

2012

Withdrawing Drugs in the U.S. Versus Other Countries

Benson Ninan

Albert I. Wertheimer

Follow this and additional works at: <http://pubs.lib.umn.edu/innovations>

Recommended Citation

Ninan B, Wertheimer AI. Withdrawing Drugs in the U.S. Versus Other Countries. *Inov Pharm*. 2012;3(3): Article 87.
<http://pubs.lib.umn.edu/innovations/vol3/iss3/6>

INNOVATIONS in pharmacy is produced by the University of Minnesota Libraries Publishing.



Withdrawing Drugs in the U.S. Versus Other Countries

Benson Ninan, Pharm.D.¹ and Albert I Wertheimer, PhD, MBA²

¹Pharmacy Intern, Rite Aid Pharmacies, Philadelphia, PA and ²Temple University School of Pharmacy, Philadelphia PA

Key Words: Drug withdrawals, dangerous drugs, UN Banned Drug list

Abstract

Since 1979, the United Nations has maintained a list of drugs banned from sale in member countries. Interestingly, there are a number of pharmaceuticals on the market in the USA that have been banned elsewhere and similarly, there are some drug products that have been banned in the United States, but remain on the market in other countries. This report provides a look into the policies for banning drug sales internationally and the role of the United Nations in maintaining the master list for companies and countries to use for local decision guidance.

Background

At present, one of the leading causes of death in the U.S. is believed to be adverse drug reactions.¹⁻¹⁴ More than 20 million patients have taken at least 1 of the 5 drugs withdrawn from the market between September 1997 and September 1998. Seven drugs that were approved in 1993 and were withdrawn shortly later have contributed to 1002 deaths.¹⁴ A study in 2002, showed that out of the 548 drugs that were approved in the U.S. between 1975-1999, fifty six (10.2 %) of them required a new black box warning or were withdrawn.¹² Thus, it is very important that the consumer as well as the practitioner become aware of dangerous drugs.

In 1979 the United Nations General Assembly first brought up the question of establishing a list of banned pharmaceutical products that could be exchanged between nations. Under resolution 37/137 (Annex I) of December 17 1982, the General Assembly requested the Secretary-General to organize the Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely restricted or Not Approved by Governments. The List is a continuing effort by the United Nations to circulate information on products that are harmful to health and the environment.²

The first issue of the List covered less than 500 products regulated by 60 governments. The fifth issue which covered both pharmaceuticals and chemicals, included over 700 products regulated by 94 governments. By the eleventh and twelfth editions, the List had grown to include more than 1100 products regulated by 115 states.² At present the most

recently updated issue is the fourteenth issue, which contains data on 66 new products with updated/new information on 22 existing products. An update of the fourteenth issue was published in 2010 adding 99 more products to the List by the actions of 38 governments.³

In 1985 the United Nations Secretariat, in conjunction with the World Health Organization (WHO) and the United Nations Environment Program (UNEP) met at the first inter-agency meeting and executed the first review of the List. The review outlined key points such as arrangements for the preparation of future issues, the need for criteria for determining the inclusion of products, the question of the legal and public health context of regulatory actions that were not included in the first issue of the List and the treatment of commercial data.² Ever since then the List has been updated annually making the information available to users through direct internet access.

Introduction

Since 1995 the List was divided into two separate issues, one focusing on pharmaceuticals and the other on chemicals, which are published in alternate years. The pharmaceuticals are further separated into monocomponent products, combination products and group products.² This paper will only focus on the 151 monocomponent pharmaceuticals that were withdrawn and why they were withdrawn by the U.N. and by specific countries such as the USA, Japan, UK, Sweden and Australia.

More specifically, this paper will compare the drugs banned in the U.S. versus the drugs banned in other prominent countries. Do we have similar policies on which drugs to withdraw or, does the U.S. act on its own when it comes to drug withdrawal?

While the U.N. may outlaw a certain drug, it is possible that the banned drug may be still available in certain countries. In

Corresponding author: Albert I Wertheimer, PhD, MBA
Temple University School of Pharmacy
Philadelphia PA 1 9140; albertw@temple.edu

