Holding pharmaceutical companies and regulatory bodies to account with evidence

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Spot the Difference

**The Times**

Millions denied life-saving statins despite guidance

Millions of patients are missing out on life-saving statins because doctors are not ordering them, new research has revealed. More than 6 million people in the UK are regularly prescribed statins to lower their risk of heart disease and stroke, but analysis suggests that nearly 30% of GPs do not prescribe them. The study, commissioned by the National Institute for Health and Care Excellence (NICE), found that many patients were not taking statins because they were not prescribed them. The report also found that patients were often not told about the benefits of statins or were not given enough information to decide whether they should take them.

**Daily Telegraph**

Statins can stop flu jab working

Some patients who take statins for their cholesterol may find that the flu vaccine is not as effective as it should be. A study published in the journal *JAMA Internal Medicine* found that statins can reduce the effectiveness of the flu vaccine by up to 50%. The study was carried out on 13,000 people who were given either statins or a placebo. Those on statins were found to have a lower immune response to the vaccine than those on the placebo.

**Daily Mail**

British Football World Cup deal ruined

David Beckham and his 2018 World Cup was handed to Russia.

**The Guardian**

We want our £2bn back over 2018 World Cup fix, says FA chief Dyke

Ministers granted Kids Company £50m despite six warnings

***Potter***

Everest secret

Mallory’s love for girl he never met

***Legends***

The Daily Telegraph

Exclusive book offer

What Remains by Tim Weaver for only £3.49

Hannah Betts is haunted by her mother’s ghost

Isil planning mass attacks on Britain, warns head of MI5
What strategies do you use to assess evidence for health claims?

* Quality of evidence
* Size of effect
* Who does it apply to?
Types of evidence affect the quality
The evidence underpinning sports performance products: a systematic assessment

Carl Heneghan,1 Jeremy Howick,1 Braden O'Neill,1 Peter J Gill,1 Daniel S Lasserson,1 Deborah Cohen,2 Ruth Davis,1 Alison Ward,1 Adam Smith,2 Greg Jones,2 Matthew Thompson1

Mythbusting sports and exercise products
Carl Heneghan and colleagues examine the evidence behind the claims made for sports and exercise products

Carl Heneghan clinical reader in evidence based medicine, Peter Gill DPhil candidate, Braden O'Neill DPhil candidate, Dan Lasserson clinical lecturer, Miriam Thake visiting research assistant, Matthew Thompson clinical reader, Jeremy Howick research fellow

How valid is the European Food Safety Authority’s assessment of sports drinks?
Matthew Thompson, Carl Heneghan, and Deborah Cohen find worrying deficiencies in the evidence used to support the health claims made for sports drinks

Sports drinks
Forty years of sports performance research and little insight gained
Carl Heneghan and colleagues take a critical look at the evidence used to back up claims that Lucozade enhances sporting performance

Carl Heneghan clinical reader in evidence based medicine, Rafael Perera university lecturer in statistics, David Nunan research fellow, Kamal Mahtani clinical lecturer, Peter Gill DPhil candidate

Centre for Evidence-Based Medicine, Department of Primary Care Health Sciences, University of Oxford, Oxford OX1 3ET, UK
‘Lucozade Sparkling energy drink, replaces lost energy quickly’

Lucozade is used by DOCTORS and NURSES in CLINICS, HOSPITALS, NURSING HOMES and SCHOOLS.
But as the military prepared to invest large sums in more arch-diagnosing light trainers, someone thought to ask if the practice of assigning running shoes by foot shape actually worked?
SPORTS DRINKS

Forty years of sports performance research and little insight gained

Carl Heneghan and colleagues take a critical look at the evidence Lucozade enhances sporting performance

Carl Heneghan clinical reader in evidence based medicine, Rafael Puello statistics, David Nunan research fellow, Kamal Mahtani clinical lecturer

Centre for Evidence-Based Medicine, Department of Primary Care Health Sciences, University of Oxford
Dr Heneghan and his team asked manufacturer GlaxoSmithKline (GSK) for details of the science behind their claims and were given what he said scientists call a "data dump" - 40 years' worth of Lucozade sports research which included 176 studies.

