

Drug Quality in Generics, Substandard Drugs & Copies

Atholl Johnston
Professor of Clinical Pharmacology



Barts and The London
School of Medicine and Dentistry

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

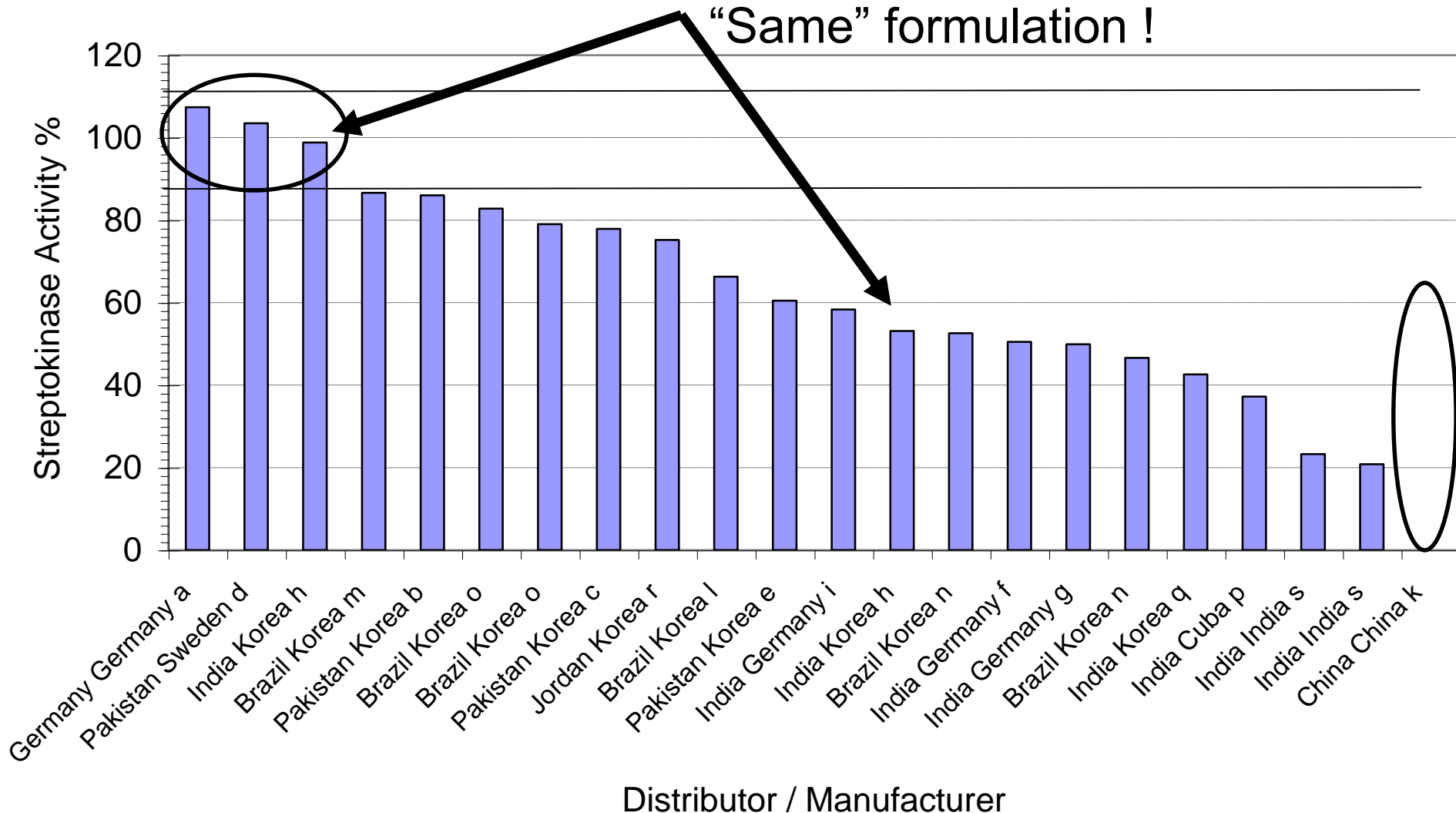
Generic Products

- 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



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 (diluent)
- 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



Plavix[®]