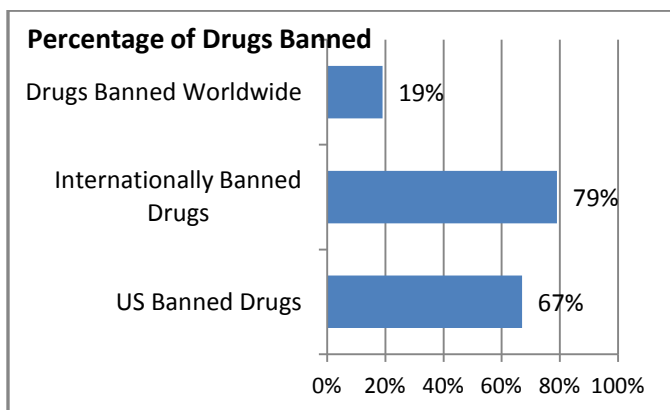
addition, this paper will investigate any lag time that may occur between the issue date of withdrawal by the U.N. and the actual date it was removed from the specific country. It is important to note that if a product is not listed as regulated by a country it does not necessarily mean that it is permitted in the country. It is highly possible that some information has not been communicated to the U.N.² as well.

Drugs Banned in the U.S.

In the United States of America, The Center for Drug Evaluation and Research (CDER) a part of the U.S. Food and Drug Administration (FDA) is in charge of evaluating new drugs for safety and effectiveness before they may be sold. After the drugs are on the market, CDER acts as a watchdog, monitoring for any side effects and for any unexpected health risks. Sometimes drugs have to be withdrawn from the market due to severe unwanted side effects that may be fatal. In 2005, new molecular entities (NME) such as valdecoxib, pemoline, and technetium (99m Tc) fanolesomab were all removed due to increased risk of serious adverse effects. Valdecoxib, a COX-2 selective inhibitor was removed from the market due to increased risk of skin reactions and cardiovascular events. Likewise pemoline, a CNS stimulant used for treatment of ADHD was removed because of fatal hepatotoxicity² (See appendix for more drugs that were removed in the U.S., Internationally, and worldwide).

Figure 1 shows the percentage of the 151 drugs we studied that were removed in the U.S. compared to the drugs that were removed internationally and worldwide.

Figure 1.



Only 67 % of the 151 drugs that were on the List were banned by the U.S, while internationally 79 % were banned. This shows clearly that the U.S is not in complete agreement with the other countries on which drugs should be banned. There are many reasons why the policies of the U.S may differ from the international world. One reason might be a monetary

benefit that drug companies/ government get from keeping a drug on the market. An example of a drug that has continued to be kept on the market is the anti-diabetic drug, rosiglitazone (Avandia). A drug might also be kept on the market in one country because it has a legitimate medical use, while in another country it may not be used medically and therefore is banned. For example, flunitrazepam, commonly known as the date rape drug “roofies”, is used for the treatment of insomnia in many European countries. However, the FDA has not approved the use of flunitrazepam and it has deemed it an illegal substance.²

Figure 1 also shows that only 19% of drugs were banned worldwide. This shows the lack of agreement on which drugs should be banned globally. It seems as if drugs that were banned worldwide had to have severe fatal adverse effects before they reached the eyes of the entire world. Drugs such as Fen-Fen which contained fenfluramine and phentermine were mainly removed after 20 years in the U.S. market due to a lawsuit which totaled over \$13 billion in legal damages and of course potential fatal pulmonary hypertension and heart valve problems.¹⁰ Both fenfluramine and its d-enantiomer, dexafluramine (Redux) were withdrawn in September 1997 worldwide. The second drug that made up Fen-fen, phentermin was banned in Sweden and the United Kingdom in 1981 and 2000 respectively. However, it is still marketed widely in the U.S.²

Figure 2.

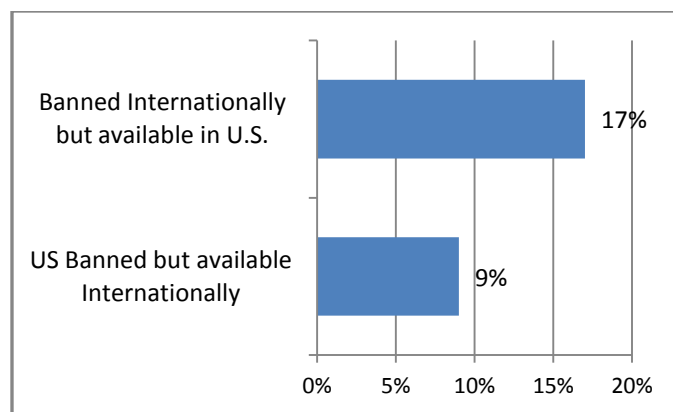


Figure 2 compares the drugs that were banned in the U.S. but are available internationally versus the drugs that are banned internationally but are available in the U.S. It shows that 9 % of the drugs banned by the U.S. are available in the international market. On the other hand, of the drugs banned internationally, 17 % are available in the U.S. This goes to show again that the policies of the U.S. may tend to be different than the rest of the World. Of the 17 % internationally banned drugs, three of the drugs are from the same class of drugs, the barbiturates. In Sweden, barbiturates

such as amobarbital, hexobarbital, pentobarbital and phenobarbital were all banned due to fatal intoxications and abuse potential. In April 2001, France suspended the production of phenobarbital due to reports of rare but severe cutaneous and mucosal reactions including Steven-Johnson Syndrome and Lyell Syndrome.² However, phenobarbital is still used vigorously in the U.S. for the treatment of epilepsy/ tonic-clonic seizures.

