The Franklin Pierce Center for Intellectual Property at the University of New Hampshire School of Law Educational Report:
Preliminary Report on Search Methodology and Patent Status of Medicines Added to the WHO EML from the 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines

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PROFESSORS
JON R. CAVICCHI, J.D., LL.M (INTELLECTUAL PROPERTY)
STANLEY P. KOWALSKI, Ph.D, J.D.

ITTI CLINIC STUDENT MEMBERS
DAVID PFLUGH, Ph.D
ALEX SAMUEL

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Table of Contents

DISCLAIMER AND SCOPE OF PROJECT……..……..…..3

INTRODUCTION.....4
Search Methodology……..…...……..5
Precision vs. Recall……..……6

INDIVIDUAL MEDICINE PATENT INFORMATION AND GLOBAL PATENT TRENDS..7
Isoflurane……..……..…7
Propofol……...……..…...9
Thiopental……...……..….12
Midazolam……...……..…14
Succimer……...……..…16
Albendazole……...…...18
Clarithromycin……....…21
Sulfamethoxazole + Trimethoprim……23
Miltefosine……...……..…26
Artesunate + Amodiaquin ……..……28
Paclitaxel……...…...……..…31
Docetaxel……...…...…….33
Tranexamic Acid ……....…35
Hydroxycarbamide……..….37
Deferoxamine (mesilate)……..……39
Deferasirox……...……..…41
Bisoprolol……....……..…43
Metoprolol……...……..…45
Carvedilol……....……..…46
Terbinafine……...…...……..…48
Terbinafine Hydrochloride…….……50
Mupirocin……...……..……52
Glucagon……...……....…54
Atracurium……...55
Misoprostol……...…...……..…57

DISCUSSION……...……59
Selection of Patent Documents……...….59
Precision and Recall in the Selection of Patent Documents……..…60
Alternative Internet Resources: Free versus Propietary……..…63

CONCLUSIONS……65

Disclaimer and Scope of Project[1]

This is solely an educational report and is neither inclusive nor comprehensive. The information provided in this report serves as a resource for initiating a search strategy aimed at providing a survey of relevant patent literature with regard to medicines listed on the WHO Essential Medicines List. This report is not a freedom-to-operate opinion (FTO), and the International Technology Transfer Institute (ITTI) Clinic at the Franklin Pierce Center for Intellectual Property (FPCIP) at the University of New Hampshire School of Law (UNH-Law) draws no conclusions, makes no opinions or representations either explicitly or implicitly, including but not limited to patent term and expiration dates, and geographic coverage.

Neither the ITTI Clinic nor UNH-Law are responsible for any errors, omissions, and limitations of data or search parameters of any data source used within this report. The patent searching platforms utilized in this report are limited to English language searching of full text patent documents and abstracts using machine translated national and bibliographic records including but not limited to those arising from DWPI and INPADOC.

Neither the ITTI Clinic nor UNH-Law are experts in the field of pharmaceutical patent law. Therefore no guarantees or opinions are expressed herein with respect to the evaluation of patents as ITTI Clinic members did not perform claim interpretation or determine the validity of claims. The tight time frame for report preparation, overall demands faced by the ITTI Clinic Student Team, and limitations imposed by both the search methodology and patent search platforms used affected the level of sophistication and the number of patents found and evaluated. As such, additional patents whether inside or outside the confines of the methodology herein, were not considered.

The confines of this report limit the data to medicines added to the EML as a result of the 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines which took place in Accra, Ghana March 21st-25th 2011. Finally, with regard to any national or regional jurisdiction patent filing, whether within or outside of the defined scope of this project, it is imperative to appreciate the difficulties of locating patents in national jurisdictions that do not report, or report infrequently, to electronic or internet patent databases. All users of this report should engage a patent professional in all jurisdictions of interest to evaluate any patents listed within this report.

[1] The Franklin Pierce Center for Intellectual Property at the University of New Hampshire School of Law Educational Report: Preliminary Report on Patent Literature, Search Methodology and Patent Status of Medicines on the WHO EML 2009, Spring 2011, p. 1.

Introduction

The World Health Organization's Model List of Essential Medicines (WHO EML) was developed as a list of medicines to support a minimum level of healthcare. [2] The first list was developed by a WHO Expert Committee in 1977. [3] "Every two years since 1977, the Model List has been updated by the WHO Expert Committee on the Use of Essential Drugs."[4] This report presents a list of preliminary patent information corresponding to medicines added to the WHO EML as a result of the 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines which took place in Accra, Ghana March 21st-25th 2011.[5] As a result of that meeting, the following modifications were approved: the addition of 16 new medicines to the EML, the deletion of 13 medicines from the EML, new indications for 4 medicines already listed on the EML, and the addition of a new dosage form or strength for 4 medicines already on the EML.[6] The new medicines added to the list were mainly added because of new evidence of safety and efficacy for treatment of a particular disease and in the case of Mupirocin and Glucagon, for "the fact that inclusion in the Model List may push prices down."[7] A summary of the additions are listed in the table below.

Medicine	Delivery Method	Dosage	Section of EML Impacted
Isoflurane	Inhalation	-	1.1.1
Propofol	Injection	10 mg/mL	1.1.2
	Injection	20 mg/mL	1.1.2
Thiopental	-	-	1.1.2
Midazolam	Injection	1 mg/mL	1.3
	Tablet	7.5 mg	1.3
	Tablet	15 mg	1.3
Succimer	Oral Solid	100 mg	4.2
Albendazole	Tablet (chewable)	400 mg	6.1.2
Clarithromycin	Tablet	500 mg	6.2.2
Sulfamethoxazole + Trimethoprim	Combination Tablet	800 mg + 160 mg	6.2.2
Miltefosine	Oral Solid	10 mg	6.5.2
	Oral Solid	50mg	6.5.2
Artesunate + Amodiaquine	Tablet	25 mg + 67.5 mg	6.5.3
	Tablet	50mg +135 mg	6.5.3
	Tablet	100 mg + 270 mg	6.5.3

[2] The Essential Medicines List for a Global Patient Population, pg 498.
[3] WHO medicines strategy: Revised procedure for updating WHO's Model List of Essential Drugs, p. 2. http://apps.who.int/gb/archive/pdf_files/EB109/eeb1098.pdf (last visited Aug. 15, 2011).
[4] *Id*.
[5] The Unedited Report, 18th Expert Committee on the Selection and Use of Essential Medicines, 21-25 March, 2011, Accra, Ghana, p. 7.
[6] *Id*. at p. 7.
[7] *Id*. at, p. 14.

Paclitaxel	Injection	6 mg/mL	8.2
Docetaxel	Injection	20 mg/mL	8.2
	Injection	40 mg/mL	8.2
Tranexamic acid	Injection	100 mg/mL	10.2
Hydroxycarbamide	Tablet	200 mg	10.3
Hydroxycarbamide	Tablet	500 mg	10.3
	Tablet	1 g	10.3
Deferoxamine (mesilate)	Injection	500 mg	10.3
Deferasirox	Oral Form	-	10.3
Bisoprolol	Tablet	1.25 mg	12.1 – 12.4
	Tablet	5 mg	12.1 – 12.3
	Tablet	10 mg	12.4
Metoprolol	-	-	12.1 - 12.4
Carvedilol	-	-	12.1 - 12.4
Terbinafine	Cream/Ointment	1%	13.1
Terbinafine Hydrochloride	Cream/Ointment	1%	13.1
Mupirocin	Cream/Ointment	2%	13.2
Glucagon	Injection	1 mg/mL	18.5
Atracurium	Injection	10 mg/mL	20
Misoprostol	Tablet	0.2 mg	22.1

Search Methodology

The search methodology used to generate this report is based on the decision tree protocol (DTP) developed by the student researchers who wrote the *Preliminary Report on Patent Literature, Search Methodology and Patent Status of Medicines on the WHO EML 2009*. When necessary, searches deviated from the DTP in order to find the relevant base patent. We define "base patent" as the earliest identified patent claiming the active pharmaceutical ingredient or method of use as listed in the EML update. A base patent does not solely claim the synthesis, purification, or method of manufacture a compound, nor does a base patent claim a use, dosage, or composition which does not include that on the EML update list. In addition to these base patents, our report explicitly lists relevant patents registered in the Orange Book as well as those listed in the Health Canada Patent Register. Relevant patents that were located that were not registered in the Orange Book nor Health Canada Patent Register are listed under the category of "Collateral Patents." These relevant patents are listed because they may have been filed more recently than the base patent or may cover the method of use of the specific dosage form prescribed by the EML or are relevant for other reasons.

Deviations from the DTP are noted in the "Comments" section for each medicine listing. One way the search methodology in this report differed from the previous report was the reduced reliance on the Orange Book. The Orange Book was used, in some instances, to help locate the base patent but other sources including the Merck Index, ChemSpider, and keyword searching

using Thomson Innovation® was relied on more often in comparison. Our experience suggests that following a rigid search strategy is not the optimal method of locating relevant base patents. A flexible approach to searching and understanding the patents in order to assess their relevancy is extremely important.

Several commercial databases were used in our research including Thomson Innovation, LexisNexis® TotalPatent, and Proquest Dialog™. The Merck Index was used to collect bibliographic information (such as CAS number, Chemical Formula, and IUPAC Name) for each medicine. Patent family maps were generated for several medicines highlighting patent trends in countries based on INPADOC, DWPI, and LexisNexis® TotalPatent Extended family information. First, family information was collected for each family with at least one member listed on the medicine data sheet. This information was exported in an Excel® readable format and sorted by country code and filing date (publication date was used if filing date was unavailable). A macro was used to facilitate sorting of the family information. Color values (Red, Orange, Yellow, and White) were assigned based on latest filing date and Mapland™, an Excel® add on, was used to plot the color values against country code data.

Precision vs. Recall [8]

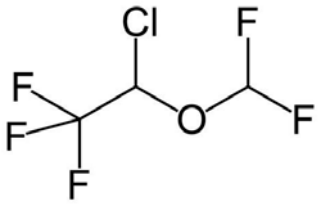
While searching for relevant patents and evaluating search strategies, the concepts of precision and recall were forefront in our minds. Precision is the fraction of retrieved documents that are relevant. Recall is the fraction of relevant documents that are retrieved. Both of these values measure the information retrieval effectiveness of a search. An optimal search strategy will find a balance between precision and recall to ensure that highest number of relevant documents are found in the least number of iterative searches.

[8] *An Introduction to Information Retrieval,* p. 155. http://nlp.stanford.edu/IR-book/pdf/irbookonlinereading.pdf (last visited Aug. 15, 2011).

INDIVIDUAL MEDICINE PATENT INFORMATION AND GLOBAL PATENT TRENDS

Isoflurane[9]

Inhalation



Use:	Inhalation anesthetic
IUPAC Name:	2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane
CAS Number:	26675-46-7
Chemical Formula:	$C_3H_2ClF_5O$
Alternative names & Trademarks	Ethane; 1-chloro-2,2,2,-trifluoroethyl difluoromethyl ether; Aerrane (Baxter); Forane (Ohmeda); Forene (Abbott).

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
GB1191778	Air Reduction Inc	N/A	1968-12-12

Orange Book Patents[10]:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

[9] Chemical structure taken from chemistry.about.com, http://chemistry.about.com/od/factsstructures/ig/Chemical-Structures---I/Isoflurane.htm (last visited Aug. 11, 2011). Unless otherwise noted, all other structures were copied from the Merck Index (Maryadele J. O'Neil ed., Merck & Co., Inc., 14th ed. 2006).

[10] No patent information was available from Health Canada, http://webprod3.hc-sc.gc.ca/pr-rdb/index-eng.jsp (last visited Aug. 11, 2011).

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
DE1814962	Airco Inc., New York, N.Y., USA	1968-12-16	Merck
US3535388	Air Reduction Inc	1969-03-21	Merck
US3535425	Air Reduction Inc	1969-12-18	Merck

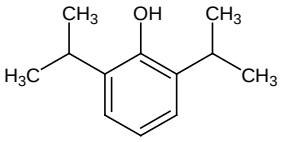
Comments:

Following the DTP, three patents were found to be listed in the Merck Index, but none were the true base patent based on earliest filing date. Both the ‘962 and ‘388 patents are in the same Derwent family as the base patent, indicating the importance of checking patent family data for the documents listed in the Merck Index. The ‘425 patent was in a different family, and had a later filing date.

See Appendices A and B for patent data.

