Prior art searching in the preparation of pharmaceutical patent applications

Edlyn S. Simmons

Profitability in the pharmaceutical industry depends upon market exclusivity, and exclusivity is largely based upon patent protection. Because patents are granted only for inventions that are new and nonobvious, it is essential that researchers know what is in the prior art before filing a patent application. For prior art searches of the pharmaceutical literature, the most useful tools are databases that index the chemical structures of organic compounds described in journals and patents, and especially those that index the Markush formulas in pharmaceutical patents.

Patents are at the very heart of the business of drug discovery[1]. Developing new drug entities and new therapies for the marketplace is extremely expensive, and the only reliable way to recover the cost of drug discovery is by obtaining market exclusivity.

Patents and market exclusivity

The most reliable way to ensure market exclusivity is by obtaining patents to protect the drugs and therapies that are developed. Patents may cover any aspect of the drug discovery process – new chemical entities, pure stereoisomers, methods of synthesis, combinations of two or more active compounds, excipients, dosage forms, cultures of microorganisms, culture media and, in some countries, genetically altered animals used in drug discovery or production. A patent grant provides the right to prevent others from making, using or selling the invention defined by the patent's claims for a limited period of time; it does not grant the right to practice the invention if there are other patents that cover aspects of the invention, and it does not take the place of regulatory approval of a drug[2–6].

The exclusivity granted by a patent is limited to the country that issues the patent, and the protection provided by the patent expires at the end of a statutory term. With these limitations, the profitability of a new drug can depend upon obtaining the strongest and broadest patent protection possible. A single drug can be covered by many patents, but chemical compounds can be claimed as new compositions of matter in only one patent. The patent that claims the compound *per se* is the most valuable; this is because the owner of that patent can prevent others from using the processes and formulations claimed in all later patents covering the compound.

There is more to patenting the results of drug discovery than getting a single patent on the active ingredient of a marketed drug. Patents are needed in each country where marketing or licensing the product is planned[7]. Filing patents in all of the world's industrialized countries is less complicated when the patents are applied for through the Patent Cooperation Treaty (PCT) (Box 1). This results in equivalent filings in as many as 94 countries, with the opportunity to convert the application into national applications in as many or as few of those countries as desired after about 2 years[8]. It is possible to obtain patents covering groups of countries

Edlyn S. Simmons, Hoechst Marion Roussel Inc., 2110 E. Galbraith Road, Cincinnati, OH 45215-6300, USA. tel: +1 513 948 7829, fax: +1 513 948 7961, e-mail: edlyn.simmons@hmrag.com

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Box 1. Useful Internet addresses

- Patent Cooperation Treaty, the World Intellectual Property Organization, patent law and patent information – http://www.wipo.org/
- STN International search service and databases – http://info.cas.org/ and http://www.fiz-karlsruhe.de
- Questel and Orbit search services and databases – http://www.questel.orbit.com/
- Dialog and DataStar search services and databases – http://www.krinfo.com/
- Beilstein Handbook and databases – http://www.beilstein.com
- Chemical Abstracts Service and its databases – http://info.cas.org/
- Derwent Information Ltd and its databases – http://www.derwent.co.uk/
- INPI and its databases – http://www.inpi.fr/
- CLAIMS and other IFI/Plenum databases – http://www.ifiplenum.com/

in Europe, Africa and the states of the former Soviet Union, but most of the PCT member countries require separate processing of patent applications and separate fees for granting patents and maintaining them in force. In each country, the drug can be protected by a single patent or by a series of patents covering different inventions relating to it. When the patent that claims the drug *per se* expires, generic competition is theoretically possible, but competition can be avoided for a longer term by building a suitable patent portfolio. For instance the following patents might comprise a portfolio:

- Patents covering related compounds can prevent competitors from developing chemically related analogs.
- Patents covering methods for synthesizing the drug can prevent eventual generic competitors from manufacturing it with the most efficient process.
- Specialized dosage forms can maintain a market niche in the presence of a simple generic dosage form.
- Patents covering methods of treating conditions that were not contemplated during the early stages of drug discovery can protect an approved drug long after the expiration of the original patent.

The patents that protect a drug need not belong to the company that markets the drug; research institutions without marketing capabilities can profit from the development of a new drug by licensing patents and know-how to a pharmaceutical company.