Another drug that is widely used in the U.S., but is banned internationally is the muscle relaxant, carisoprodol (Soma). In November 2007, the European Medicines Agency (EMA) recommended the suspension of marketing authorization after evidence of abuse and addiction from taking carisoprodol for back pain. Both Norway and Sweden have pulled carisoprodol off the market due to problems of dependence and intolerable side effects. As of 2008, the UK had planned to pull carisoprodol off the market due to increased risk of abuse, addiction, intoxication, and psychomotor impairment.¹

As of March 26 2010, the abuse potential of carisoprodol was brought to light in the U.S, as the DEA issued a Notice of hearing discussing the plan to place carisoprodol as a controlled substance. However, as of today carisoprodol is not a controlled substance under federal regulations while certain states consider it to be a controlled substance. These states include Alabama, Arizona, Arkansas, Florida, Georgia, Hawaii, Indiana, Kentucky, Louisiana, Massachusetts, Minnesota, Mississippi, New Mexico, Nevada, Oklahoma, Oregon and Texas.⁴ While it is not a controlled substance in many states carisoprodol is only approved for short term use and prescribers are encouraged not to prescribe the drug to people with a background of addiction. It is interesting to notice that carisoprodol's metabolite, meprobamate which has significant anxiolytic properties was banned in Sweden in 1981 due to potential for abuse and addiction.² The UK was also planning to remove meprobamate due to severe side effects.¹ In the U.S. it has been classified as C-IV and was the best-selling tranquilizer for a long time before being replaced by the benzodiazepines.

A very controversial drug that has caused 13,000 lawsuits, while bringing in annual sales peaking at approximately \$2.5 billion for GlaxoSmithKline in 2006, was the antidiabetic drug, rosiglitazone (Avandia). Rosiglitazone has been associated with increased risk of heart failure by 64 % over a seven year period.⁷ In September 2010, the EMA suspended the drug from the European market completely.⁵ The U.S. however, continues to market the drug with a black boxed warning.

Only 9% percent of drugs banned by the U.S. are available internationally as shown in Figure 2. In November 2000, the FDA issued a public health advisory against the use of phenylpropanolamine, a psychoactive drug used as a stimulant, decongestant, and anorectic. Due to increased risk of strokes in young women, FDA requested the suspension of marketing of this drug and removed phenylpropanolamine from all OTC formulations in 2005.¹¹ While Canada has also withdrawn the drug, Europe continues to market it as a prescription and OTC drug. In the UK, it is sold in combinations with acetaminophen and caffeine as a cough and cold medication.

Another drug that has been banned in the U.S. but is available outside the U.S is pergolide (Permax), a dopamine receptor agonist used for the treatment of Parkinson's disease. Permax was approved in 1988 as an adjunctive therapy with levodopa in Parkinson's disease. Valvular heart disease was first described in association with pergolide in 2002. In 2003, the FDA asked Lilly to add valvulopathy (abnormality of cardiac valves) to the warnings section of Permax labeling. In 2006, the warning was upgraded to a black box warning, the FDA's strongest form of warning, because of new data concerning risks of heart valve damage. In 2007, it was removed from the U.S market due to increased rates of valvular dysfunction that were associated with using the drug. Pergolide is still used in other countries such as the UK and Australia for the treatment of Parkinson's disease, hyperprolactinemia and restless leg syndrome.⁸

Figure 3.

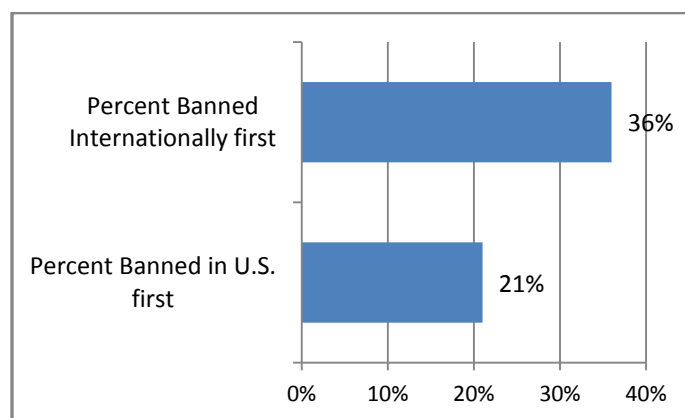


Figure 3 shows the percentage of the 151 drugs we studied that were banned in the U.S. first versus the percentage of drugs banned first in the other countries (UK, Australia, Sweden, and Japan). Approximately 36 % of the drugs banned were first banned internationally before they were banned in the U.S. Only 21 % of the drugs were banned by the U.S. first