Propofol

Injection: 10 mg/ml, 20 mg/ml



Use:	Intravenous anesthetic
IUPAC Name:	2,6-Bis(1-methylethyl)phenol
CAS Number:	2078-54-8
Chemical Formula:	$C_{12}H_{18}O$
Alternative names & Trademarks	2,6-di-isopropylphenol; disoprofol; 2,6-di(propan-2-yl)phenol; Ansiven (Abbott); Diprivan (AstraZeneca); Disoprivan (AstraZeneca); Rapinovet (Schering-Plough Vet.)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
GB1472793	Imperial Chem Ind Ltd	N/A	1974-03-28

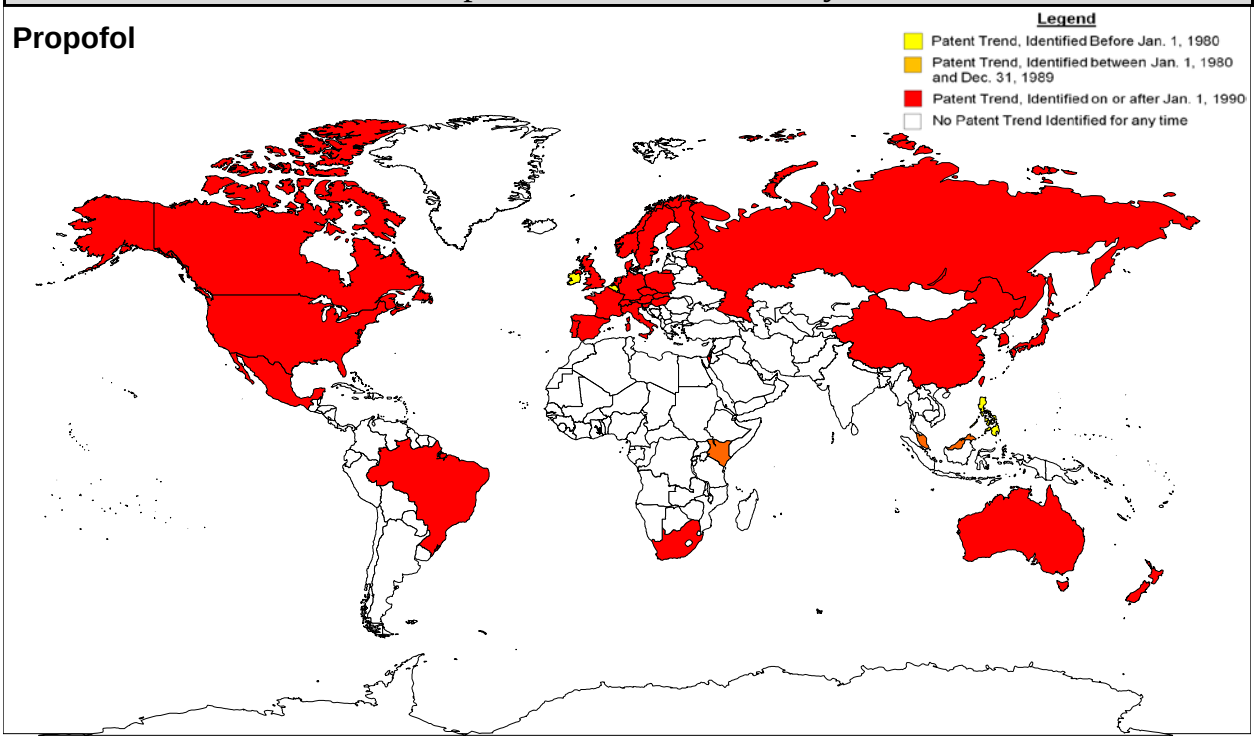
Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US5714520	AstraZeneca	N/A	1995-03-22
US5731355	AstraZeneca	N/A	1997-02-18
US5731356	AstraZeneca	N/A	1997-02-18
US5908869	AstraZeneca	N/A	1998-01-30

Collateral Patent Documents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
US2831898	Ethyl Corp	1954-04-29	Merck
WO1996001243A1	Archimica S.P.A.	1995-06-28	Cited ‘898
US4056635	ICI LTD	1975-03-19	Cited by ‘243
US4447657	Universal Oil Products, Inc.	1982-11-10	Merck

World Map Generated from Family Data[11]



Regional Office Patent Trend	
African Intellectual Property Organization	
African Regional Intellectual Property Organization	
Eurasian Patent Office	Identified after Jan. 1, 1990
European Patent Office	
Gulf Cooperation Council	
World Intellectual Property Organization	Identified after Jan.1,1990

Comments:

Propofol is another example where the patents listed in the Merck Index are not the base patents. In this case, both Merck patents are directed only towards methods of synthesis, not use or composition of matter of an anesthetic agent. Instead, the description of the '898 patent discloses:

Compounds of this class . . .have superior germicidal and insecticidal properties. Also, because of their vastly increased solubility they serve as superior antioxidants in hydrocarbon fuels and lubricants, as well as antioxidants for rubber compositions. Another use of this class of compounds is as plasticizers [sic] and resin ingredients.

[11] Lexis Total Patent extended family data was used to construct world maps, https://www.lexisnexis.com/totalpatent (last visited Aug. 11, 2011). However, this database is not covered by the data listed in the appendices.

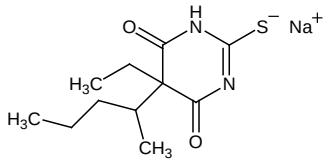
To find the base patent, a forward citation analysis was performed on the ‘898 patent. Forward citation analysis, as opposed to text searching of a patent database, preserves the precision of a search by maintaining a narrow focus (i.e. limited recall of results) on a given compound or class of compounds. One of the latest citation documents was the PCT application listed under Collateral Patent Documents, and this application claimed the use of propofol as an anesthetic. Backward citation analysis was performed on the PCT application to identify the earliest cited use of propofol as an anesthetic, which was the ‘635 patent. However, a check of the bibliography of the ‘635 patent revealed an even earlier patent, the ‘793 base patent. In summary, the base patent was discovered by a highly precise search, including both a forward and backward citation analysis and a search of priority data.

The listed Orange Book patents are all in a single patent family and are all related to more modern continuous infusion formulations. Older formulations are likely to be in the public domain, but a check of the legal status of the other listed documents would be necessary to confirm this. Thus, even though a particular medicine may have active patents listed in the Orange Book, those patents may not, and probably do not, cover all known formulations of that drug. Both the Merck patents and the Orange Book patents identified for propofol using the DTP illustrate the necessity of actually reading the patents in order to ascertain what those patents specifically cover.

See Appendices A and B for patent data.

Thiopental

Injection



Use:	Short-acting anesthetic (intravenous).
IUPAC Name:	5-Ethyldihydro-5-(1-methylbutyl)-2-thioxo-4,6(1*H*,5*H*)-pyrimidinedione monosodium salt
CAS Number:	71-73-8
Chemical Formula:	$C_{11}H_{17}N_2NaO_2S$
Alternative names & Trademarks	5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid sodium salt; thiomebumal sodium; penthiobarbital sodium; thiopentone sodium; thionembutal; Intraval Sodium (RPR); Nesdonal Sodium (RPR); Pentothal Sodium (Abbott); Trapanal (Byk Gulden)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US2153729	Abbott Laboratories	N/A	1934-04-16

Orange Book Patents[12]:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
US2876225	Abbot Laboratories	1956-06-13	Merck
US3109001	Abbot Laboratories	1959-08-24	Merck

[12] No patent information was available from Health Canada, http://webprod3.hc-sc.gc.ca/pr-rdb/index-eng.jsp (last visited Aug. 11, 2011).

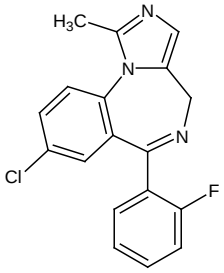
Comments:

Thiopental fits nicely within the DTP. Three patents were listed in the Merck Index, and the one with the earliest filing date was considered to be the base patent. The other two are listed as collateral patents.

See Appendices A and B for patent data.

Midazolam

Injection: 1 mg/ml
Tablet: 7.5 mg, 15 mg



Use:	Anesthetic (intravenous); anticonvulsant; sedative, hypnotic.
IUPAC Name:	8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine
CAS Number:	59467-70-8
Chemical Formula:	$C_{18}H_{13}ClFN_3$
Alternative names & Trademarks	Dormicum (Roche); Hypnovel (Roche); Versed (Roche)

Base Patent (injectable):

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
DE2540522	F Hoffmann-La Roche & Co Ag Basel CH	N/A	1975-09-11

Base Patent Document (tablet):

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
GB199717770A	R. P. Scherer Limited	N/A	1997-08-21

Orange Book Patents (injectable)[13]:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

[13] The tablet form is apparently not approved for use in either the USA or Canada.

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
US4280957	Hoffmann La Roche	1978-05-15	Merck

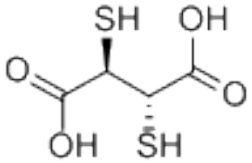
Comments:

The Merck Index listed two patents which were family members; the earlier German patent was taken as the base patent and the US document was listed as a collateral patent. However, both of these patents concerned the injection form. To find a base patent for the tablet form, which is a different composition of matter, a PCT application was located on the patents section of ChemSpider.com.[14] ChemSpider.com is an excellent alternative to begin a highly precise medicine patent search as the website provides preselected patents for each chemical. The British patent listed as the base patent is the priority document for the PCT application located on ChemSpider.com. Again, this emphasizes the importance of checking priority data on each relevant patent identified. No world map was generated for midazolam because the patent family concerning the tablet form have all apparently lapsed or not issued as patents, although this should be confirmed by a more thorough freedom-to-operate report.
See Appendices A and B for patent data. A pdf of the British application listed as the tablet form base document was not conveniently available.

[14] ChemSpider is a website operated by the Royal (UK) Society of Chemistry, http://www.chemspider.com/ (last visited Aug. 11, 2011).

Succimer[15]

Oral solid: 100 mg



Use:	A water soluble chelating agent, used as an antidote for heavy metal poisoning.
IUPAC Name:	(2*R*,3*S*)-*rel*-2,3-Dimercaptobutanedioic acid
CAS Number:	304-55-2
Chemical Formula:	$C_4H_6O_4S_2$
Alternative names & Trademarks	*meso*-2,3-dimercaptosuccinic acid; , 2,3-disulfanylbutanedioic acid, DMS; DMSA; Chemet (McNeil)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US4962127A	Cedars Sinai Medical Center	N/A	1989-03-17

Orange Book Patents[16]:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Comments:

No patents for succimer were located by following the DTP. Again, ChemSpider.com was used as an alternative starting point for a highly precise patent search[17]. ChemSpider.com listed several patents covering the use of succimer as a chelating agent to reduce excess silicon in the blood. The US patent given as the base patent had the earliest filing date of the ChemSpider.com patents. To ascertain whether any other earlier patent existed concerning the

[15] Chemical structure taken from Chemical Book, http://www.chemicalbook.com/ChemicalProductProperty_EN_CB9142563.htm (last visited Aug. 11, 2011). Chemical Book was selected by a Google search of internet resources. Unless otherwise noted, all other structures were copied from the Merck Index (Maryadele J. O'Neil ed., Merck & Co., Inc., 14th ed. 2006).

[16] No patent information was available from Health Canada, http://webprod3.hc-sc.gc.ca/pr-rdb/index-eng.jsp (last visited Aug. 11, 2011).

[17] ChemSpider is a website operated by the Royal (UK) Society of Chemistry, http://www.chemspider.com/ (last visited Aug. 11, 2011).

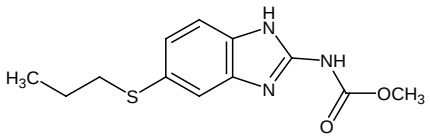
use of succimer as a therapeutic chelating agent, a patent search was conducted using Thomson Innovation[18] to broaden the recall of patent documents. The patent search did not return any other relevant documents. To ascertain whether the search was missing documents because various chemical names exist for each medicine, a Wikipedia[19] article on succimer was consulted, and the common name for this compound, especially as used in the patent literature, was found to be dimercaptosuccinic acid. This alternate name was included in the search terms, but the patent search still did not return any other relevant documents.
See Appendices A and B for patent data.

[18] http://thomsonreuters.com/products_services/legal/legal_products/intellectual_property/thomson_innovation/ (last visited Aug. 11, 2011).

[19] http://www.wikipedia.org/ (last visited Aug. 11, 2011). Wikipedia is another good alternative source of free information about medicines, although the data should always be confirmed using another independent reference source.

Albendazole

Chewable tablet: 400 mg



Use:	Anthelmintic.
IUPAC Name:	[5-(Propylthio)-1*H*-benzimidazol-2-yl]carbamic acid methyl ester
CAS Number:	54965-21-8
Chemical Formula:	$C_{12}H_{15}N_3O_2S$
Alternative names & Trademarks	methyl 5-(propylthio)-2-benzimidazolecarbamate; 5-(propylthio)-2-carbomethoxyaminobenzimidazole; Albenza (GSK); Eskazole (GSK); Valbazen (Pfizer); Zentel (GSK). Sulfoxide derivative: Albendazole oxide; ricobendazole; rycobendazole; Rycoben (Novartis).

