, Fail

Gomez Y et al. Journal of Pharmaceutical and Biomedical Analysis 34, 341–348, 2004
Generic Clopidogrel Hydrolysis Product

87%, 14/18, Fail

Gomez Y et al. Journal of Pharmaceutical and Biomedical Analysis 34, 341–348, 2004
Generic Clopidogrel
Total Impurities

88%, 16/18, Fail

Gomez Y et al. Journal of Pharmaceutical and Biomedical Analysis 34, 341–348, 2004
Generic Clopidogrel

- Compared to Plavix®
  - Their amount of impurities was higher
  - The content of clopidogrel was lower
  - The dissolution profiles were different

Gomez Y et al. Journal of Pharmaceutical and Biomedical Analysis 34, 341–348, 2004
False Registration Data

FOR IMMEDIATE RELEASE
Feb. 25, 2009

FDA Takes New Regulatory Action Against Ranbaxy’s Paonta Sahib Plant in India
Agency halts review of drug applications from plant due to evidence of falsified data; invokes Application Integrity Policy

The U.S. Food and Drug Administration today announced that a facility owned by India-based Ranbaxy Laboratories falsified data and test results in approved and pending drug applications. The facility, Paonta Sahib, has been under an FDA Import Alert since September 2008.
Continued Quality Issues

US FDA pulls 27 ANDAs for drugs made at banned Ranbaxy plants

22-Aug-2012

Related topics: QA/QC, Regulations, Regulatory & Safety

Ranbaxy has asked the US FDA to withdraw 27 ANDAs for products previously made at Indian manufacturing facilities hit with consent decree earlier this year.

The Indian firm told the Bombay Stock Exchange (BSE) the ANDAs in question “do not pertain to current business and will have a negligible impact on...business in USA,” adding that the withdrawal will allow it to focus on applications that are of “greater importance.”

The withdrawal – detailed in the US Federal Register – is the latest stage in Ranbaxy’s efforts to address quality problems at its plants in Dewas, Batamandi and Paonta, which have been the subject of a US Food and Drug Administration (FDA) import ban since 2008.

22 Aug 2012
One of the recurring allegations made in the latest letter is that tests purporting to cover stability analysis over a nine month period were actually carried out on the “same day or within a few days of each other.”
Dirty medicine
May 15, 2013 9:03 AM ET

The epic inside story of long-term criminal fraud at Ranbaxy, the Indian drug company that makes generic Lipitor for millions of Americans.

By Katherine Eban

features.blogs.fortune.cnn.com/2013/05/15/ranbaxy-fraud-lipitor/, accessed June 14th 2013
Sun Pharmaceutical to acquire Ranbaxy in $4bn deal

India’s Sun Pharmaceutical has agreed to acquire rival Ranbaxy - majority owned by Japan’s Daiichi Sankyo - in an all-stock deal worth $4bn (£2.4bn).

The combined entity will be India's largest pharma company and the world's fifth-biggest generic drugs maker.

It comes at a time when Ranbaxy is under the scrutiny of US regulators who have imposed import bans on drugs manufactured at some of its facilities.

Related Stories

- Unit of Sun Pharma hit by US ban
- Indian drug firm suspends shipments
- US bans more products from Ranbaxy
Sun Pharma: Division of Indian drugmaker in US import ban

Sun Pharma said it had started taking steps to address the FDA's concerns.

The US has banned imports from a division of India's Sun Pharmaceutical Industries, one of the country's biggest drugmakers.

US regulators said the unit was not "operating in conformity with good manufacturing practices".

Related Stories

Indian drug firm suspends shipments
European Medicines Agency recommends precautionary recall of batches of clopidogrel-containing medicines from Acino Pharma GmbH
Recall due to good manufacturing practice (GMP) failure at active substance manufacturer site

EMA Clopidogrel Recall

- API from Glochem Industries Ltd, Visakhapatnam (India), GMP violations
- The Marketing Authorisation Holder Acino Pharma GmbH
  - A1 Pharma,
  - Clopidogrel Acino
  - Clopidogrel Acino Pharma
  - Clopidogrel Acino Pharma GmbH
  - Clopidogrel Hexal
  - Clopidogrel Ratiopharm
  - Clopidogrel Ratiopharm GmbH
  - Clopidogrel Sandoz
FDA finds contaminated drug ingredient at GSK Ireland plant

BY VRINDA MANOCHA
Tue Apr 1, 2014 8:27pm BST

(REUTERS) - The U.S. Food and Drug Administration found that a drug ingredient manufactured at a GlaxoSmithKline Plc plant in Ireland was contaminated and said the company did not take sufficient action to resolve the problems.

GSK said the ingredient was paroxetine, used to make its antidepressant drugs Paxil and Seroxat.

The company said it had proposed a recall of certain batches of the drugs from wholesalers but there was no risk of harm to patients taking these drugs.
Generic drugmakers' woes put focus on quality over price

Bill Berkrot  New York  Last Updated: March 26, 2014 | 16:47 IST

TAGS: Ranbaxy Laboratories | Sun Pharma | Dr Reddy's | Wockhardt | generic drugs | USFDA | Food and Drug Administration | Indian drugmakers

A spate of regulatory warnings for India's generic drug manufacturers will add a new emphasis on the quality of such medicines in an industry long dominated by the ability to deliver treatments as cheaply as possible, analysts say.
Warfarin Formulations

Anticoagulation

Resource Use and Cost Implications of Switching Among Warfarin Formulations in Atrial Fibrillation Patients

Winghan Jacqueline Kwong, Siddhesh Kamat, and Christy Fang

The Annals of Pharmacotherapy . 2012 December, Volume 46, 1609-16
“The use of both generic and branded formulations of warfarin interchangeably, or the use of generics from more than one manufacturer, was associated with increased use of all-cause health care resources and total costs in patients with AF.”

The Annals of Pharmacotherapy 2012 December, Volume 46
Switching from Brand-Name to Generic Medications

• **Conclusions**
  - Physicians underestimate the frequency of generic substitution
  - May not be as economically profitable as once hoped
  - Generic substitution may give rise to compliance issues
  - Must be done in collaboration with the patient and with close monitoring
  - Medication regulatory boards should consider adding a warning label on generic medications

Desmarais JE, Beauclair L, Margolese HC. CNS Neuroscience & Therapeutics 17 (2011) 750–760
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