before they were also banned by the rest of the world. For the remaining 43%, differences were not detected. This shows that the U.S. may no longer be leader in observing, reporting and removing dangerous drugs from the market. This might be because the drug might have been introduced first internationally before it became available in the U.S. Thus, the time for the FDA to see any adverse effects from the drug might have lagged in comparison to other countries. For example, troglitazone, a thiazolidinediones used to treat diabetes was first introduced by a Japanese company. Due to an idiosyncratic reaction leading to hepatitis it was only approved in January 1997 in the U.S. However, it was already on the world market years before and was voluntarily removed in December 1997 in the UK and Japan due to concerns of hepatotoxicity.² Since the U.S. was late to approve the drug, logically they were only able to withdraw the drug by 2000.

Another drug that the U.S. was slow in removing from the market was the well known prescribed pain killer, dextropropoxyphene also called as propoxyphene (Darvon-N). This drug was usually combined with acetaminophen under the brand, Darvocet. Dextropropoxyphene which has been on the market for more than 25 years came under fire in 1978 by consumer groups who claimed it caused suicides in many of the patient. The manufacturing company, Eli Lilly minimized the news and persuaded doctors that dextropropoxyphene was safe as long it was not mixed with alcohol. In 2004, products containing only dextropropoxyphene were removed in U.K. and later in June 2009, the EMEA recommend gradual withdrawal of all products containing dextropropoxyphene from the European Union.⁶

A month later in the U.S., the FDA still decided to continue marketing dextropropoxyphene with a black box warning for the risk of overdose. On November 19 2010, the FDA finally pulled all forms of dextropropoxyphene from the market due to risk of heart arrhythmias. It is alarming that a drug such as dextropropoxyphene that had a high potential risk of causing heart problems was on the market for more than 20 years before it was completely removed. It is estimated that over 10 million people may have used these products.⁹

Conclusion

Drug withdrawal is an important task that involves continued surveillance and pharmacovigilance and is as important as the process of drug discovery and production. Since the establishment of the List, the dissemination of information on which drugs are banned has become easier. Nevertheless, countries tend to have different policies on which drugs to withdraw and when to withdraw them. The U.S. is on its own

time course compared to other countries such as UK, Japan, Australia and Sweden and withdraws drugs based on the FDA's decisions. Likewise in order for a drug to be withdrawn globally, the side effects usually have to be severe enough to catch the attention of the entire world. In addition most of the time, drugs are kept on the market for many years before they are found to be more harmful than good. While there might be monetary benefits for each country in keeping these drugs on the market, the U.N. must step up the visibility of the withdrawal of dangerous drugs list.

References

1. "Carisoprodol and meprobamate: risks outweigh benefits." *Drug Safety Update*. MHRA, 03 Sept 2010. Web. 22 Jun 2011.
<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084737>.
2. "Consolidated List of Products." *World Health Organization*. United Nations, 2005. Web. 22 Jun 2011.
<http://apps.who.int/medicinedocs/documents/s16780e/s16780e.pdf>.
3. "Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments." *United Nations*. United Nations, 2009. Web. 22 Jun 2011.
<http://www.un.org/esa/coordination/CL-14-Final.for.Printing.pdf>.
4. "Drugs and Chemicals of Concern: Carisoprodol." *Office of Diversion Control*. DEA, June 2009. Web. 22 Jun 2011.
[http://www.dea.gov/diversion.usdoj.gov/drugs_concern/carisoprodol.htm](http://www.dea.gov/diversion/usdoj.gov/drugs_concern/carisoprodol.htm).
5. "European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim." *European Medicines Agency*. EMEA, 2011. Web. 23 Jun 2011.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001119.jsp&murl=menus/news_and_events/.
6. "European Medicines Agency (EMA) recommends withdrawal of dextropropoxyphene-containing medicines." *MHRA*. MHRA, 25 June 2009. Web. 23 Jun 2011.
<http://www.mhra.gov.uk/NewsCentre/CON049300>.
7. "Ex-Regulator Said to Testify GlaxoSmithKline Withheld Study." *Bloomberg Businessweek* 10 July 2010: 23 Jun 2011.
<http://www.businessweek.com/news/2010-07-10/ex-regulator-said-to-testify-glaxosmithkline-withheld-study.html>.