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
EP1675474	Novartis AG	N/A	2004-07-29

Orange Book Patents[20]:

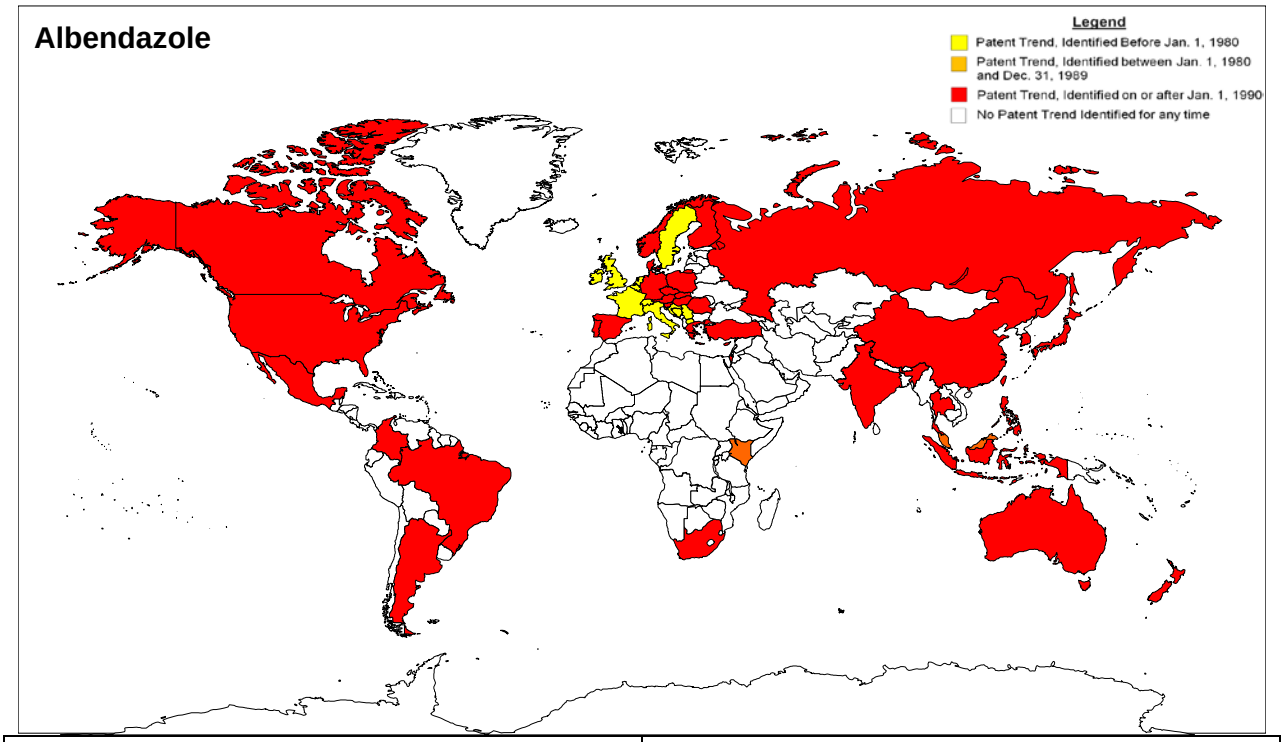
Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
US3915986	SmithKline Corporation	1974-06-19	Merck
US3956499	SmithKline Corporation	1975-08-07	'986 family
US5637603	Eli Lilly and Company	1995-04-25	Google Patents
US6051604	Procter & Gamble	1995-12-07	Google Patents

[20] A chewable tablet containing albendazole does not appear to be approved for use in the USA. Health Canada likewise lists no patent information, and approval in Canada appears to be limited to veterinary use.

World Map Generated from Family Data[21]



Regional Office Patent Trend	
African Intellectual Property Organization	Identified before Jan. 1, 1980
African Regional Intellectual Property Organization	
Eurasian Patent Office	
European Patent Office	Identified after Jan. 1, 1990
Gulf Cooperation Council	
World Intellectual Property Organization	Identified after Jan.1,1990

Comments:

Identification of relevant patents covering a chewable patent containing albendazole proved especially difficult. The patent listed in the Merck Index ('986) claimed only the synthesis of the molecule (termed methyl 5-propylthio-2-benzimidazolecarbamate). An analysis of the patent family of '986 revealed other members that claimed the use of albendazole as an antiparasitic/anthelmintic agent (the '499 patent is listed as a representative of this group). This indicates the importance of reading the patent documents to ascertain the specific scope of the patent. While these patents claimed and/or disclosed oral administration of albendazole, a chewable tablet was not indicated. Thus, further patent searching was required to increase the recall of document results.

[21] Lexis Total Patent extended family data was used to construct world maps, https://www.lexisnexis.com/totalpatent (last visited Aug. 11, 2011). However, this database is not covered by the data listed in the appendices.

ChemSpider.com had been used for other medicines in this report as an alternative starting point for finding the relevant base patent[22]. ChemSpider.com lists selected patents from USA patents and applications, European patents and applications, PCT applications, and abstracts from Japanese patents. The documents are highly precise in their limitation to claims concerning the individual chemical compounds. In contrast, ChemSpider.com also lists patents identified through Google Patents[23]. The Google Patent listings are always more extensive (i.e. Google Patents tends to have high recall). None of the more precise documents listed on ChemSpider.com disclosed or claimed a chewable tablet containing albendazole, so an advanced search was performed using Google Patents to improve its rate of precision[24]. Two patents were identified, '603 and '604. However, both of these patents merely disclosed a potential chewable tablet containing albendazole in combination with other medicines, but neither specifically claimed such a formulation. Thus further searching was indicated.

Given the nature of this report, searching using Google Patents was preferred as a it is a freely-available source of patent data. Given the difficulty in identifying an appropriate base patent, the proprietary database Thomson Innovation was used[25]. Using similar search terms to the Google Patents search, the '474 patent was selected as this patent specifically claimed a chewable tablet containing only albendazole. The claims were limited to veterinary use. Given the '603 and '604 patents, the scope of '474 may be strictly limited to that particular formulation.

Additionally, a comment needs to be made concerning the map shown. The data used to generate this map contained patents issued by several countries that no longer exist. A Soviet Union patent is indicated on the map as just Russia, while an East German patent was translated to the entire modern country of Germany. A Yugoslavian patent was shown by coloration of the individual modern countries of Serbia and Montenegro, Macedonia, Croatia, Bosnia And Herzegovina, and Slovenia. A more detailed examination of the patent laws in these countries is warranted to determine the accuracy of this depiction.

See Appendices A and B for patent data.

[22] ChemSpider is a website operated by the Royal (UK) Society of Chemistry, http://www.chemspider.com/ (last visited Aug. 11, 2011).

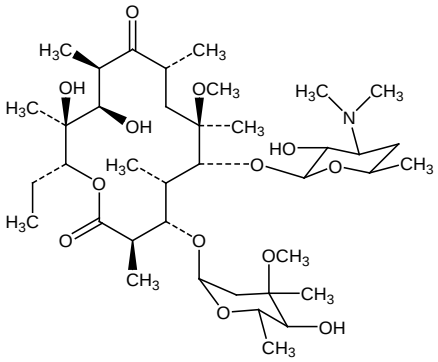
[23] http://www.google.com/patents (last visited Aug. 11, 2011). Unless specific publication numbers are known, an advanced search is always recommended on Google Patents to obtain optimal precision versus recall (see discussion).

[24] Search terms were: (albendazole or benzimidazolecarbamate) and chewable.

[25] http://thomsonreuters.com/products_services/legal/legal_products/intellectual_property/thomson_innovation/ (last visited Aug. 11, 2011).

Clarithromycin

Tablet: 500 mg



Use:	Antibiotic
IUPAC Name:	6-*O*-Methylerythromycin
CAS Number:	81103-11-9
Chemical Formula:	$C_{38}H_{69}NO_{13}$
Alternative names & Trademarks	Biaxin (Abbott); Clarosip (Grünenthal); Clathromycin (Taisho); Cyllind (Abbott); Klacid (Abbott); Klaricid (Abbott); Macladin (Guidotti); Naxy (Sanofi Winthrop); Veclam (Zambon); Zeclar (Abbott)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
JP1456831	Taisho Pharmaceutical Co. Ltd	N/A	1980-06-04

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US6010718	Abbott Laboratories	N/A	1997-04-11
US6551616	Abbott Laboratories	N/A	1999-10-13

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
EP41355	Taisho Pharmaceutical Co. Ltd	1981-05-27	Merck
US4331803	Taisho Pharmaceutical Co. Ltd	1981-05-19	Merck

Comments:

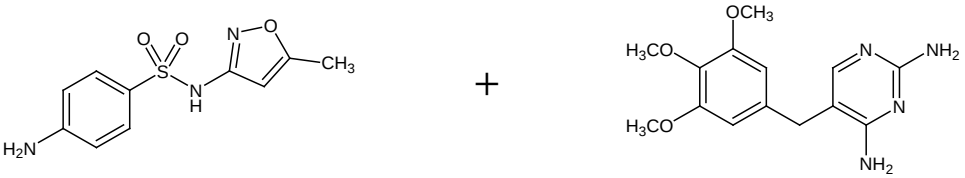
Following the DTP, two patents were found in the Merck Index. Both patents were in the same patent family, but the earliest priority document for these two patents was the Japanese patent given as the base patent. The two Merck patents are listed under Collateral Patents, and the US patent is presented in Appendix B as an image of the base patent was not available.

The Orange Book listed two patents, both from the same patent family, but these claim an improved, extended-release formulation of clarithromycin. Other, older formulations may be in the public domain, but a true freedom-to-operate report would be necessary for an accurate determination of the status of a particular formulation of any medicine on the EML. In this instance, nine other pharmaceutical companies have FDA-approved formulations of clarithromycin listed in the Orange Book, but give no active patents for these alternative formulations.

See Appendices A and B for patent data.

Sulfamethoxazole + Trimethoprim

Combination tablet: 800 mg + 160 mg



Use:	Antibiotic used to treat infections of the respiratory tract, renal and urinary tract, and skin, particularly in HIV patients.
IUPAC Name: (sulfamethoxazole)	4-Amino-*N*-(5-methyl-3-isoxazolyl)benzenesulfonamide
IUPAC Name: (trimethoprim)	5-[(3,4,5-Trimethoxyphenyl)methyl]-2,4-pyrimidinediamine
CAS Number: (sulfamethoxazole)	723-46-6
CAS Number: (trimethoprim)	738-70-5
CAS Number: (combination)	8064-90-2
Chemical Formula: (sulfamethoxazole)	$C_{10}H_{11}N_3O_3S$
Chemical Formula: (trimethoprim)	$C_{14}H_{18}N_4O_3$
Alternative names & Trademarks: (sulfamethoxazole)	*N*1-(5-methyl-3-isoxazolyl)sulfanilamide; 5-methyl-3-sulfanilamidoisoxazole; 3-sulfanilamido-5-methylisoxazole; 3-(*p*-aminophenylsulfonamido)-5-methylisoxazole; sulfisomezole; sulfamethylisoxazole; sulfamethoxizole; Gantanol (Roche); Sinomin (Shionogi)
Alternative names & Trademarks: (trimethoprim)	2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine; Instalac (Virbac); Monotrim (Duphar); Proloprim (Wellcome); Syraprim (Wellcome); Tiempe (DDSA); Trimanyl (Tosse); Trimogal (Lagap); Trimopan (Berk); Trimpex (Roche); Uretrim (Bastian); Wellcoprim (Wellcome).
Alternative names & Trademarks: (combination)	Co-trimoxazole; Abacin (Benedetti); Apo-Sulfatrim (Apotex); Bactramin (Roche); Bactrim (Roche); Baktar (Shionogi); Chemotrim (Rosemont); Drylin (Merckle); Eusaprim (GSK); Fectrim (DDSA); Gantaprim (Lenza); Gantrim (Geymonat); Imexim (Cimex); Kepinol (Pfleger); Laratrim (Lagap); Linaris (R.A.N.); Microtrim (Chephasaar); Nopil (Mepha); Oraprim (A.T.I.); Septra (Monarch); Septrin (GSK); Sigaprim (Dumex);

	Sulfotrim (Nattermann); Sulprim (Polfa); Sumetrolim (EGYT); Supracombin (Grünenthal); Suprim (Valeas); Teleprim (Procter & Gamble); Thiocuran (Sagitta); Trigonyl (Hoyer); Trimesulf (LPB); Uroplus (Shionogi)

Base Patent for Combination:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
GB1499672	Wellcome Foundation	Burroughs Wellcome Co.	1974-02-14

Merck Patents for Components (trimethoprim only):

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Published or Filed
US3049544	Burroughs Wellcome	N/A	1962-08-14
US3341541	Hoffmann La Roche	N/A	1965-07-09

Orange Book Patents[26]:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Collateral Patents (combination):

Patent	Patent Listed Assignee/Country	Date Filed	Source
EP200252	Yamanouchi Europ BV	1986-04-07	ChemSpider
US4209513	Burroughs Wellcome Co.	1978-04-14	ChemSpider

Comments:

For combination medicines, base patents should be determined for each component as well as the combination. For the combination of sulfamethoxazole and trimethoprim (co-trimoxazole or TMP-SMX), no true base patents which claimed a method of use or composition of matter for the individual components were identified. The Merck Index supplied patent information for only trimethoprim (given above) but both patents listed are only for the synthesis of the molecule.

Again, as the DTP did not reveal a base patent for the combination, ChemSpider.com was used as a starting point[27]. Patents claiming the indicated combination were identified from two

[26] No patent information was available from Health Canada, http://webprod3.hc-sc.gc.ca/pr-rdb/index-eng.jsp (last visited Aug. 11, 2011).