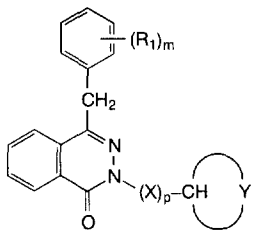
Patents and prior art

The patent-examining procedure in each country determines whether a claimed invention meets the formal requirements for filing a patent application in that country and whether the claims define a patentable invention – one that is new, useful, and not obvious over the prior art. The examiner determines whether the invention is patentable by performing a search of the scientific literature and comparing the claimed invention with the references retrieved in the search. The standard for patentability is extremely high – no part of the claimed invention may have been known to the public before the patent application was filed, and no part of the invention may be obvious from anything known to the public. The standard of inventiveness used by patent offices is that an invention is not patentable if the differences between the claimed invention and the nearest prior art reference would be obvious to an ordinary worker in the relevant field. Unless a claimed drug molecule has unexpected properties, it would probably not be patentable if its isomer, homolog or isostere had been described previously.

To be granted a patent, the applicant must persuade the Patent Offices that the claimed invention is new, useful and inventive. To be new enough to warrant a patent, the claimed invention must never have been described in the prior art[9]. Prior art consists of everything known before the filing of the patent application, including any publication of any kind – scientific journals, books, patents and gray literature, such as the text and illustrations of manuals and marketing brochures published by equipment manufacturers. Patents are more than certificates granting exclusive rights to an invention: their detailed specifications represent a major part of the scientific literature[10] and the right to exclude others from using an invention is granted by governments in exchange for these details. Similar to articles in the journal literature, patent specifications include the experimental details of laboratory experiments but, unlike journal articles, they give generalized descriptions of work that has never been performed in a laboratory. Chemical compounds are typically described in a generic form known as Markush structures[11], which define large numbers of different substances.

A typical Markush structure is illustrated in Figure 1.

Typically, a patent covering a new drug describes a broadly defined genus of compounds in Markush format, provides a general method of synthesis, gives an explanation of the expected pharmaceutical utility of the compounds, and supplies examples of the synthesis of a limited number of compounds together with their pharmacological test results. Because patent applications must be filed early in the drug discovery process, no approved generic name is given for the lead compound in a series of novel compounds: finding the patent that originally claimed a well-known drug is more complicated than merely searching a patent database for its generic name.



R_1 = H, OH, CF_3, halogen, lower alkoxy or lower alkyl
m = 1 or 2
X = C_{1-3} lower alkylene
p = 0 or 1

= a mono-, bi- or tricyclic residue having 3–8 C-atoms and 1–2 N-atoms that are substituted by H or C_{1-4} lower alkyl

Figure 1. *Generic structure adapted from US patent 3,813,384.*

Research scientists read the key journals in the field, and are usually confident that they are not duplicating the work of others. However, this is not enough to make certain that a new drug or therapy is patentable. The prior art includes both the usual kinds of chemical literature and much more besides. Most modern patent applications are published before they are examined; there are patent documents published by all industrialized and many developing countries. Hence, the patent literature includes both examined granted patents and unexamined patent applications, some of which describe trivial, inoperable or scientifically invalid inventions. Patentability searches must also include the journal literature, as new drugs can be anticipated by reports in obscure journals with narrow circulation, in foreign language publications, and in the abstracts of presentations given at scientific meetings and conferences. A PhD dissertation shelved in a university library is as much a part of the prior art as an article published in the *Journal of Medicinal Chemistry*. So too is an apparatus illustrated in a supplier's catalog or even a technique performed in a science fiction movie.

Prior art and patent claim drafting

It would be futile to file patent applications with claims that encompass compounds or therapies that have been described in the prior art. Patent office procedures allow applicants to amend applications after filing in order to limit the claims to patentable subject matter, but some patent applications are drafted in a way that makes appropriate amendments impossible. Rather than abandoning a valuable new therapy, it is sometimes possible to obtain a patent by demonstrating either that the properties of the claimed compounds are distinct from those of closely related prior art compounds or that the differences between them are sufficient to render the new compounds patentable under the patent law. But it is far better for the patent application to claim only compounds, processes or therapies that are not described in, or suggested by, the prior art. To be certain that the claims describe only new and nonobvious inventions, it is best to perform a patentability search before drafting patent claims. Ascertaining whether an invention is patentable involves what has been called the paradox of patentability searching: to search everywhere and find nothing[12].