8. "FDA Announces Voluntary Withdrawal of Pergolide Products Agency Working with Product Manufacturers." *FDA*. FDA, 29 March 2007. Web. 23 Jun 2011.
<http://www.fda.gov/newsevents/newsroom/pressannouncements/2007/ucm108877.htm>.
9. "FDA pulls common pain med off the market." *CNN* 19 November 2010: Web. 23 Jun 2011.
<http://www.cnn.com/2010/HEALTH/11/19/fda.removes.drug/>.
10. "Fen-Phen Case Lawyers Say They'll Reject Wyeth Offer." *New York Times* (2005): 22 Jun 2011.
<http://query.nytimes.com/gst/fullpage.html?res=9505E7D6133AF934A25751C0A9639C8B63>.
11. "Information by Drug Class Drug Safety and Availability Information by Drug Class - FDA Letter to Manufacturers of Drug Products Containing Phenylpropanolamine (PPA)." *FDA*. FDA, 3 November 2000. Web. 23 Jun 2011.
<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm150774.htm>.
12. Lasser, Karen, Paul Allen, and Steffie Woolhandler. "Timing of New Black Box Warnings and Withdrawals for Prescription Medications." *JAMA*. 305.24 (2002): 2493.
13. "Withdrawn List." *FDA*. FDA, n.d. Web. 22 Jun 2011.
http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_TOC.htm.
14. Wood AJ. The safety of new medicines: the importance of asking the right questions. *JAMA*. 281 (1999): 1753-1754.

Appendix: Drugs Banned in the U.S., Internationally, and Worldwide

| Drugs Banned in U.S. | Effective Date | Drugs Banned But Available in U.S. | Banned in other Countries (UK, Sweden, Japan, Australia) | Effective Date | Grounds for Removal |
|-----------------------------------|----------------|------------------------------------|--|----------------------|--|
| Acetanilide | | | JPN | Jul 1971 | Aplastic anaemia |
| Acetylfurtrizine | | | JPN | Jul 1977 | Superseded by safer and more effective preparations. |
| Alclofenac | | | UK | 1979 | Skin rashes and mutagenic activity |
| Amfepramone | | | SWE | Jan 1981 | Potential for abuse |
| Amfepramone HCl | | | UK | Apr 2000 | Risks outweigh benefits |
| Amphetamine | 1973 | | | | High risk of abuse and dependence |
| Aminoglutethimide | 1966 | | | | Serious toxic effects to thyroids, ovaries, adrenals and uteri of female rats caused sexual precocity and masculinization of young females |
| Aminophenazone | Nov 1977 | | AUS, JPN, UK, SWE | 1965, Dec 1977, 1989 | Importation inhibited due to bone marrow suppression and fatal agranulocytosis Not known if marketed in U.S. |
| Amilprilose | Jan 1994 | | | | Lack of efficacy and safety |
| Amobarbital | | | SWE | July 1985 | Fatal intoxications and abuse |
| Aphrodisiac drugs | Jan 1990 | | | | Unsafe and of doubtful effectiveness |
| Aprobarbital | | | SWE | July 1985 | Fatal intoxications and abuse |
| Aristolochia | | | UK | July 1999 | End-stage renal failure |
| | | Aristolochic Acid | UK, AUS | Sept 2004 | Nephrotoxic and carcinogenic |
| Astemizole | 1999 | | | | QT prolongation |
| Azaribine | Aug 1976 | | | | Thromboembolism |
| Benzympenicillin sodium (topical) | Feb 1972 | | | | Lack of effectiveness compared to risk |
| Benoxaprofen | 1982 | | | | |