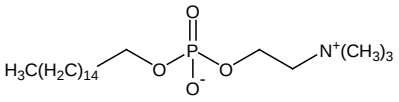
[27] ChemSpider is a website operated by the Royal (UK) Society of Chemistry, http://www.chemspider.com/ (last visited Aug. 11, 2011).

independent applicants, and these are listed as collateral patents. The base patent given is the earliest patent from either family of the two ChemSpider.com patents. However, all of these patents relate to rapid release formulations of this combination of medicines. According to the Wikipedia article on trimethoprim[28], the combination has been is use in the United Kingdom since 1969. Thus an even earlier base patent may exist, but, if so, it could not be identified with the methodologies employed.
See Appendices A and B for patent data.

[28] http://en.wikipedia.org/wiki/Trimethoprim (last visited Aug. 12, 2011).

Miltefosine

Oral Solid: 10 mg, 50 mg



Use:	Antineoplastic; antiprotozoal (Leishmania).
IUPAC Name:	2-[[(Hexadecyloxy)hydroxyphosphinyl]oxy]-*N*,*N*,*N*-trimethylethanaminium inner salt
CAS Number:	58066-85-6
Chemical Formula:	$C_{21}H_{46}NO_4P$
Alternative names & Trademarks	choline phosphate hexadecyl ester, hydroxide, inner salt; hexadecyl 2-(*N*,*N*,*N*-trimethylamino)ethyl phosphate; *n*-hexadecylphosphorylcholine; hexadecylphosphocholine; HPC; Impavido (Zentaris); Miltex (Baxter).

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
CA2318260	Asta Medica AG	N/A	1998-01-22

Orange Book Patents[29]:

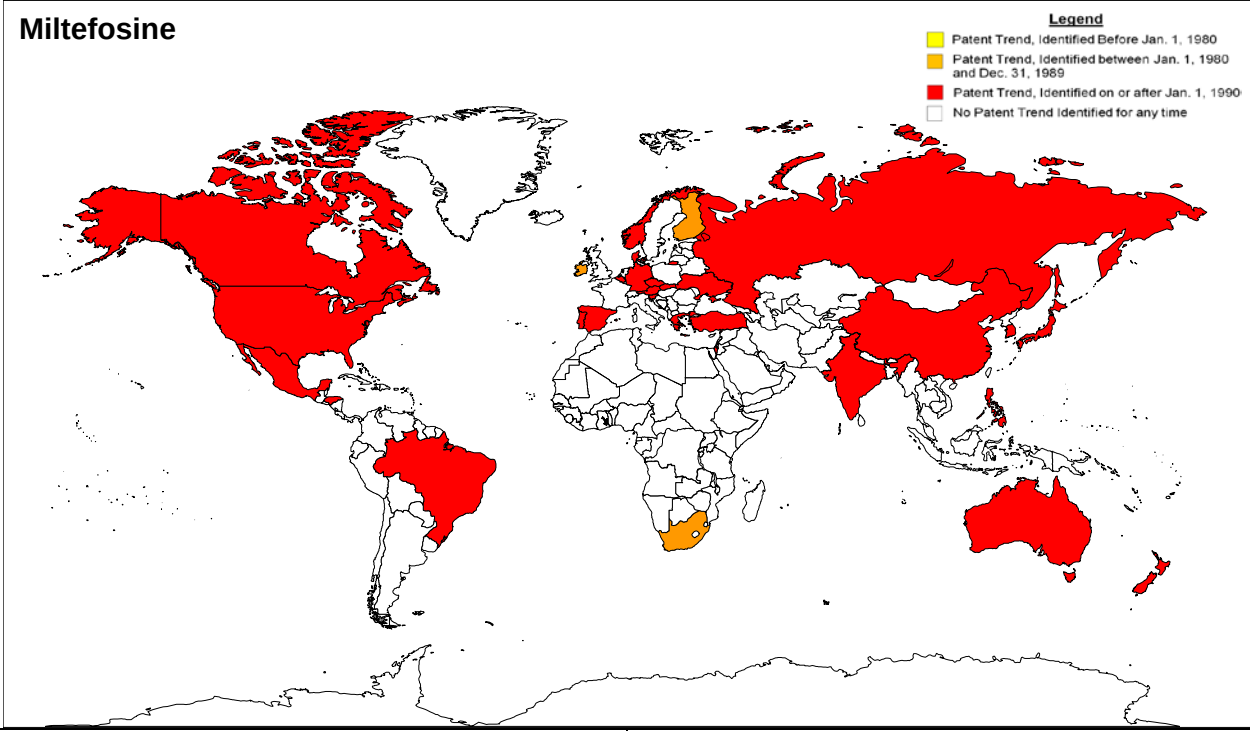
Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
EP225608	Max Planck Gesellschaft zur Förderung der Wissenschaften E.V.	1986-12-04	Merck
US4837023	Max Planck Gesellschaft	1987-10-02	Merck
US6544551	Asta Medica AG	2000-07-24	ChemSpider

[29] No patent information was available from Health Canada, http://webprod3.hc-sc.gc.ca/pr-rdb/index-eng.jsp (last visited Aug. 11, 2011).

World Map Generated from Family Data[30]



Regional Office Patent Trend	
African Intellectual Property Organization	
African Regional Intellectual Property Organization	
Eurasian Patent Office	
European Patent Office	Identified after Jan. 1, 1990
Gulf Cooperation Council	
World Intellectual Property Organization	Identified after Jan. 1, 1990

Comments:

Following the DTP, two patents were found to be listed in the Merck Index. However, both of these patents claimed the use of miltefosine as an antineoplastic agent. Thus, both patents are listed as collateral patents. A search of ChemSpider.com revealed a US patent that claimed the use of miltefosine in treating leishmaniasis[31]. A check of the priority data revealed an earlier Canadian patent that is given as the base patent and the US patent is listed as a collateral patent, although it is in the same family as the base patent.

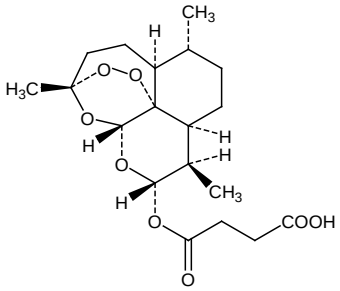
See Appendices A and B for patent data.

[30] Lexis Total Patent extended family data was used to construct world maps, https://www.lexisnexis.com/totalpatent (last visited Aug. 11, 2011). However, this database is not covered by the data listed in the appendices.

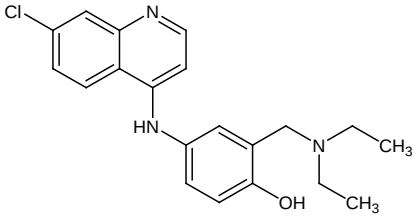
[31] ChemSpider is a website operated by the Royal (UK) Society of Chemistry, http://www.chemspider.com/ (last visited Aug. 11, 2011).

Artesunate + Amodiaquin[32]

Combination tablet: 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg



+



Use:	Antimalarial.
IUPAC Name: (artesunate)	Butanedioic acid mono[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*R*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-yl] ester
IUPAC Name: (amodiaquin)	4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]phenol
IUPAC Name: (combination)	N/A
CAS Number: (artesunate)	88495-63-0
CAS Number: (amodiaquin)	86-42-0
CAS Number: (combination)	N/A
Chemical Formula: (artesunate)	$C_{19}H_{28}O_8$
Chemical Formula: (amodiaquin)	$C_{20}H_{22}ClN_3O$
Alternative names & Trademarks: (artesunate)	artesunic acid; dihydroqinghaosu hemisuccinate;
Alternative names & Trademarks: (amodiaquin)	4-[(7-chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol; 7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline; 7-chloro-4-(3-diethylaminomethyl-4-hydroxyphenylamino)quinoline; 4-(3′-diethylaminomethyl-4′-hydroxyanilino)-7-chloroquinoline; Dihydrochloride dehydrate derivative: CAM-AQ1; Camoquin (Parke-Davis); Flavoquine (Aventis)
Alternative names & Trademarks: (combination)	N/A

[32] The Unedited Report, 18th Expert Committee on the Selection and Use of Essential Medicines, 21-25 March, 2011, Accra, Ghana, lists amodiaquine spelled with an "e", but the more common usage, and the majority of the patent literature, omits this final letter. A typographical error also appears in the second dosage formulation.

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
DE3715378	Hoechst AG	N/A	1987-05-08

Merck Patents for Components (amodiaquin only):

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US2474819	Parke Davis & Co	N/A	1945-01-08
US2474821	Parke Davis & Co	N/A	1949-07-05

Orange Book Patents[33]:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Collateral Patent:

Patent	Patent Listed Assignee/Country	Date Filed	Source
US5219865	Hoechst AG	1992-04-09	ChemSpider
CN101623270	Shanghai Fosun Pharmaceutical (Group) Co. Ltd.	2008-12-10	Innovation

Comments:

For combination medicines, base patents should be determined for each component as well as the combination. For the combination of artesunate and amodiaquin, no true base patents which claimed a method of use or composition of matter for the individual components were identified. The Merck Index supplied patent information for only amodiaquin (given above) but both patents listed are only for the synthesis of the molecule.

Again, as the DTP did not reveal a base patent for the combination, ChemSpider.com was used as an alternative but precise starting point[34]. A US patent was found on ChemSpider.com that claimed usage of the desired combination as an antimalarial drug at the indicated dosages. This US patent is listed as a collateral patent, and its early priority document, the German patent, is given as the base patent. However, this entire patent family may no longer be legally valid. This should be confirmed by a more thorough freedom-to-operate report.

[33] No patent information was available from Health Canada, http://webprod3.hc-sc.gc.ca/pr-rdb/index-eng.jsp (last visited Aug. 11, 2011).

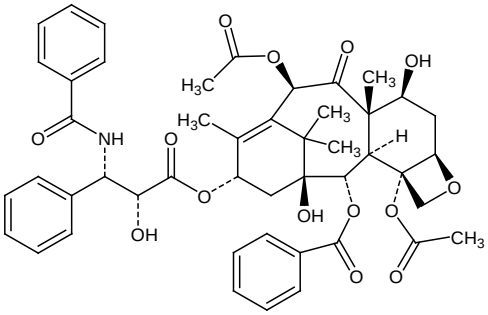
[34] ChemSpider is a website operated by the Royal (UK) Society of Chemistry, http://www.chemspider.com/ (last visited Aug. 11, 2011).

To ascertain whether the German patent was truly the earliest patent claiming this combination and indication, a search was performed using Thomson Innovation[35]. No earlier patents were identified, but a recent Chinese patent was discovered. Given the other patents presented in this report, the scope of this Chinese patent may be limited. This patent also has no family members filed in other nations.
See Appendices A and B for patent data.

35 http://thomsonreuters.com/products_services/legal/legal_products/intellectual_property/thomson_innovation/ (last visited Aug. 11, 2011).

Paclitaxel

Injection: 6 mg/ml



Use:	Antineoplastic; antirestenotic.
IUPAC Name:	(α*R*,β*S*)-β-(Benzoylamino)-α-hydroxybenzenepropanoic acid (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester
CAS Number:	33069-62-4
Chemical Formula:	$C_{47}H_{51}NO_{14}$
Alternative names & Trademarks	5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine; taxol A; Anzatax (Faulding); Paxene (Ivax); Taxol (BMS).

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Health Canada Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
CA2086874	Bristol-Myers Squibb Co	N/A	1993-01-07
CA2132936	Bristol-Myers Squibb Co	N/A	1994-09-26
CA2189916	Gill, Parkash S	N/A	1996-11-08
CA2155947	Vivorx Pharmaceuticals	N/A	1994-02-22

	Inc		
CA2267498	Vivorx Pharmaceuticals Inc	N/A	1997-09-24

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
N/A	N/A	N/A	N/A

Comments:

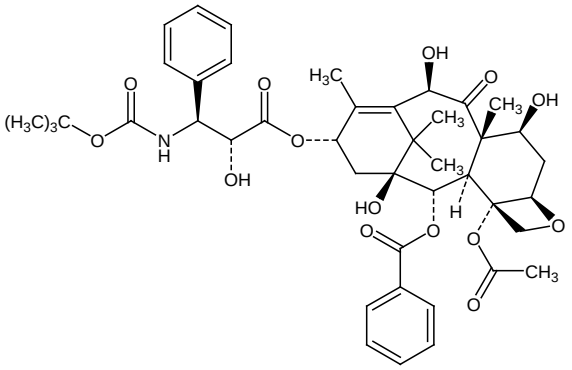
Paclitaxel (or taxol) does not appear to have a base patent. Paclitaxel was discovered in 1967 and the use of paclitaxel as an antitumor agent was published in the scientific literature[36,37]. As such, Paclitaxel itself is in the public domain. However, there are many patents claiming methods of purification, artificial synthesis, or administration to a patient, or claiming means of formulation of this medicine. The patents listed by Health Canada[38] are good examples of this. The '936, '947, and '498 patents all claim specific formulations of paclitaxel. The '874 patents claims a means of administration. Only the '916 claims a novel use of paclitaxel in treating Kaposi's sarcoma patients. However, the '916 has apparently lapsed, as have the '874 and '936 patents. This indicates that invalid patents are probably not regularly removed from the site.

Generic forms of paclitaxel appear to be readily available[39]. A thorough freedom-to-operate report would be necessary to determine the exact status of a particular formulation, indication, or method of administration, but the medicine itself is in the public domain.
See Appendices A and B for patent data.