Dr Heneghan said the mountain of data included 101 trials that the Oxford team were able to examine before concluding: "In this case, the quality of the evidence is poor, the size of the effect is often minuscule and it certainly doesn't apply to the population at large who are buying these products.

"Basically, when you look at the evidence in the general population, it does not say that exercise is improved [or that] performance is improved by carbohydrate drinks."

In response, GlaxoSmithKline said they disagreed with the Oxford team's conclusions:

"Over 40 years of research experience and 85 peer-reviewed studies have supported the development of Lucozade Sport and all our claims are based on scientific evidence that have been reviewed and substantiated by the European Food Safety Authority."

GSK is also the manufacturer of the Maxinutrition range of sports supplements, which is endorsed by some of Britain's top athletes, including the Olympic triathlon team and the Rugby Football Union.

Some of GSK's supplements in the Maxinutrition range contain branch chain amino acids which are found in muscle protein. The company says these amino acids "help hard-training athletes recover faster after intense exercise". The supplements sell for as much as £34 a tub.
Preventing Future Joint Failures: Role of Regulatory Data
Overview of Device Regulation

Introduction

FDA’s Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.

- Radiation-emitting Electronic Products

Medical devices are classified into Class I, II, and III. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval. A description of device classification and a link to the Product Classification Database is available at “Classification of Medical Devices.”

- Medical Device Listing,
- Premarket Notification 510(k), unless exempt, or Premarket Approval (PMA),
- Investigational Device Exemption (IDE) for clinical studies
- Quality System (QS) regulation,
- Labeling requirements, and
- Medical Device Reporting (MDR)

Establishment Registration - 21 CFR Part 807

Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their
**Background:** Unlike prescription drugs, medical devices are reviewed by the US Food and Drug Administration (FDA) using 2 alternative regulatory standards: (1) premarket approval (PMA), which requires clinical testing and inspections; or (2) the 510(k) process, which requires that the device be similar to a device already marketed (predicate device). The second standard is intended for devices that the FDA deems to involve low or moderate risk.

**Methods:** We analyzed the FDA’s high-risk List of Device Recalls from 2005 through 2009. Using FDA data, we determined whether the recalled devices were approved by the more rigorous (PMA) process, the 510(k) process, or were exempt from FDA review.

**Results:** There were 113 recalls from 2005 through 2009 that the FDA determined could cause serious health problems or death. Only 21 of the 113 devices had been approved through the PMA process (19%). Eighty were cleared through the 510(k) process (71%), and an additional 8 were exempt from any FDA regulation (7%). Cardiovascular devices comprised the largest recall category, with 35 of the high-risk recalls (31%); two-thirds were cleared by the 510(k) process (66%; n=23). Fifty-one percent of the high-risk recalls were in 5 other device categories: general hospital, anesthesiology, clinical chemistry, neurology, or ophthalmology.

**Conclusions:** Most medical devices recalled for life-threatening or very serious hazards were originally cleared for market using the less stringent 510(k) process or were considered so low risk that they were exempt from review (78%). These findings suggest that reform of the regulatory process is needed to ensure the safety of medical devices.

*Arch Intern Med. 2011;171(11):1006-1011.*
*Published online February 14, 2011.*
*doi:10.1001/archinternmed.2011.30*
Imported by: Smyths Toys Ltd.,
Galway, Rep. of Ireland.
Please retain all information relating to this product for future reference.
Not suitable for children under 3 years of age due to small parts.
European System: How to obtain a CE mark

1. SELECT A NOTIFIED BODY
2. NB INPSECTS QUALITY MANAGEMENT SYSTEM AND ISSUE CERTIFICATE
3. DESIGN DEVICE COMPLETE TECHNICAL FILE
4. GIVE YOURSELF A CE MARK, SIGN A DECLARATION OF CONFORMITY
5. NOTIFIED BODY REVIEWS TECHNICAL FILE AT NEXT VISIT
Problems with the system
Medical-device recalls in the UK and the device-regulation process: retrospective review of safety notices and alerts

C Heneghan,1 M Thompson,1,2 M Billingsley,3 D Cohen3

ABSTRACT

Background: Medical devices are used widely for virtually every disease and condition. Although devices are subject to regulation, the number of recalls, the clinical data requirements for regulation and the impact on patient safety are poorly understood.