| | | | | | |
|---|---|--|-----------|------------------------------------|---|
| Bithionol | Oct 1967 | | JPN | July 1971 | Photosensitivity and cross-photosensitivity with other chemicals |
| Boric acid and borates (topical use in infants) | 1985 | | UK JPN | July 1985 | Dead in infants |
| Bromfenac | Jun 1998 | | | | Hepatic failure |
| Bromocriptine | Sep 1989 | | | | Risk of rebound effect and only 10 % benefit therapeutically |
| Bunamiodyl | 1964 | | SWE | 1964 | Repeat doses may be associated with oliguria, renal tubular necrosis, and death |
| Calamus | Nov 1968 | | | | Animal carcinogenicity |
| Cerivastatin | Aug 2001 | | Worldwide | Aug 2001 | Increased risk of rhabdomyolysis especially when used with gemfibrozil |
| Chloroform | Jul 1976 | | JPN,UK | May 1976 | Liver cancer in mice and rats |
| Cisapride | Apr 2000 | | UK, JPN | Jul 2000, Oct 2000, Dec 2002 | Cardiac events |
| Clioquinol | Nystaform removed (Clioquinol & nystatin) | | JPN, SWE | Sep 1970, Jun 1975 | Causes subacute myelo-optic neuropathy (SMON) |
| Cobalt (non-radioactive forms) | Jul 1967 | | | | Lack of effectiveness in treating iron deficiency anemia and causes severe toxicity |
| Coumarin | | | AUS | Aug 15 1996 | Death from hepatotoxicity in women |
| Cyclandelate | Dec 1996 | | | | Not effective vasodilator |
| Dalkon shield | 1974 | | UK | 1985 | Increase risk of PID |
| Dantron | Mar 30 1987 | | JPN, UK | Feb 1987, Apr 1987- May 2000 | Carcinogenic and genotoxicity |
| Dexamfetamine | 1973 | | | | Abuse and high risk of dependence |
| Dexfenfluramine hydrochloride/Fenfluramine | Sept 1997 | | Worldwide | | Heart valve problems and pulmonary hypertension |
| Dibenzepin hydrochloride | | | SWE | Jan 1983 | Fatal suicidal attempts |
| Diethylaminoethoxyhexestrol | | | JPN | Dec 1970 | Liver toxicity |
| Difurazone | | | JPN | Jul 1977 | Superseded by safer and more effective products |
| Dihydrostreptomycin | Sep 1970 | | | | Ototoxicity |

| | | | | | |
|-----------------------------|-----------------------------------|--|--|-----------------------|---|
| Dihydroxymethylfuratrizine | | | JPN | July 1977 | Superseded by safer and more effective products |
| Dilevalol | Aug 9 1990 | | JPN | Aug 9 1990 | Worldwide removal- Liver toxicity |
| Dimazole | Jul 1977 | | | | Neurotoxic –available in 40 countries |
| Dinoprostone | | | UK | July 19 1990 | Uterine hypertonia and foetal distress |
| Domperidone(injectable) | Jan 31 1985 | | All | Jan 31 1985 | Worldwide removal-cardiotoxicity |
| Droperidol | | | UK | Mar 2001 | Cardiac events |
| Droxicam | | | E.U. | Dec 14 1994 | Suspended marketing authorization due to hepatic damage |
| Ephedra | Jan 02 2004 | | | | Heart attack and stroke |
| Erythrityl tetranitrate | 1998 | | | | Lack of efficacy for management, prophylaxis or treatment of angina |
| Erythromycin estolate | | | SWE | | Severe cholestatic hepatitis and jaundice |
| Ethyl nitrite (spirit) | Jun 26 1980 | | | | Risk of fatal methaemoglobinaemia and poisoning in some infants |
| Factor IX | | | SWE | 1984 | Reports of infections with HIV (the AIDS virus) in patients treated with drug |
| Factor VIII | | | UK | Oct 1986 | Reports of infections with HIV (the AIDS virus) in patients treated with drug |
| Fenclofenac | 1980s | | UK | 1985 | Fatal skin Rashes |
| Feprazone | | | UK | Mar 30 1984 | Concern of risk/benefit ratio- only available in 7 countries |
| Flosequinan | October 1993 | | UK | Jul 1993 | Increased hospitalization and death |
| Flunitrazepam | Not approved by FDA- illegal drug | | Available in other countries for treatment of insomnia | | |
| Furazolidone | 1991 | | Japan | Jul 1977 | Superseded by safer and more effective preparations |
| Glafenine | | | E.U. Worldwide | Jan 14 1992, May 1992 | Risk of serious anaphylactic reactions |
| Grepafloxacin hydrochloride | Oct. 27, 1999 | | UK Worldwide | Oct 1999 | Cardiac arrhythmias; QT prolongation |