[36] http://en.wikipedia.org/wiki/Paclitaxel (last visited Aug. 12, 2011).
[37] Wani M.C., Taylor, H.L., Wall, M.E, Coggon, P., and McPhail, A.T. 1971. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus Brevifolia*. J. Am. Chem. Soc. 93(9): 2325 – 27.
[38] http://webprod3.hc-sc.gc.ca/pr-rdb/index-eng.jsp (last visited Aug. 11, 2011).
[39] *See e.g.* http://breast-cancer.emedtv.com/taxol/generic-taxol.html (last visited Aug. 12, 2011).

Docetaxel

Injection: 20 mg/ml; 40 mg/ml



Use:	Antineoplastic.
IUPAC Name:	(α*R*,β*S*)-β-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-hydroxybenzenepropanoic acid (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester
CAS Number:	114977-28-5
Chemical Formula:	$C_{43}H_{53}NO_1$
Alternative names & Trademarks	*N*-debenzoyl-*N*-(*tert*-butoxycarbonyl)-10-deacetyltaxol; Taxotere (Aventis).

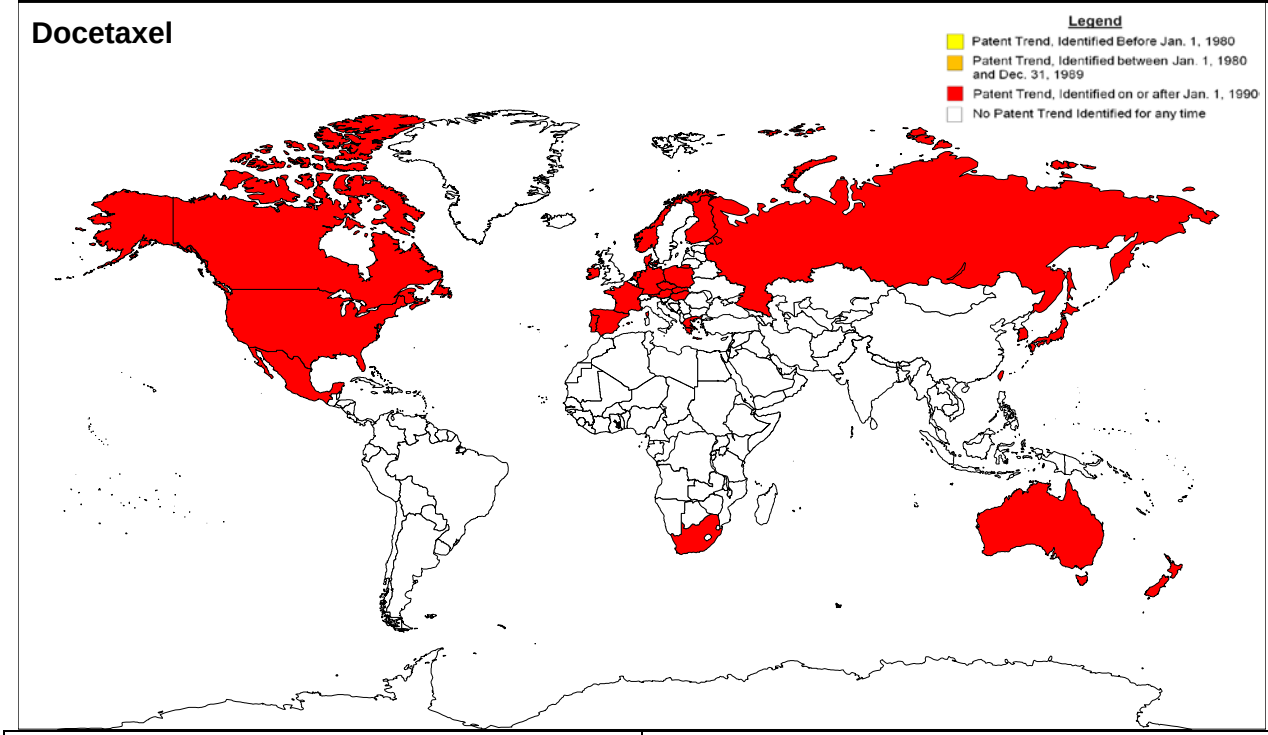
Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
EP253738	Rhone Poulenc Sante	Aventis Pharma S.A.	1987-07-16

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US4814470	Rhone Poulenc Sante	Aventis Pharma S.A.	1987-07-14
US5698582	Rhone Poulenc Rorer Sa	Aventis Pharma S.A.	1995-03-03
US5714512	Rhone Poulenc Rorer Sa	Aventis Pharma S.A.	1995-12-07
US5750561	Rhone Poulenc Rorer Sa	Aventis Pharma S.A.	1995-04-12

World Map Generated from Family Data[40]



Regional Office Patent Trend	
African Intellectual Property Organization	
African Regional Intellectual Property Organization	
Eurasian Patent Office	
European Patent Office	Identified after Jan. 1, 1990
Gulf Cooperation Council	
World Intellectual Property Organization	Identified after Jan. 1, 1990

Comments:

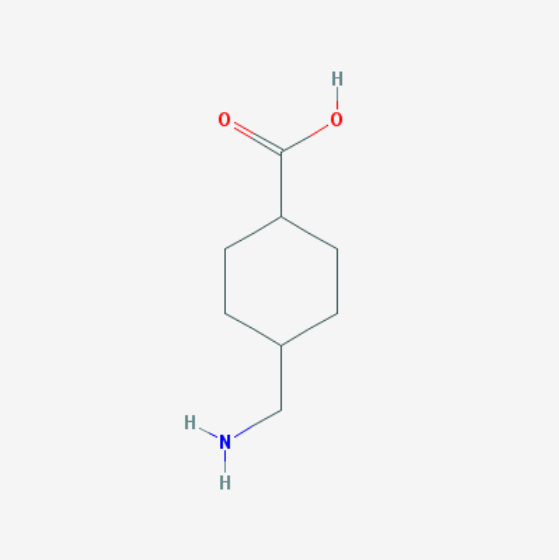
Docetaxel is an artificial derivative of paclitaxel (taxol). Characterization of the patent coverage on docetaxel fits nicely within the DTP. The European base patent is the priority document for patent '470, which is listed in the Orange Book. Both the European patent and patent '470 are listed in the Merck Index. One other patent in this family (FR2601675) was issued co-incidently with the European base patent. The other Orange Book patents, '582, '512, and '561, are all in a second patent family.

See Appendices A and B for patent data.

[40] Lexis Total Patent extended family data was used to construct world maps, https://www.lexisnexis.com/totalpatent (last visited Aug. 11, 2011). However, this database is not covered by the data listed in the appendices.

Tranexamic Acid[41]

Injection: 100 mg/mL



Use:	Injection for traumatic hemorrhage.
IUPAC Name:	*trans*-4-(Aminomethyl)cyclohexanecarboxylic acid
CAS Number:	1197-18-8
Chemical Formula:	$C_8H_{15}NO_2$
Alternative names & Trademarks	Anvitoff (Abbott); Cyklokapron (Pfizer); Exacyl (Sanofi-Synthelabo); Spiramin (Mitsui); Spotof (CCD); Tranex (Lusofarmaco); Transamin (Daiichi); Ugurol (Rottapharm)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
GB949512A	Mitsubishi Chem Ind Ltd	Mitsubishi Chem Ind Ltd	1961-5-15

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Note: No patents listed in Health Canada Patent Register.

[41] Chemical structure taken from PubChem database, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5526 (last visited Aug. 13, 2011). Unless otherwise noted, all other structures were copied from the Merck Index (Maryadele J. O'Neil ed., Merck & Co., Inc., 14th ed. 2006).

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
JP67023018B	DAIICHI SEIYAKU CO	1964-05-23	Thomson Innovation
WO1994015904A1	PHARMACIA AB; JOENSSON NILSAAKE	1993-12-30	Thomson Innovation
NL6503605	DAIICHI SEIYAKU CO	1965-03-22	Merck
US3499925	DAIICHI SEIYAKU CO	1965-02-24	Merck

* NL6503605 and US3499925 are members of the same INPADOC and DWPI patent family.

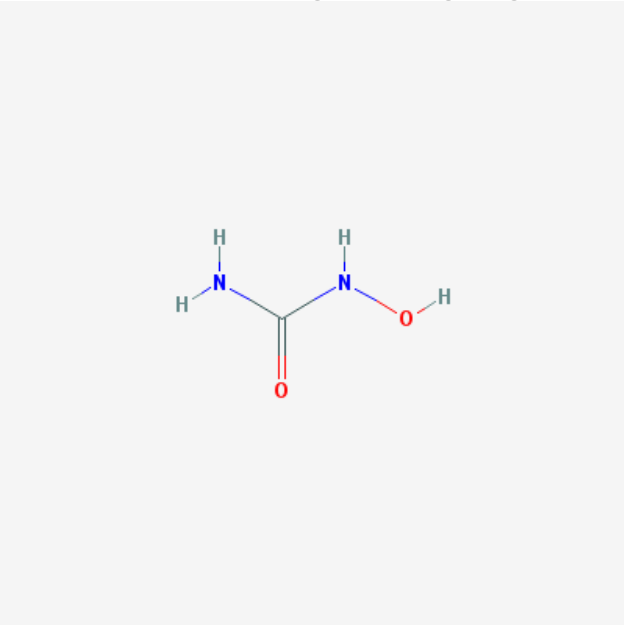
Comments:

Forward and reverse citation analysis was used to locate the base patent which was cited by US4483867A which was cited by US7351740B2 which cited the US Merck patent (US3499925). JP67023018B was included as a collateral patent because both Merck patents cite this patent for priority. WO1994015904A1 was included as a collateral patent because it covers a method of making and the applicant is the same applicant as that listed in the orange book and which covers the same dosage form listed in the EML. No orange book patents or patents listed in the Health Canada patent register.

See Appendices A and B for patent data. The full patent documents of WO1994015904A1 and JP67023018B were not conveniently available.

Hydroxycarbamide[42]

Tablet: 200 mg, 500 mg, 1 g



Use:	Treatment of sickle cell disease
IUPAC Name:	Hydroxyurea
CAS Number:	127-07-1
Chemical Formula:	$CH_4N_2O_2$
Alternative names & Trademarks	Droxia (BMS); Hydrea (BMS); Litalir (BMS)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
FI100454B1	Leiras Oy	N/A	1995-01-30

Priority document from ‘1A1 (see below).

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Note: No patents listed in Health Canada Patent Register.

Collateral Patent Documents:

Patent	Patent Listed Assignee/Country	Date Filed	Source

[42] Chemical structure taken from PubChem database, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3657 (last visited Aug. 13, 2011).

EP806951A1	Leiras Oy	1996-01-25	Thomson Innovation

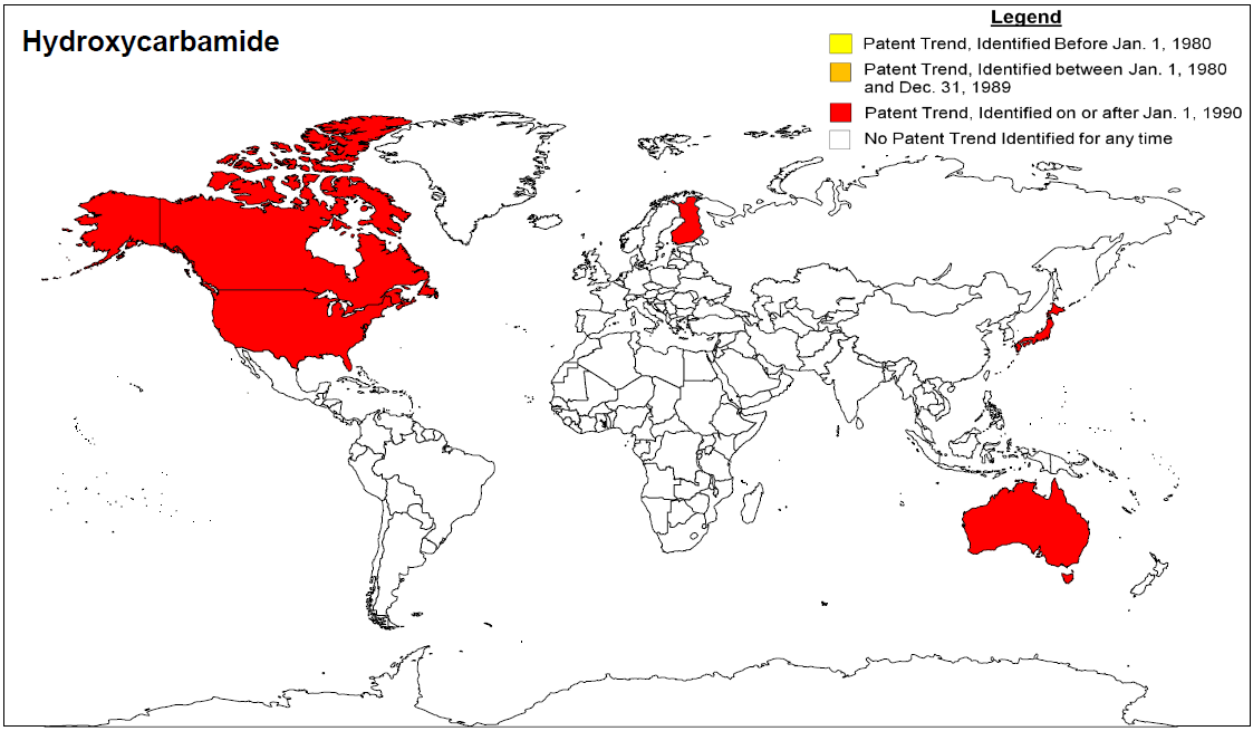
* FI100454B1and EP806951A1are members of the same INPADOC and DWPI patent family.