- 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

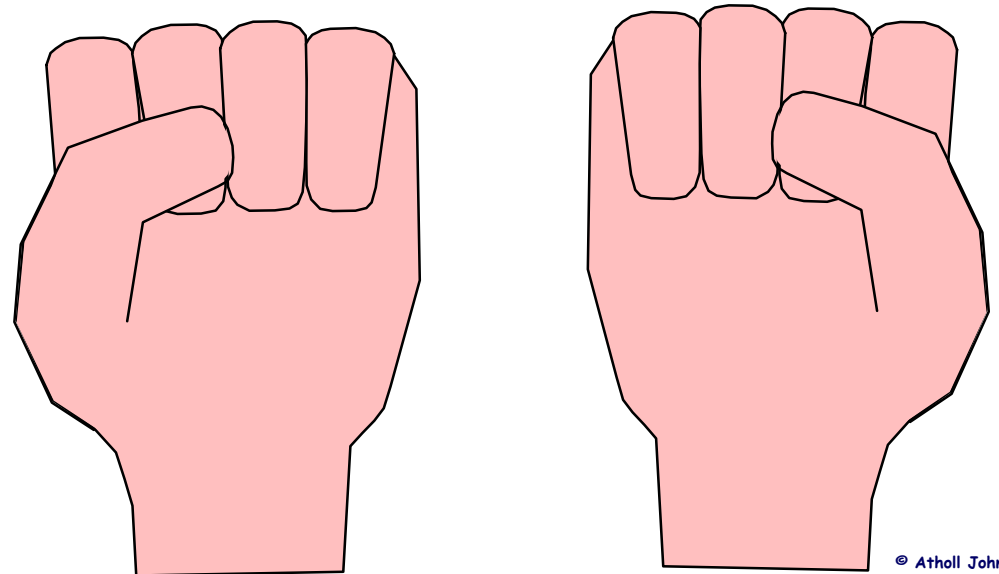
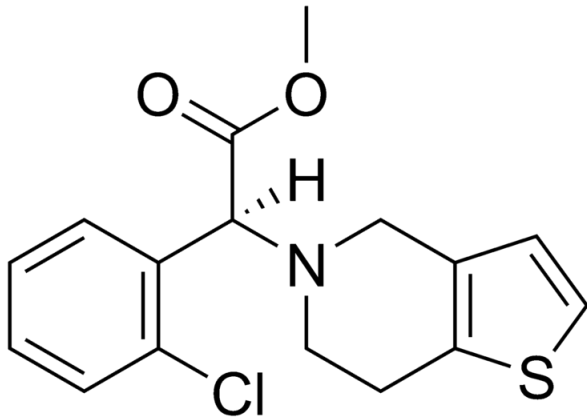
- Hypersensitivity reactions
- Peripheral neurotoxicity
- Dyslipidaemia
- Inhibition of
 - P-glycoprotein
 - Cyp3A4

Poor Quality Drugs Content

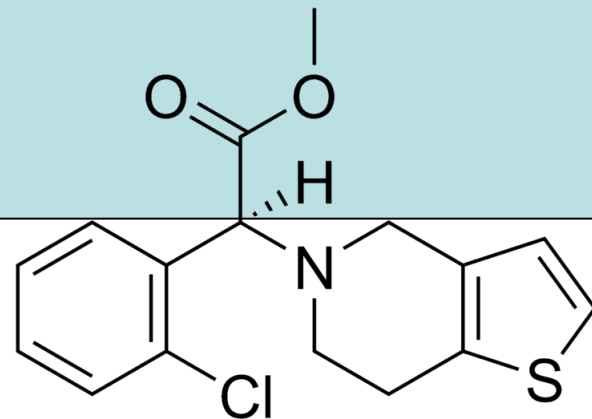
Drug, Isoforms, Isomers
& Impurities

Clopidogrel

- Has an asymmetric carbon atom
- Therefore exists in R & S forms
- S-form has anti-platelet activity
- R-form does not



Plavix[®]



- 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



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Journal of Pharmaceutical and Biomedical Analysis
34 (2004) 341–348