| | | | | | |
|--|-------------|-----------------|----------------------------|----------------------|---|
| Guanofuracin | N/A | | JPN | Jul 1977 | Superseded by safer and more effective preparations. |
| Halogenated salicylanilides | Dec 1 1975 | | JPN | Jan 1976 | Disabling skin disorders and photosensitivity in humans. |
| Heptabarb | | | SWE | Jul 1984 | Fatal intoxication and abuse |
| | | Hexachlorophene | JPN | Mar 1972 | Banned in nursing powder preparations due to brain edema. Carcinogenic? |
| Hexobarbital | | | SWE | Oct 1984 | Fatal intoxication and abuse |
| Hyoscine methonitrate | | | SWE | Jun 1981 | Removed from appetite suppressant formulations |
| Indoprofen | 1984 | | UK Worldwide removal | Dec 1983, 1984 | Severe GI reactions Carcinogenicity in rats |
| Iodinated casein strophanthin (neo-barine) | Oct 1964 | | | | Thyrototoxic side effects |
| Isocarboxazid | | | JPN | Nov 1974 | Lack substantial evidence of efficacy and safety |
| Isoxicam | 31 Oct 1985 | | Worldwide | | Fatal skin reactions |
| Laetrile | 24 Mar 1987 | | AUS | Feb 20 1986 | Importation of drug prohibited due to lack of efficacy and toxicity; can be potentially fatal |
| Levacetylmethadol | 23 Aug 2003 | | E.U. | 2001 | Pro-arrhythmic potential |
| Levamphetamine | 1973 | | | | Evidence of abuse and high risk of dependence |
| Loperamide (Drop formulations) | 1990 | | All | 1990 | Worldwide removal due to cases of paralytic ileus |
| L-Tryptophan | Nov 17 1989 | | UK,SWE, JPN | Dec 1989 May 1990 | Eosinophilia-myalgia syndrome |
| Lynestrenol | 1970 | | AUS | 1980 | Mammary tumours in the beagles |
| Mephesisin | | | JPN | Jul 1976 | Lack of substantial evidence of efficacy and safety. |
| Meproamate | | | SWE | Jan 1981 | Potential for abuse and lack of efficacy |
| Metamizole sodium | Jun 27 1977 | | AUS SWE | 1965, 1999 | Prohibited the importation; fatal agranulocytosis |
| Methapyrilene | 1992 | | UK,AUS | 1979, 1980 | Carcinogenicity in rodents |
| Methiodal sodium | | | SWE | Jan 1975 | Induced muscle spasms, safer alternates available |
| Metofoline | Mar 1965 | | Not available outside U.S. | | Eye changes and corneal opacities in dogs |
| Metrodin HP | | | UK | Feb 2003 | Creutzfeldt-Jakob Disease |

| | | | | | |
|------------------------|----------|---------------|---------------------|------------------------------------|---|
| Mibefradil | 1998 | | UK | Jul 1998 | Numerous drug interactions |
| Nebacumab | 1993 | | Worldwide | | Increased mortality |
| Nialamide | | | JPN | Nov 1974 | Lack substantial evidence of efficacy and safety |
| | | Nifedipine | AUS | Mar 1996 | 10 mg withdrawn due to serious adverse effects related to rapid release and higher peaks. Committee has deferred ruling on 5 mg for 12 months |
| Nitrendipine | | | AUS | | Registration refused on grounds of inadequate data on pharmacokinetics |
| Nitrofurantoin | | | JPN | Jul 1977 | Superseded by safer and more effective preparations |
| Nomifensine | Jan 1986 | | Worldwide | | Haemolytic anaemia |
| Noscapine | | | UK | 1991 | Cough mixtures containing noscapine were withdrawn and all other noscapine products were placed under Rx only due to concerns of genotoxicity |
| Oxyphenbutazone | | | SWE, UK | Jan 1985 | Blood dyscrasias. All products in UK have been revoked except eye ointment |
| Oxyphenisatine acetate | Feb 1972 | | AUS, JPN, UK | 1972, 1978 | Fatal liver disease, jaundice UK-all removed except suppositories for single-dose use |
| Pentobarbital | | | SWE | Jul 1985 | Fatal intoxications and abuse |
| Pexiganan | Mar 2000 | | | | Not approved-lack of efficacy |
| Phenacetin | Nov 1983 | | UK,SWE,JP N, | Mar 1980, Jul 1982, Aug 1982 | Carcinogenicity and renal damage, hemolytic anemia, methaemoglobinaemia |
| Phenformin | Nov 1978 | | SWE,UK | Oct 1978, 1982 | Severe lactic acidosis |
| | | Phenobarbital | SWE | Jul 1985 | Abuse potential and fatal intoxication |
| Phenolphthalein | | | European Union, JPN | Dec 1997, Jan 1998 | skin reactions, potassium loss and atonia |
| | | Phentermine | SWE,UK | Jan 1981, Apr 2000 | Potential for abuse; risk outweighs benefit |
| Phenylpropanolamine | Nov 2000 | | | | Hemorrhagic stroke; JPN, UK evidence is weak but package includes new warnings |
| Pipamazine | Jul 1969 | | | | Lack of proof of efficacy and safety |
| Piperazine | | | SWE | 1983 | Carcinogenic and mutagenic potential |