Comments:

Base patent (FI100454B1) is cited for priority by EP806951A1 which was the earliest patent (located by searching Thomson Innovation) to describe the method of use of hydroxyurea for treatment of sickle cell disease. No orange book patents or patents listed in the Health Canada patent register. One patent (US2705727) listed in Merck for this drug but did not appear to be relevant to pharmaceutical use.

See Appendices A and B for patent data.

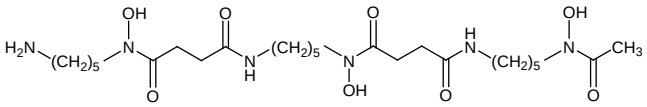
World Map Generated from Family Data



Regional Office Patent Trend	
African Intellectual Property Organization	
African Regional Intellectual Property Organization	
Eurasian Patent Office	
European Patent Office	Identified before Jan. 1, 1990
Gulf Cooperation Council	
World Intellectual Property Organization	Identified before Jan. 1, 1990

Deferoxamine (mesilate)

Powder for injection: 500 mg



Use:	Iron chelator; treatment of sickle cell disease.
IUPAC Name:	*N*'-[5-[[4-[[5-(Acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-*N*-(5-aminopentyl)-*N*-hydroxybutanediamide
CAS Number:	70-51-9
Chemical Formula:	$C_{25}H_{48}N_6O_8$
Alternative names & Trademarks	*N*-[5-[3-[(5-aminopentyl)hydroxycarbamoyl]propionamido]pentyl]-3-[[5-(*N*-hydroxyacetamido)pentyl]carbamoyl]propionohydroxamic acid; 1-amino-6,17-dihydroxy-7,10,18,21-tetraoxo-27-(*N*-acetylhydroxylamino)-6,11,17,22-tetraazaheptaeicosane; desferrioxamine B

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
BE609053	Ciba Geigy	N/A	1961-10-11

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Note: No patents listed in Health Canada Patent Register.

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Published	Source
US3471476	Ciba AG	1969-10-07	Merck

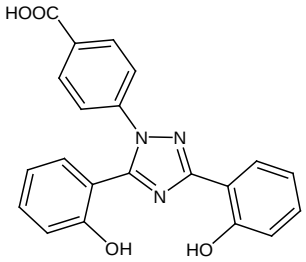
Comments:

No orange book patents or patents listed in the Health Canada patent register. Following DTP, base patent was older of two patents listed in Merck and describes a compound with anti-anaemia properties which is identical to the properties listed in the EML for this medicine. The collateral patent listed was another Merck patent but describes a method of manufacturing.

See Appendices A and B for patent data. The full patent document of BE609053 was not conveniently available.

Deferasirox

Oral form



Use:	Oral iron chelator; treatment of sickle cell disease.
IUPAC Name:	4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid
CAS Number:	201530-41-8
Chemical Formula:	$C_{21}H_{15}N_3O_4$
Alternative names & Trademarks	Exjade (Novartis)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US4528196	Department of Health and Human Services	N/A	1981-02-23

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US6596750	Novartis AG	Novartis AG	2002-09-23
US6465504	Novartis AG	Novartis AG	2000-10-30

Health Canada Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
CA2255951	Novartis AG	N/A	1997-06-24

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
WO9749395	Novartis AG	1997-06-24	Merck
US6465504	Novartis AG	2000-10-30	Merck

* WO9749395, US6465504, US6596750, and CA2255951are members of the same INPADOC patent family.

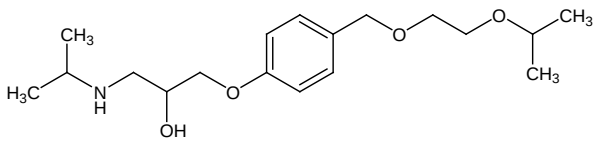
Comments:

Base patent was found by backward citation analysis in Thomson Innovation. The base patent is cited by both Merck patents and both Orange book patents.

See Appendices A and B for patent data. The full patent document of CA2255951 was not conveniently available.

Bisoprolol

Tablet: 1.25 mg; 5 mg; 10 mg



Use:	Treatment of angina, arrhythmias and hypertension
IUPAC Name:	1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol
CAS Number:	66722-44-9
Chemical Formula:	$C_{18}H_{31}NO_4$
Alternative names & Trademarks	(±)-1-[[α-(2-isopropoxyethoxy)-*p*-tolyl]oxy]-3-(isopropylamino)-2-propanol; (±)-1-[*p*-(2-isopropoxyethoxymethyl)phenoxy]-3-(isopropylamino)-2-propanol; Concor (Merck KGaA); Detensiel (Merck-Clévenot); Emconcor (Merck KGaA); Emcor (Merck KGaA); Euradal (Lacer); Isoten (Lederle); Monocor (Am. Cyanamid); Soprol (Lederle); Zebeta (Lederle)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
BE859425	Merck Patent GMBH	N/A	1977-10-06

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Note: No patents listed in Health Canada Patent Register.

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
US4258062	Merck Patent GMBH	1979-05-30	Merck

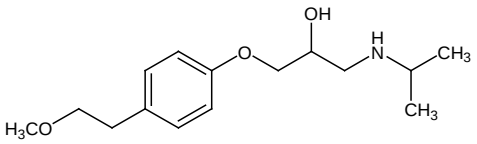
*US4258062 and BE859425 are members of the same INPADOC and DWPI patent family.

Comments:

No orange book patents available. No patents listed in the Health Canada patent register. Base patent was older of two Merck patents. Collateral patent (US4258062) was also listed in Merck and matches pharmaceutical use of base patent.

See Appendices A and B for patent data.

Metoprolol



Use:	Treatment of heart failure.
IUPAC Name:	1-[4-(2-Methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-2-propanol
CAS Number:	37350-58-6
Chemical Formula:	$C_{15}H_{25}NO_3$
Alternative names & Trademarks	(±)-1-(isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol; Selo-Zok (AstraZeneca); Toprol-XL (AstraZeneca)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
DE2106209	Aktiebolaget Haessle Moelndal SE	N/A	1971-02-10

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Note: No patents listed in Health Canada Patent Register.

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
US3998790	Aktiebolaget Hassle	1974-01-15	Merck

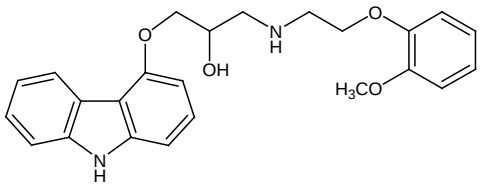
* DE2106209 and US3998790 are members of the same INPADOC and DWPI patent family.

Comments:

No orange book patents or patents listed in the Health Canada patent register. DTP was followed and base patent was older of two Merck patents.

See Appendices A and B for patent data.

Carvedilol



Use:	Treatment of heart failure.
IUPAC Name:	1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol
CAS Number:	72956-09-3
Chemical Formula:	$C_{24}H_{26}N_2O_4$
Alternative names & Trademarks	Coreg (GSK); Dilatrend (Roche); Dimitone (Erco); Eucardic (Roche); Kredex (GSK); Querto (Byk Gulden)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
DE2815926	Boehringer Mannheim GmbH	N/A	1978-04-13

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
RE40000E1	SB Pharmco Puerto Rico Inc.	N/A	2003-11-25

Note: No patents listed in Health Canada Patent Register.

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
US4503067	Boehringer Mannheim GmbH	1983-04-04	Merck

* DE2815926 and US4503067 are members of the same INPADOC and DWPI patent family.

Comments:

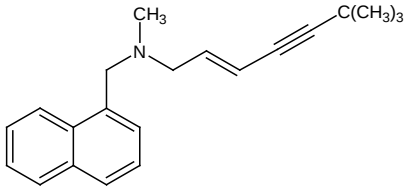
No patents listed in the Health Canada patent register. Collateral patent that was listed in Merck is of the same patent family as base patent. An additional patent was listed in the Orange Book with patent number (RE40000*PED) but could not be located in several patent databases

including Thomson Innovation, Google Patents, and LexisNexis TotalPatent. Lack of availability in these patent databases suggests the possibility that Orange Book patent entry was erroneous.

See Appendices A and B for patent data.

Terbinafine

Cream 1%



Use:	Antifungal medicine
IUPAC Name:	*N*-[(2*E*)-6,6-Dimethyl-2-hepten-4-ynyl]-*N*-methyl-1-naphthalenemethanamine
CAS Number:	91161-71-6
Chemical Formula:	$C_{21}H_{25}N$
Alternative names & Trademarks:	*trans*-*N*-methyl-*N*-(1-naphthylmethyl)-6,6-dimethylhept-2-en-4-ynyl-1-amine;

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
EP896A2	Sandoz Ltd.	N/A	1978-08-07

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Health Canada Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
CA2052229	Oreal	N/A	1991-09-25
CA2062341	Oreal	N/A	1992-03-05
CA2068957	Sandoz Ltd	N/A	1992-05-19

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
EP24587A1	Sandoz AG	1980-08-06	Merck
US4755534	Sandoz Ltd.	1984-09-04	Merck

* EP24587 and US4755534 are members of the same INPADOC and DWPI patent family.

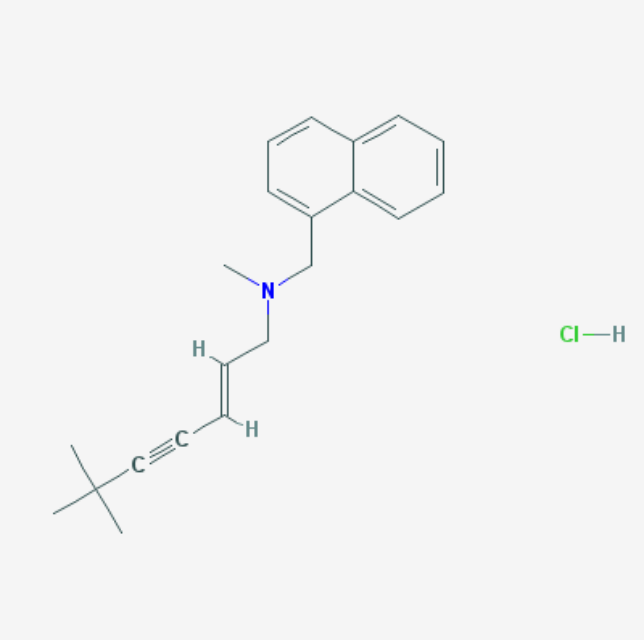
Comments:

No patents listed in Orange Book. Base patent was found by using reverse citation search in Thomson Innovation. Both Collateral patents, which were listed in Merck, cite to Base patent.

See Appendices A and B for patent data.

Terbinafine Hydrochloride[43]

Ointment 1%



Use:	Antifungal medicine
IUPAC Name:	*N*-[(2*E*)-6,6-Dimethyl-2-hepten-4-ynyl]-*N*-methyl-1-naphthalenemethanamine
CAS Number:	78628-80-5
Chemical Formula:	$C_{21}H_{25}N.HCl$
Alternative names & Trademarks	Lamisil (Novartis)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
KR1997006278A	Hanil Synthetic Fiber Co. Ltd.	N/A	1995-07-25

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

[43] Chemical structure taken from PubChem database, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5282481 (last visited Aug. 13, 2011).