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

Y. Gomez, E. Adams*, J. Hoogmartens

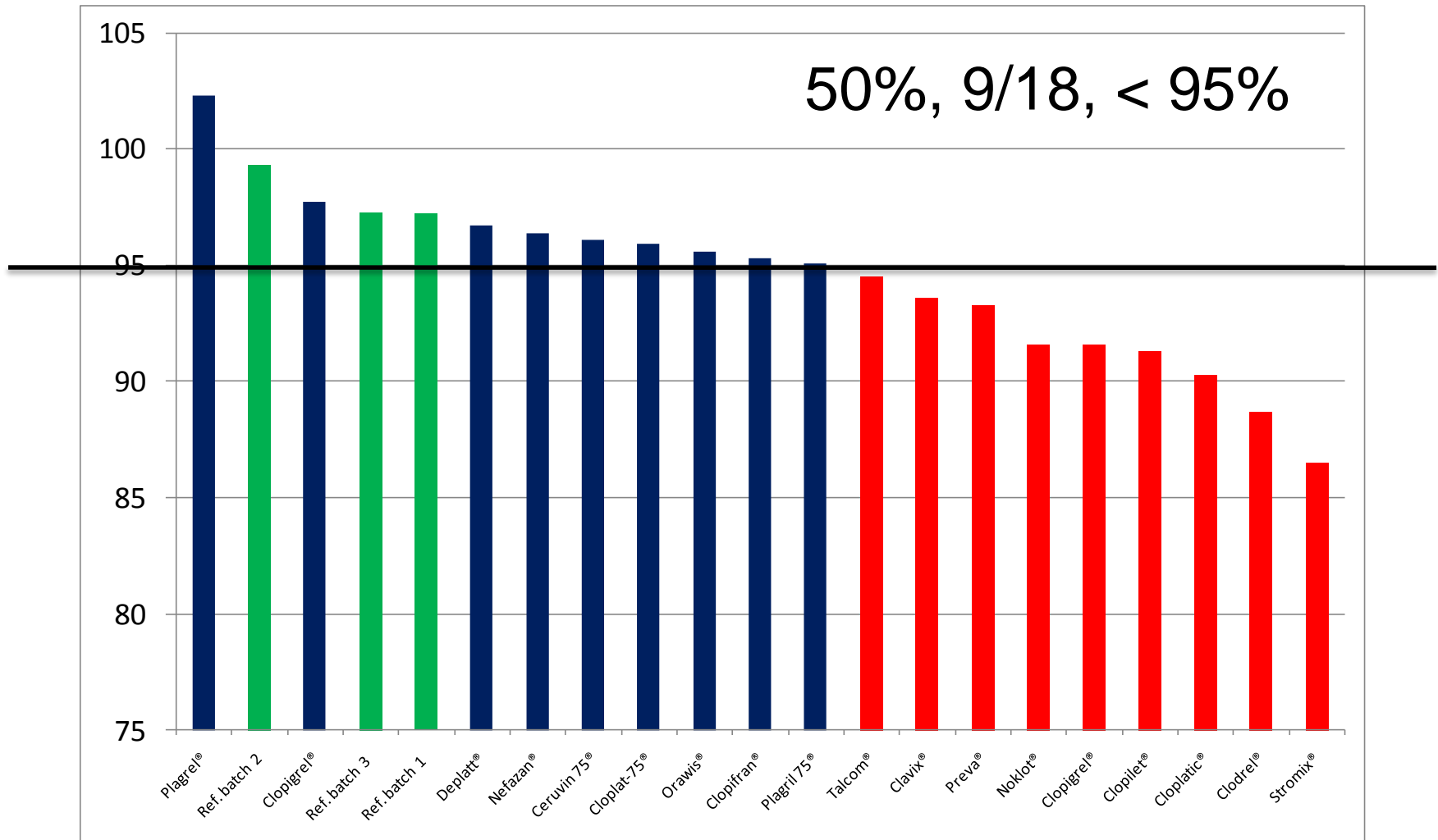
Laboratorium voor Farmaceutische Chemie en Analyse van Geneesmiddelen, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Van Evenstraat 4, B-3000 Leuven, Belgium

Received 16 May 2003; received in revised form 22 September 2003; accepted 24 September 2003