Methods: The authors defined a device using European directives and used publicly available information on the Medicines and Health Regulatory Authority website to determine the number of devices recalled from January 2006 to December 2010. Two reviewers independently assessed Field Safety Notices and Medical Device Alerts. The authors wrote to manufacturers to obtain further information and clinical data, and summarised data by year. Conformité Européenne classification, indication, and Food and Drug Administration recall system of severity.

objects such as simple bandages to high-end MRI scanners. Estimates suggest there is a vast array of devices in circulation, with some 500 000 medical devices worldwide available to healthcare providers and patients.1

Because of their vital role in healthcare, medical devices require regulatory approval. In Europe, they are subject to council directives of the European Union (EU) which stipulate that ‘devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients.’2–4

These directives require medical-device manufacturers to display Conformité Européenne classification, registration, and national or EU market authorisation. If a manufacturer does not comply with the directive, they are liable for fines, criminal charges, and imprisonment.5–7

In the USA, federal law governs medical device regulation, and the Food and Drug Administration (FDA) defines the term medical device as a ‘component, part, or accessory of a medical device;’ including all products intended for use in the diagnosis, cure, treatment or prevention of a disease or injury, and all products intended to affect the structure or any function of the body through chemical or other means. FDA studies show that medical device recalls are not limited to implantable medical devices; surgical, diagnostic, and corrective devices can also be affected.8,9

In the USA, medical devices are classified into three categories based on the degree of risk to the patient: Class I, II, and III. Class I devices pose a low risk and usually require manufacturer certification. Class II devices are considered intermediate risk, and manufacturers are also required to register with the FDA. Class III devices pose the greatest risk, and manufacturers are required to file a premarket approval (PMA) application, following a year of market surveillance study.
Total number of field safety notices and medical-device alerts per year (2006 to 2010).

Tamiflu
Don't give Tamiflu or Relenza to under-12s, warn researchers

• Swine flu drugs may have side-effects that outweigh benefits
• Government stresses 'safety first' approach for severe symptoms

Antiviral drugs such as Tamiflu and Relenza that form the cornerstone of the government's fight against swine flu should not be given to those under the age of 12, researchers claimed today.

They called on the Department of Health to immediately reassess its pandemic flu policy after finding that side-effects from medicines such as Tamiflu could outweigh any benefit.

The research, by Dr Matthew Thompson, a clinical scientist and Oxford GP, and Dr Carl Heneghan, a GP and clinical lecturer at Oxford University, found that in some children Tamiflu caused vomiting, which can lead to dehydration and complications.

James Sturcke
guardian.co.uk, Monday 10 August 2009 12.52 BST
Article history
New methods - Systematic review of unpublished Clinical Study Reports – the case of neuraminidase inhibitors for influenza
Roche agrees to release all trial data on Tamiflu drug

The drug company Roche, which makes Tamiflu, has announced it will give researchers access to all its trial data for the influenza drug, the BMJ reports.

Roche had previously been criticised for failing to grant access to the results of all
611  Reduction in the Symptoms and Complications of Influenza A and B in Patients Treated with Oseltamivir (the Time-to-Treatment Study Group)