Health Canada Patents:

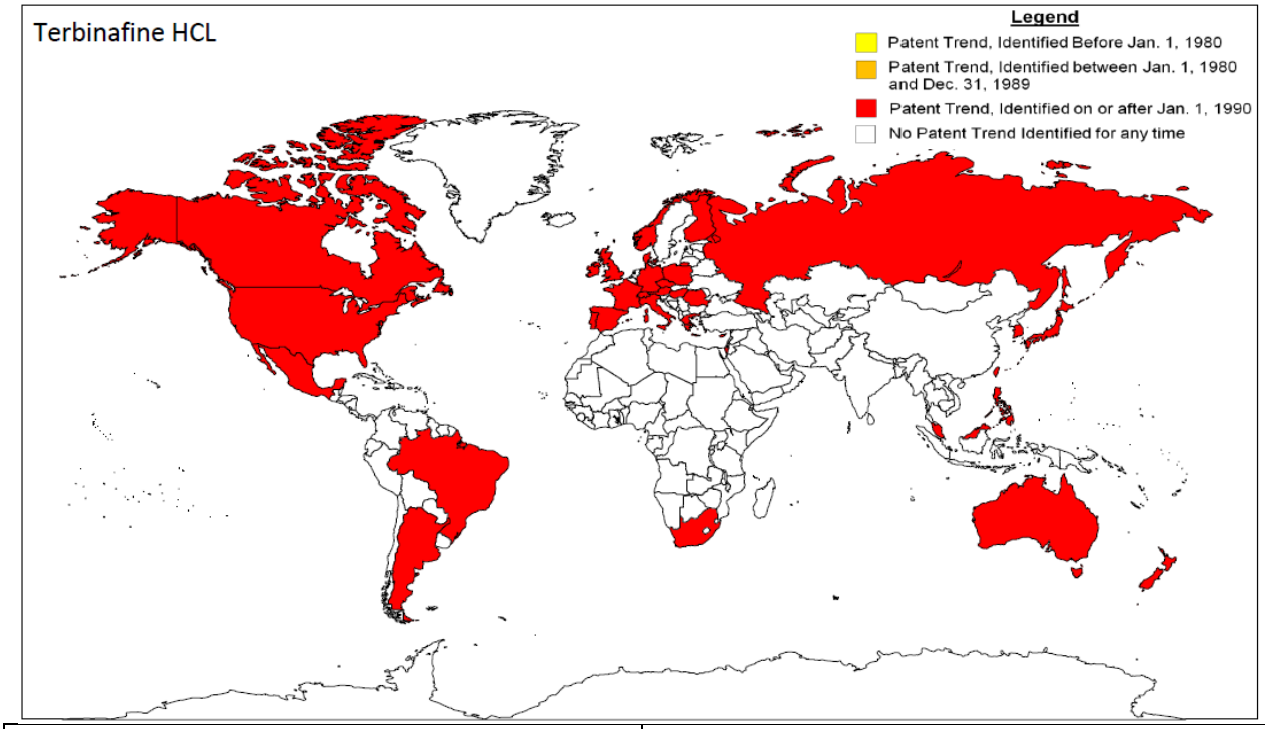
Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
CA2052229	Oreal	N/A	1991-09-25
CA2062341	Oreal	N/A	1992-03-05
CA2068957	Sandoz Ltd	N/A	1992-05-19

Comments:

No patents listed in Orange Book nor in the Health Canada Patent Register. Base patent was found by keyword searching through Thomson Innovation. Base patent was the earliest patent located covering the compound. Base patent also covers the process of making and also mentions its pharmaceutical use as an antimycotic (antifungal) agent.

See Appendices A and B for patent data. The full patent document of KR1997006278A was not conveniently available.

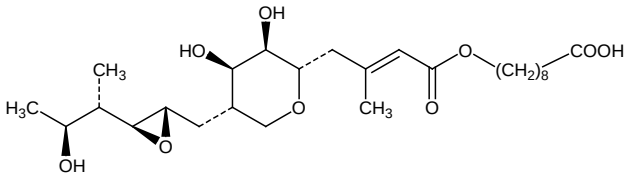
World Map Generated from Family Data



Regional Office Patent Trend	
African Intellectual Property Organization	
African Regional Intellectual Property Organization	
Eurasian Patent Office	
European Patent Office	Identified before Jan. 1, 1990
Gulf Cooperation Council	
World Intellectual Property Organization	

Mupirocin

Ointment/Cream: 2%



Use:	Treatment for superficial bacterial infections.
IUPAC Name:	2*E*)-5,9-Anhydro-2,3,4,8-tetradeoxy-8-[[(2*S*,3*S*)-3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]-3-methyl-L-*talo*-non-2-enonic acid, 8-carboxyoctyl ester
CAS Number:	12650-69-0
Chemical Formula:	$C_{26}H_{44}O_9$
Alternative names & Trademarks:	pseudomonic acid A; *trans*-pseudomonic acid; Bactoderm (Pfizer); Bactroban (GSK); Turixin (GSK)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
GB1395907A	Beecham Group Ltd.	N/A	1971-06-12

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US6013657	Agis Industries Ltd.	N/A	1998-07-08
US6025389	Smithkline Beecham Corp.	N/A	1997-07-25

Note: No patents listed in Health Canada Patent Register.

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
DE2227739	Beecham Group Ltd.	1972-06-07	Merck
US3977943	Beecham Group Ltd.	1975-07-07	Merck
US4071536	Beecham Group Ltd.	1976-05-07	Merck
DE2842358	Beecham Group Ltd.	1978-09-28	Merck
US4222942	Beecham Group Ltd.	1978-09-29	Merck

* GB1395907A, DE2227739, US3977943, and US4071536 are members of the same INPADOC and DWPI patent family.

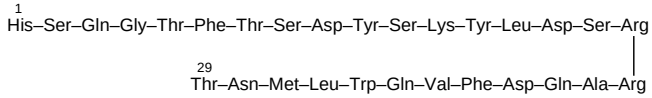
Comments:

No patents listed in Health Canada Patent Register. Base patent located by reverse citation analysis using Thomson Innovation. Base patent cited by three Collateral patents for priority. Collateral patents were located from Merck database.

See Appendices A and B for patent data.

Glucagon

Injection: 1 mg/mL



Use:	Treatment of acute severe hypoglycemia.
IUPAC Name:	N/A
CAS Number:	9007-92-5
Chemical Formula:	$C_{153}H_{225}N_{43}O_{49}S$
Alternative names & Trademarks	Glukagon; hyperglycemic-glycogenolytic factor; HG-factor; HGF

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
GB1202607	Novo Terapeutisk Labor AS	N/A	1968-01-10

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Note: No patents listed in Health Canada Patent Register.

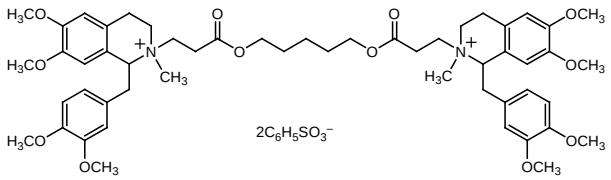
Comments:

No patents listed in Orange Book nor in the Health Canada Patent Register. Base patent identified by keyword search through Thomson Innovation. Base patent was the earliest patent located that described the compound, method of preparation, as well as dosage form.

See Appendices A and B for patent data.

Atracurium

Injection: 10 mg/mL



Use:	Muscle relaxant.
IUPAC Name:	2,2'-[1,5-Pentanediylbis[oxy(3-oxo-3,1-propanediyl)]]bis[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium] dibenzenesulfonate
CAS Number:	64228-81-5
Chemical Formula:	$C_{65}H_{82}N_2O_{18}S_2$
Alternative names & Trademarks	2-(2-carboxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium benzenesulfonate pentamethylene ester; *N*,*N*'-dimethyl-*N*,*N*'-(4,10-dioxa-3,11-dioxotridecylene)-1,13-bis-tetrahydropapaverinium dibesylate; Tracrium (GSK)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
GB1579822	Wellcome Foundation	N/A	1976-10-29

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Note: No patents listed in Health Canada Patent Register.

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
DE2655883	The Wellcome Foundation Ltd. London	1976-12-09	Merck
US4179507	Burroughs Wellcome Co.	1976-12-09	Merck

* GB1579822, DE2655883, and US4179507are members of the same INPADOC and DWPI patent family.

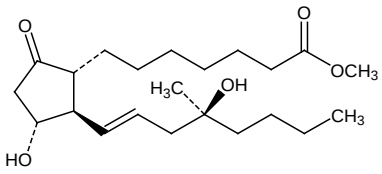
Comments:

Reverse citation was used to identify the base patent which was cited by both Collateral patents. Collateral patents were located in Merck database. No patents listed in Orange Book nor in the Health Canada Patent Register.

See Appendices A and B for patent data.

Misoprostol

Tablet: 0.2 mg



(11*R*, 16*S*)-Form

Use:	For the prevention of postpartum hemorrhage.
IUPAC Name:	(11α,13*E*)-11,16-Dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester
CAS Number:	59122-46-2
Chemical Formula:	$C_{22}H_{38}O_5$
Alternative names & Trademarks	(±)-methyl-(1*R*,2*R*,3*R*)-3-hydroxy-2-[*(E)*-(4*RS*)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate; (±)-15-deoxy-(16*RS*)-16-hydroxy-16-methyl-PGE_1 methyl ester; Cytotec (Pfizer)

Base Patent:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
US3965143	G. D. Searle & Co.	1974-03-26	Merck

Orange Book Patents:

Patent	Patent Listed Assignee/Country	Current Listed Assignee/Country	Date Filed
N/A	N/A	N/A	N/A

Note: No patents listed in Health Canada Patent Register.

Collateral Patents:

Patent	Patent Listed Assignee/Country	Date Filed	Source
BE827127	SEARLE & CO G D	N/A	1975-03-25

*US3965143 and BE827127 are members of the same INPADOC and DWPI patent family.

Comments:

No patents listed in Orange Book nor in the Health Canada Patent Register. DTP was followed and base patent is older of two listed Merck patents both of which describe a compound

that inhibits blood platelet aggregation which is similar to the illness (post-partem hemorrhage) cited by the EML as the reason for its addition.

See Appendices A and B for patent data. The full patent document of BE827127 was not conveniently available.

Discussion

The goals of this report are:

1) As in the previous report[44], "[t]o place in the public domain a detailed report on the present [2011] patent status of medicines that were . . . added to the Model List" in March, 2011[45], and
2) To test and refine the Decision Tree Protocol (DTP) methodology described in the previous report.

The number of patents cited in this report has increased over the previous report, due to the inclusion of a new category of Collateral Patents. Collateral patents are relevant documents that were identified and are distinct from the base patent. For example, Orange Book patents rarely included the base patent, and the Merck Index often listed multiple patents for each chemical compound. If only one, or none, of these listed patents were the base patent, these Merck patents were instead included as collateral patents. The criteria used to select the base patent were presented above for each individual medicine, but are also summarized below to help explain and justify any deviations from the DTP. In some cases, the DTP was not adequate for identification of a base patent, and alternative methodologies were used. Each of these methodologies is evaluated in terms of Precision and Recall, and any patents that are necessary to understand the path taken to find the true base patents are also included as collateral patents. Finally, an evaluation is made of the additional sources of information not employed previously but used in this report for alternative methodologies.

Selection of Patent Documents

The patent status includes identification of a base patent for each medicine or combination of medicines. A base patent is the document with the earliest filing date which claims the use or composition of matter indicated for each medicine on the EML. For example, midazolam appeared on the EML update as both an injectable form and in tablet form, thus different base patents are given for the different forms or compositions of matter. A medicine can also have different uses, such as miltefosine, which was originally patented as an antineoplastic agent but appears on the EML list as a medicine to treat leishmaniasis. Thus, the base patent for miltefosine is the document that claims the use that was discovered later and not the initial description of the drug. The use or composition of matter is to be contrasted with the synthesis or method of manufacture of the compound, as exemplified by propofol. A 1954 patent claims the synthesis of propofol, but not until 1974 was the use of propofol as an anesthetic claimed in a patent. This later patent is the base patent for propofol as it appears on the EML update.

[44] The Franklin Pierce Center for Intellectual Property at the University of New Hampshire School of Law Educational Report:Preliminary Report on Patent Literature, Search Methodology and Patent Status of Medicines on the WHO EML 2009, Spring 2011, p. v.

[45] [45] The Unedited Report, 18th Expert Committee on the Selection and Use of Essential Medicines, 21-25 March, 2011, Accra, Ghana.

A base patent is thus selected for its relevance to the individual medicine and the particular use, dosage, and formulation listed on the EML update. To determine if a patent is relevant, the claims must be read to ascertain the true scope of that patent. The title and abstract are often overly generic or even misleading, although a Derwent title and abstract, if available, can be helpful to understanding the patent. When a relevant patent is located, based on the agreement of the patent claims and the description of the medicine on the EML update, the bibliography of the patent should be checked to determine whether an earlier priority document exists. If so, that earlier document is the base patent instead. For several of the medicines included in this report, the patents listed in the Merck Index actually had earlier priority documents so the Merck patents should never be assumed to be base patents.

It is important to remember that a patent is typically limited in jurisdiction (e.g. a US patent is only enforceable in the USA), time (usually 20 years from the filing date), and scope (only one narrowly-defined invention claimed per patent). Significantly, each of these parameters can change. Countries can cease to exist, such as the former Soviet Union and Yugoslavia, or countries can merge, such as East and West Germany. PCT applications and applications filed in other regional patent offices are not enforceable until those applications have entered the national phase in individual countries and issued as valid patents. Similarly, the effective time period for a patent can increase due to patent term adjustments or the issuance of certificates of protection, or, in contrast, patents can (and often do) lapse due to nonpayment of maintenance fees. Finally, the scope of the patent's claims can change because of reissues, re-exams, disclaimers, and litigation. For all of the above reasons, this report does not describe the freedom-to-operate for any of the medicines, and the legal status of each of the listed patents will need to be verified at a specific point in the future for each individual nation and each particular medicine for its given use, dosage, and formulation. The relevant patents listed in this report were selected to assist such a determination of legal status.