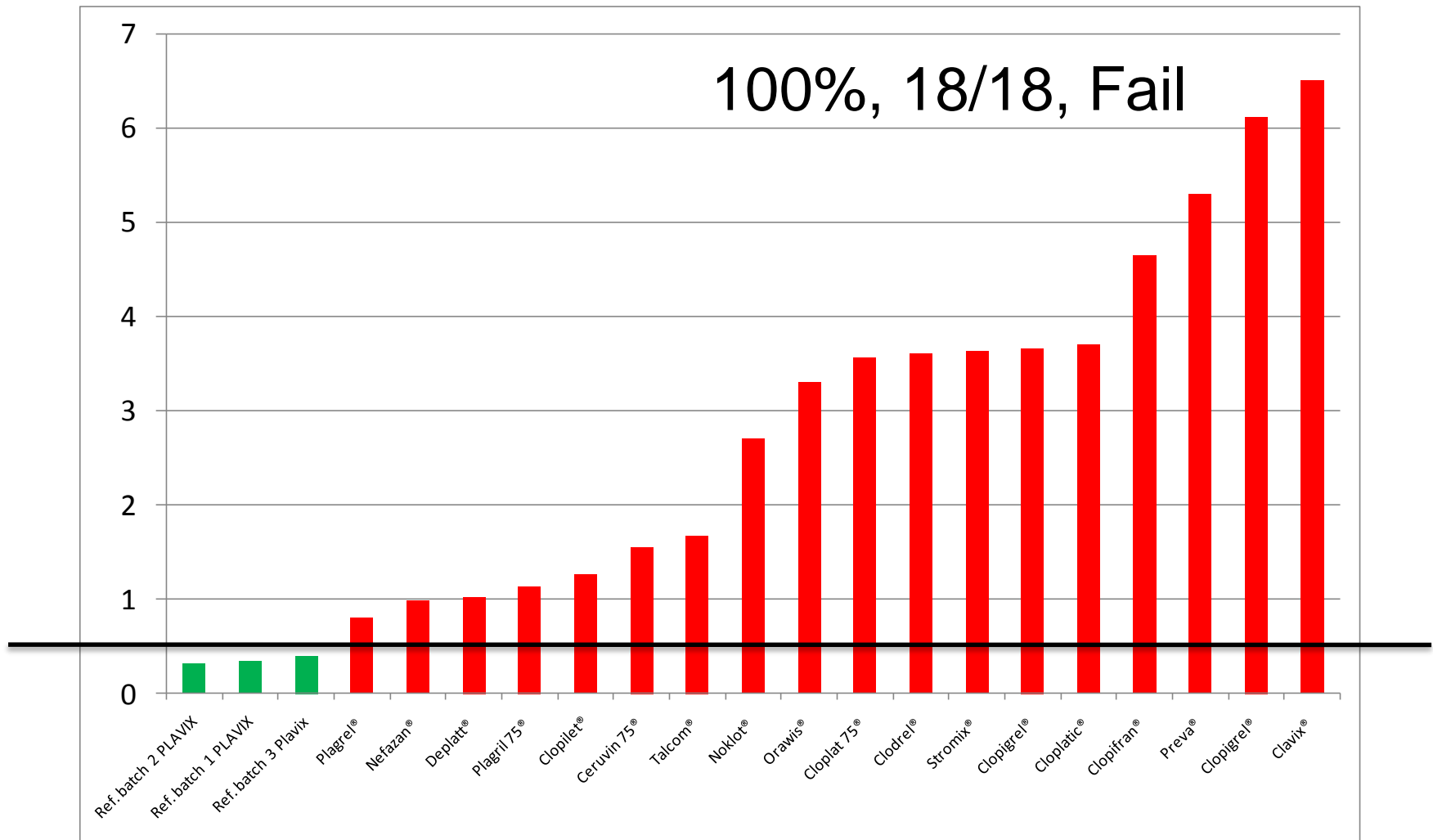
Generic Clopidogrel

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

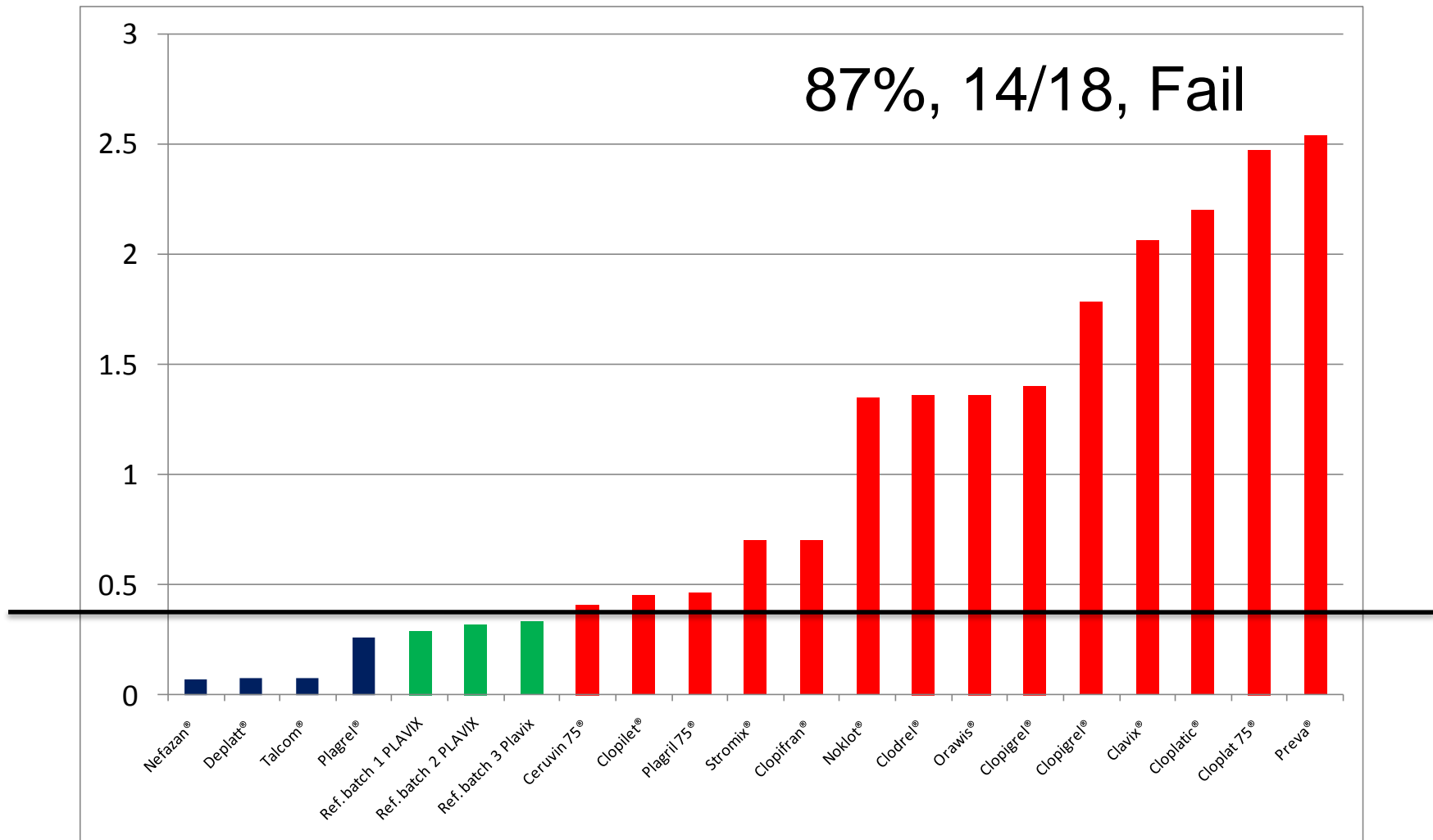
Generic Clopidogrel Content



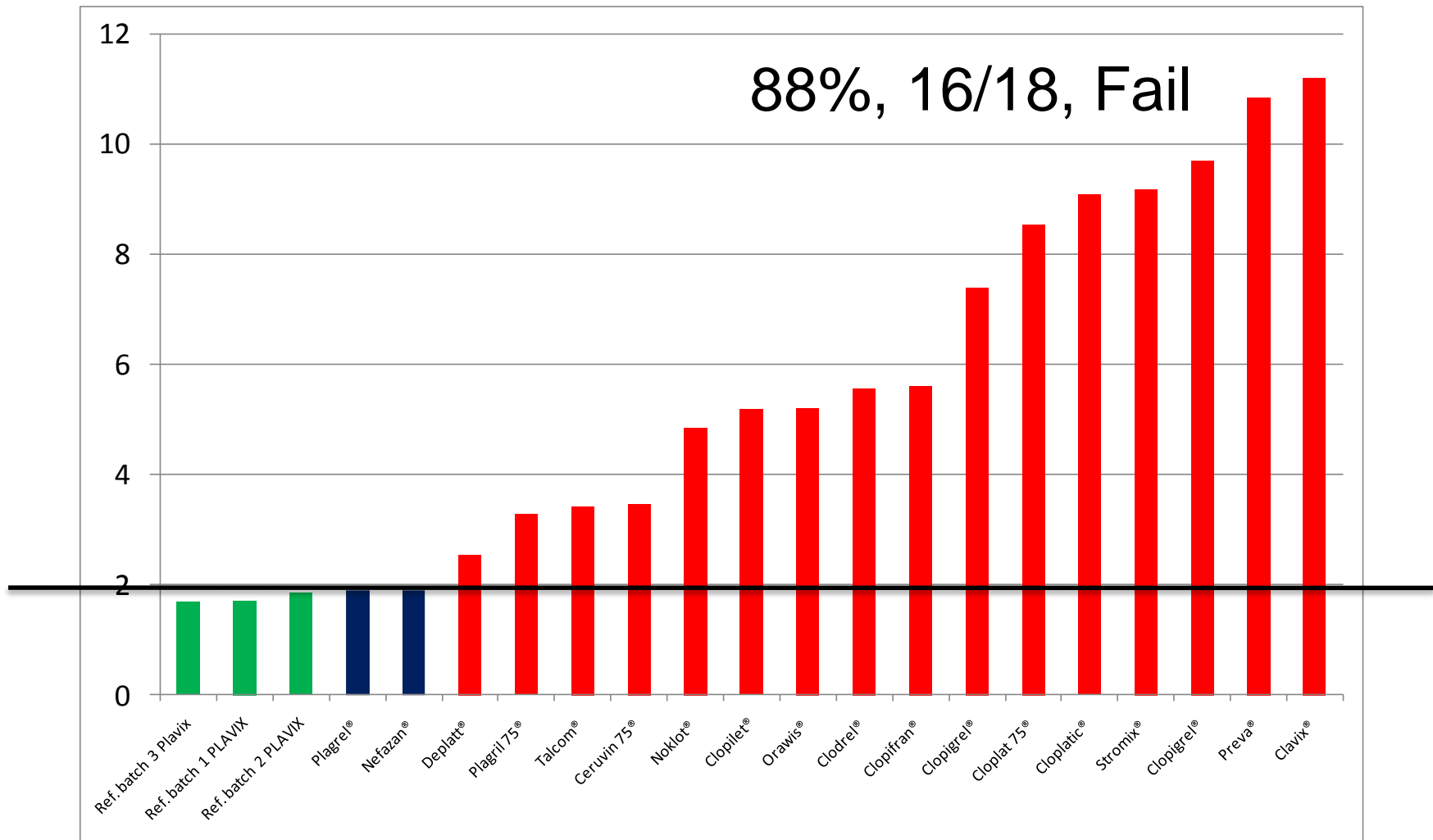
Generic Clopidogrel R-Isomer



Generic Clopidogrel Hydrolysis Product



Generic Clopidogrel Total Impurities



Generic Clopidogrel

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

False Registration Data

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FDA NEWS RELEASE

FOR IMMEDIATE RELEASE

Feb. 25, 2009

Media Inquiries:

Rita Chappelle, 301-796-4672

Consumer Inquiries:

888-INFO-FDA

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.

25 Feb 2009

Continued Quality Issues



Breaking News on Global Pharmaceutical Technology & Manufacturing

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

Continued Quality Issues

in-Pharma
Technologist.com

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.*”

The withdrawal – delisting from the 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

Dirty Medicine - CNN Money



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



Ranbaxy in the News

April 2014

Sun Pharmaceutical to acquire Ranbaxy in \$4bn deal



Some of Ranbaxy's manufacturing facilities have faced US scrutiny

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 Pharmaceutical Industries

March 2014

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

EMA Clopidogrel Recall

25 March 2010
EMA/179606/2010
Press Office

Press release

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

Accidental Contamination

FDA finds contaminated drug ingredient at GSK Ireland plant

BY VRINDA MANOCHA

Tue Apr 1, 2014 8:27pm BST

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04/01/2014

(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 file Reuters photo of Ranbaxy Laboratories' office.

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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

RESEARCH REPORTS

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

Warfarin formulations

“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.”

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

Contact Details

Atholl Johnston

BSc BA MSc PhD CSci ERT FFPM FBPharmacols FRCPath

Professor of Clinical Pharmacology



Barts and The London

School of Medicine and Dentistry

Charterhouse Square
London, EC1M 6BQ, UK

A.Johnston@qmul.ac.uk

 +44-20-7882 6055, Fax +44-20-7882 3408