JOHN J TREATOR, Univ of Rochester, Rochester, NY

Oseltamivir is an oral inhibitor of the neuraminidase enzyme of influenza A and B viruses with significant virologic and clinical efficacy in man. Oseltamivir was studied in a multicenter, placebo-controlled, double-blind, symptom-duration-stratified study. Subjects who met a case definition of influenza consisting of fever ≥100°F with at least one respiratory (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches/pains, fatigue, headache and chills/sweats) were randomized 2:1 to 75mg oseltamivir (O) or placebo (P) p.o. bid for 5 days. 1459 patients were enrolled at 164 US study sites. The patient population ranged in age from 13 to 80 years, 16% were vaccinated and over 50% had underlying medical conditions (6% with COPD/asthma). A total of 1063 (73%) had laboratory documented influenza infection; 81% had influenza A; 19% had influenza B. The presence of cough and fever were independent predictors of influenza infection. The median duration of illness, defined as the time to alleviation of all 7 major flu symptoms, was 120.5 hrs in influenza-infected P recipients and 96.3 hrs in O recipients (p< 0.0001). The median duration of each of the individual symptoms included in the symptom scores was also decreased by oseltamivir, as follows: chills/sweats (34% reduction), cough (31%), fatigue (33%), headache (29%), myalgia (24%), nasal congestion (42%), sore throat (20%), and fever (33%). Severity of illness, as measured by the area under the curve of symptom scores, was reduced by treatment (P=1049 score-hours, O=837 score-hours, median difference 203, 95% CI 117-289). Lower respiratory tract complications reduced with O included bronchitis (P 4%, O 2%) and pneumonia (P 2%, O 0.3%). The results of this study are very similar to those reported in a phase III trial conducted in the U.S. (38th ICAAC, 1998) and demonstrate a consistent beneficial effect of early antiviral treatment of influenza with oseltamivir in populations including adolescents, the elderly and others with co-morbid conditions.
Final Clinical Study Report — Protocol M76001: A randomized, double-blind, placebo-controlled, multicenter study of efficacy based on the time to treatment of influenza infection with the neuraminidase inhibitor Ro 64-0796 (also known as GS 4104). Research Report No. 181376/March 14, 2000

Date of Report: March 14, 2000
Study Dates: 12/24/98 – 2/19/99
Trial Phase: IIIb

Name of Principal Investigator(s): (see Module II)
Affiliation:

Personnel Responsible for Clinical and Statistical Analyses:

[Redacted] MD
Medical Science Leader, Medical Sciences, Medical Affairs, Roche Laboratories, Inc.
Effectiveness of Tamiflu

Do these results apply to my patients?

Does this treatment make a difference?
Professor Phin and Dr Moll (Public Health England) in the BMJ 2015

‘when oseltamivir prophylaxis was used in cases of known exposure within a household, a situation akin to that in care homes, the risk reduction increased to 80%
Do these results apply to my patients?

Individuals were excluded if they had cancer, immunosuppression, chronic liver or renal disease, were taking steroids, or had unstable or uncontrolled renal, cardiac, pulmonary, vascular, neurologic or metabolic (diabetes, thyroid disorders, adrenal disease) disorders, hepatitis or cirrhosis. Subjects with known significant renal disease (defined as a creatinine clearance <30mL/min) were also excluded as were those with known cardiac failure resulting in limitation of physical activity.

Welliver R, et al.

WV 15799 CSR
Do these results apply to my patients?

Only 17 (1.8%) contact cases aged over 65 were included in the study.
Tamiflu reduces the duration of symptoms by 16 hours.

No effect on rates of hospitalisation.

No effect on any bacterial infection in children.

For every 100 people treated 3 would self-report they don’t have pneumonia.

However, in the 5 trials that used an objective diagnosis of pneumonia there was no effect.
If a million people take Tamiflu in a pandemic, 45,000 will experience vomiting, 31,000 will experience headache, 10,000 will have renal complications and 11,000 psychiatric side-effects.
Tamiflu: Millions wasted on flu drug, claims major report

By James Gallagher
Health and science reporter, BBC News

10 April 2014 | Health

Hundreds of millions of pounds may have been wasted on a drug for flu that works no better than paracetamol, a landmark analysis has said.

The UK has spent £473m on Tamiflu, which is stockpiled by governments globally to prepare for flu pandemics.

The Cochrane Collaboration claimed the drug did not prevent the spread of flu or reduce dangerous complications, and only slightly helped symptoms.

The manufacturers Roche and other experts say the analysis is flawed.