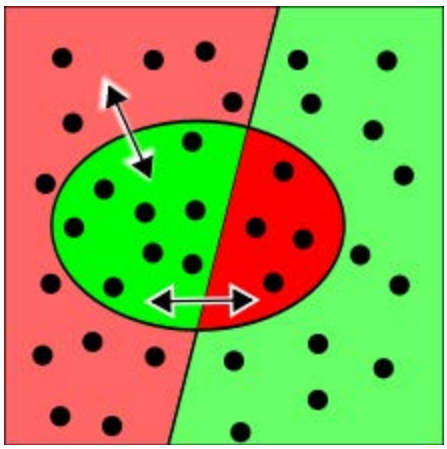
Precision and Recall in the Selection of Patent Documents[46,47]

Worldwide, the number of patent documents, including patents (issued, re-issued, and re-examined) and applications, is over 60 million[48]. Selecting relevant documents from such a huge dataset can be difficult, and this type of document retrieval is governed by the mathematical theory of Precision and Recall. Precision is the percentage of retrieved documents that are relevant (number of retrieved relevant documents/total number of retrieved documents)., while recall is defined as the fraction of relevant documents retrieved (i.e. number of retrieved relevant documents/total number of existing relevant documents) These concepts are illustrated in figure below:

[46] *See* Wikipedia, the free encyclopedia, http://en.wikipedia.org/wiki/Precision_and_recall

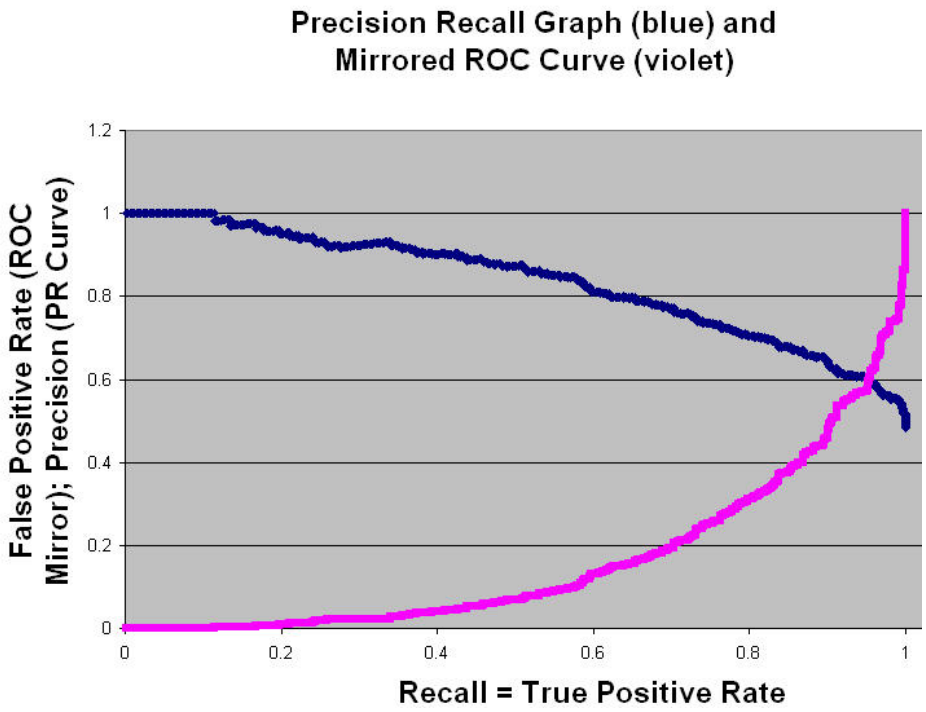
[47] *See also* J. Davis and M. Goadrich, The relationship between precision-recall and ROC curves, Proceedings of the 23rd International Conference on Machine Learning, Pittsburgh, PA, 2006.

[48] Based on data from 2007. http://www.taeus.com/article.php?id=66 (last visited Aug. 14, 2011).



In this figure the relevant items are to the left of the straight line while the retrieved items are within the oval. The red regions represent errors. On the left these are the relevant items not retrieved (false negatives), while on the right they are the retrieved items that are not relevant (false positives). **Precision** and **recall** are the quotient of the left green region by respectively the oval (horizontal arrow) and the left region (diagonal arrow).[49]

Thus, any set of retrieved of documents will always include a certain fraction of irrelevant documents, also termed false positives. As a search attempts to capture an ever higher fraction of relevant documents, the sensitivity of the search will decrease because the proportion of false positives will increase. In the extreme, every relevant document can only be captured if every irrelevant document is also captured, as depicted in the following graph[50]:

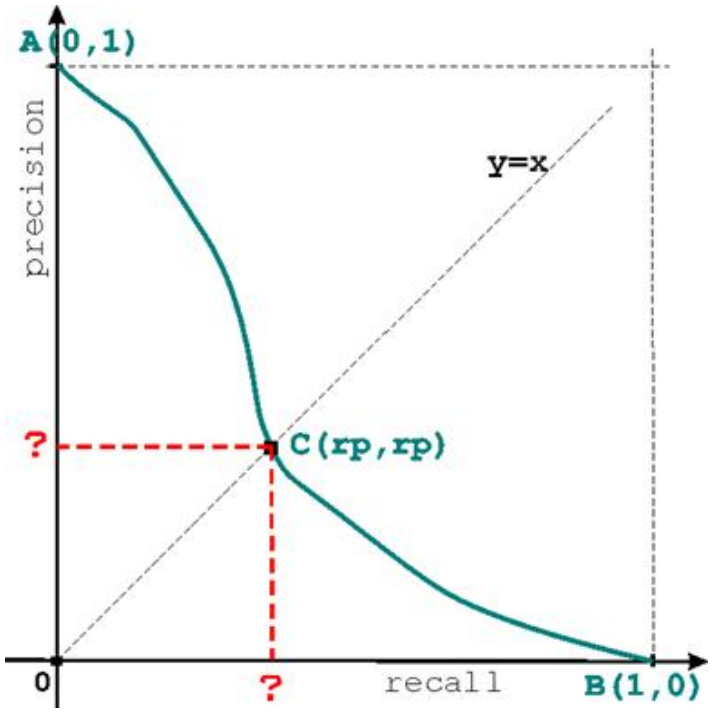


[49] http://en.wikipedia.org/wiki/Precision_and_recall (last visited Aug. 12, 2011).

[50] Precision Recall Graph, Mirrored ROC Curve, www-csli.stanford.edu (last visited Aug. 12, 2011).

Stated another way,

> a high **recall** means you haven't missed anything but you may have a lot of useless results to sift through (which would imply low **precision**). High **precision** means that everything returned was a relevant result, but you might not have found all the relevant items (which would imply low **recall**).[51]



An optimal balance (point C in the graph above[52]) must therefore be achieved between precision (degree of relevance of all retrieved documents) and recall (fraction of relevant documents retrieved). In terms of patent searching, and in particular searching for relevant patents claiming the indicated drugs on the EML, a person deciding on that balance point must have experience in patent searching in general, knowledge concerning the technology involved, and an understanding of the goal of the search. The purpose of the methodology described in the previous report and refined in this update is to provide a framework for such a decision-making process.

The refined DTP provides boundaries and guidelines for conducting a precise search with sufficient recall in an efficient amount of time. Patents listed in the Merck Index monographs are typically early patents claiming the subject chemical, while Orange Book patents are active patents claiming some aspect of the approved medicine. Thus, Merck patents are often the base patents of the medicines, although a check of the priority data is always warranty. Priority data is a small, highly precise set of data from which a relevant result can always be retrieved. If the Merck patents claim the manufacture but not the desired use or composition of matter, then a

[51] Wikipedia, the free encyclopedia, http://en.wikipedia.org/wiki/Precision_and_recall (last visited Aug. 12, 2011).
[52] http://www.ccs.neu.edu/home/jaa/CSG339.06F/Homeworks/hw.01.html (last visited Aug. 14, 2011).

researcher can work forward from the Merck patents using citations and patent family member data to locate the relevant base patent. Patent family data is another highly precise data set because the family is focused on a particular chemical compound. Cited patents are also a precise data set, although a citation can be made for a number of different reasons (e.g. same use with a different compound), so the citation should always be checked for relevance by reading the claims of the cited patent.

At the opposite boundary, Orange Book patents are rarely base patent but rather these patents tend to claim some modern improvement in use, formulation, or manufacture. However, the Orange Book patents are a good starting point from which to work backward using family member data and citation analysis (i.e. searching a highly precise dataset) to find the base patent. Working forward and backward in an iterative manner from the boundaries of the Merck Index and the Orange Book but within the relevant data of family members and citations, a base patent can be located in most situations[53]. When a base patent cannot be located using this methodology, then alternative resources or traditional patent searching techniques can be used.

Alternative Internet Resources: Free versus Proprietary

Free internet resources were always preferred for this report to assure the general accessibility of the methodology described herein. The two resources most often used in this report were ChemSpider.com[54] and Wikipedia[55]. Each entry on ChemSpider.com contains a patents section. These patents are listed because their claims concern the specific chemical indicated. Thus, this represents a pool of preselected, highly precise data that can serve as an alternative starting point for a base patent search. Again, starting from the most relevant patent listed on ChemSpider.com, forward and backward searching of citations and patent family members can usually yield a base patent that was not discoverable using the Merck Index or the Orange Book as starting points. ChemSpider.com is also an excellent alternative to the Merck Index for chemical data, such as CAS numbers, chemical formulae, and alternate chemical names.

Wikipedia, while it rarely lists patents, can be used to gain a historical perspective on a given drug or to determine the scope of commercial activity surrounding a particular medicine[56]. It is particularly useful when the medicine listed on the EML update is not approved for use in the United States and thus does not appear at all in the Orange Book[57]. Wikipedia is a general source of data, and therefore is not as precise a source of data as ChemSpider.com. Wikipedia does serve to summarize the characteristics of medicines and provide clues as to where and how to search for more relevant data by providing alternative names, commercial manufacturers who

[53] See the propofol data sheet for a specific example of such a methodology.
[54] ChemSpider is a website operated by the Royal (UK) Society of Chemistry, http://www.chemspider.com/ (last visited Aug. 11, 2011).
[55] http://www.wikipedia.org/ (last visited Aug. 15, 2011).
[56] See entries for sulfamethoxazole/trimethoprim and paclitaxel for examples.
[57] The chewable tablet form of albendazole is a particular example.

would be listed as patent assignees, and a time frame for when the medicine entered the marketplace.

When all other methods of determining a base patent have failed, then actual patent searching is warranted, if only to confirm a negative result. Alternative chemical names located through the Merck Index, ChemSpider.com, or Wikipedia are useful search parameters to improve the rate of recall (i.e. number of relevant patents retrieved). Google Patents[58] is a free resource that tends to return a large number of results (high recall) although the relevance of the results tends to low (poor precision). Google Patents is best used when enough is known about the target medicine to construct a focused advance search. Other free patent resource websites include WIPO Patentscope[59] and Espacenet[60], but these sites often require more experience with traditional patent search methods in order to return the most relevant results. Thomson Innovation[61] is a proprietary resource whose primary benefit is access to Derwent titles and abstracts which can make interpreting patents significantly easier. Innovation also has an extensive patent database, an easy-to-use interface, and convenient export functions for data analysis, although the cost may be prohibitive to some users.

On a final note, the Health Canada website[62] was also evaluated as an alternative to the US FDA's Orange Book. Both are public sources of information. In few instances, patents were located on the Health Canada list when none were available from the Orange Book. However, the Health Canada patents were often not particularly relevant, and expired patents remained on the Health Canada lists. Health Canada may be useful as an alternative to the Orange Book in some limited circumstances, such as if a medicine is approved for use in Canada but not the USA, but not as a general substitute.

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[58] [58] http://www.google.com/patents (last visited Aug. 11, 2011).

[59] http://www.wipo.int/patentscope/search/en/search.jsf (last visited Aug. 15, 2011).

[60] http://www.epo.org/searching/free/espacenet.html (last visited Aug. 15, 2011).

[61] http://thomsonreuters.com/products_services/legal/legal_products/intellectual_property/thomson_innovation/ (last visited Aug. 11, 2011).

[62] [62] http://webprod3.hc-sc.gc.ca/pr-rdb/index-eng.jsp (last visited Aug. 11, 2011).

Conclusions

The Decision Tree Protocol (DTP) described in the previous was adequate to a certain point. The Merck Index and the Orange Book listed patents that could form a boundary for precise searching for a relevant base patent. An iterative process of forward and backward searching of a limited dataset (bibliographic priority data, patent family members, or cited patents) could, in most cases, result in the desired base patent. Reading the claims of patent is always necessary to determine relevance. ChemSpider.com provided an excellent alternative, but still highly precise, resource for base patent searching. Wikipedia can be used to place the medicine in context and to help limit the search parameters. Actual patent searching of full text databases was performed only in a few instances and only as a last resort when the number of results (i.e. rate of recall) was too low using the established methodology. Thus, this report demonstrated a certain amount of flexibility was necessary in the DTP but provided boundaries to ensure the relevance and efficiency of a base patent search.

Appendix A

Full patent information is presented on a representative member of each patent family mentioned in this report. The information is separated according to the medicine claimed by the patent families. The data was exported from Thomson Innovation[63]. The data is only presented in the electronic version of this report.

63 http://thomsonreuters.com/products_services/legal/legal_products/intellectual_property/thomson_innovation/ (last visited Aug. 11, 2011).

Appendix B

Electronic images (pdf files) of the representative patents are presented on the CD-ROM version of this report. Note that some images were not available. In some cases images other family members were substituted or could be available, but see Appendix A for the full information on each patent family.