| | | | | | |
|---|-------------|--|-----------|----------------|---|
| Pirprofen | Sep 30 1990 | | Worldwide | | Fatal liver toxicity |
| Pituitary-chorionic gonadotropin (injectable) | Jul 1972 | | | | Risk of eliciting antibodies to animal protein, leading to allergic reactions |
| Polidexide sulfate | | | UK | 1977 | Oculo-mucocutaneous syndrome |
| Polyoxyethylated castor oil | Jun 1984 | | Worldwide | | Severe anaphylactoid reactions and haematological changes including hyperlipidaemia, altered blood viscosity and erythrocyte aggregation |
| Practolol | | | SWE, UK | May 1975, 1977 | Only IV preparation available others removed due to evidence of oculo-mucocutaneous syndrome |
| Prasterone | 1985 | | | | Lack of efficacy and safety of long-term use |
| Prenylamine | 1989 | | Worldwide | | Polymorphic ventricular tachycardia |
| Pumactant | | | UK | Apr 2000 | Higher mortality rate in neonates |
| Pyrrrolizidine | | | UK | Mar 1993 | Liver toxicity |
| Remoxipride | Mar 1994 | | Worldwide | | Aplastic anaemia |
| Sertindole | | | UK | Dec 1998 | Cardiac arrhythmias |
| Somatropin (pituitary-derived) | Aug 1985 | | UK | May 1985 | Reports of death from development of Creutzfeldt-Jakob disease |
| Strychnine and salts | | | JPN | 1987 | No demonstrated therapeutic value |
| Sulfamethizole | | | SWE | Feb 1984 | Adverse reactions and low sales; replaced by newer safer antibiotics |
| Sulfamethoxyipyridazine | | | SWE | Feb 1984 | Adverse reactions and low sales; renal toxicity, sometimes fatal exfoliative dermatitis and erythema multiforma, hemolytic anemia/aplastic anemia |
| Sulfathiazole | Sep 1970 | | | | Serious adverse reactions as listed above |
| Suloctidil | 1985 | | Worldwide | | Hepatitis |
| Suprofen | May 1987 | | Worldwide | | Sales had diminished to point product was no longer economically viable |

| | | | | | |
|--|----------|------------------------|------------------|------------------------------|--|
| Temafloxacin | Jun 1992 | | Worldwide | | Hypoglycaemia, haemolytic anaemia, renal failure, hepatitis and anaphylactic reactions |
| Terconazole | | | SWE | Jul 1991 | Vaginal suppositories containing 80 mg and 160 mg terconazole was withdrawn due to febrile reactions |
| Terfenadine | 1998 | | | | Associated with rare, but serious heart problems when taken with certain antibiotics and antifungals; JPN,UK available with warnings |
| Terodiline | 1992 | | Worldwide | | Ventricular tachycardia, heart block and bradycardia associated |
| Tetracycline (pediatric) | Jan 1979 | | AUS | 1991 | Stain teeth and retard bone growth |
| Thenalidine | Jul 1958 | | UK, SWE, AUS | 1961, 1976,1980 | Severe neutropenia |
| Tienilic acid | Jan 1980 | | | | Liver toxicity |
| Tolcapone | | | EME,UK, AUS, | Nov 1998, Feb 1999 | Hepatotoxic |
| Tolrestat | Nov 1996 | | Worldwide | | Hepatic necrosis and death |
| | | Triazolam | AUS JPN UK | Apr 1986, Mar 1992, Jun 1993 | 0.50mg and 0.25mg triazolam were not approved due to risk of adverse effects. 0.125mg triazolam were approved for the treatment of insomnia. Dose should not exceed 0.5 mg. Reversible psychiatric adverse effects, particularly loss of memory and depression |
| | | Troglitazone | UK, JPN | Dec 1997 | Severe hepatocellular damage, hepatic necrosis and hepaticfailure |
| | | Trovafloxacin mesilate | EME | May 1999 | Marketing authorization suspended due to hepatic events |
| Urethane | Mar 1977 | | JPN | Jul 1975 | Carcinogenicity |
| Vinarol and viga (dietary supplements) | Apr 2003 | | | | Unlabeled presence of sildenafil |
| Vinbarbital | | | SWE | Jul 1984 | Fatal intoxications and abuse |
| Zimeldine | Jul 1983 | | Worldwide | | Hypersensitivity reactions and neurological complications |
| Zomepirac | Mar 1983 | | | | Serious allergic reactions, including five deaths from anaphylaxis |