Patentability search example

The usefulness of a patentability search in preparing a patent application with an advantageous claim scope is illustrated schematically in Figure 2. In this hypothetical example, a chemist synthesizes a series of compounds with related chemical structures (shown as hexagons in Figure 2a), and a pharmacologist tests the compounds and finds that they show similar activity in laboratory assays. Having thus established that they are co-inventors of a group of compounds that share a useful pharmacological activity, the scientists provide their data to a patent attorney or agent, and together they propose a generic claim scope that results in a Markush structure (represented by the circle in Figure 2b). This shows a core substructure common to all of the active compounds and includes as alternatives all of the functional groups present in any of them.

The proposed generic claim scope includes compounds that were never made, but it is reasonable to assume that they would share the same therapeutic effect if they were made and tested. These hypothetical compounds should be included in the patent claims, if possible, to prevent competitors from developing them. Before filing a patent application covering the proposed generic scope, a patentability search is performed, and the search reveals that there are

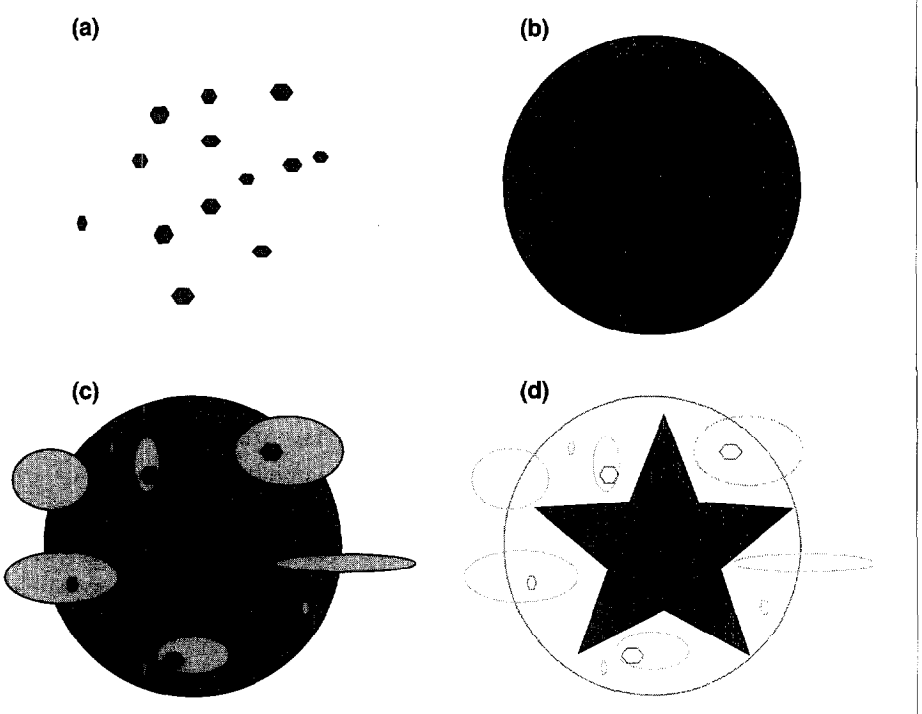
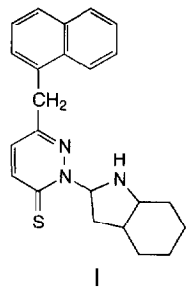


Figure 2. *Hypothetical example of preparation of a patent application with an advantageous claim scope. (a) Experimental results for a chemical series; (b) proposed claim scope (blue) for coverage of experimental results; (c) prior art references (green) to compounds overlapping with proposed claim scope; (d) Claim scope revised to exclude prior art compounds.*



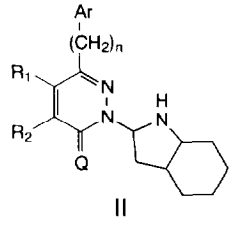
I

Figure 3. *Hypothetical compound synthesized in the laboratory.*

references in the prior art that overlap with the proposed claim scope, as shown by the ellipses in Figure 2c. The references include a few of the compounds that were made and tested as well as other compounds, both specific and generic, that were never made but were included in the proposed claim scope. Claiming these compounds as new would guarantee that the patent application would be rejected. However, with the knowledge that the proposed claim scope includes compounds that are not patentable to them, the inventors can revise the generic scope of their claims so that only new compounds, shown by the star in Figure 2d, are covered. By filing claims of the new scope, the inventors can minimize the cost and delay involved in the patenting process.

For a less generalized example of this situation, imagine that the compound invented by our hypothetical chemist has the structure I, shown in Figure 3. After studying the activity of this compound, biologists working with the chemist find that the compound antagonizes serotonin in rats. The chemist synthesizes some similar compounds, finding that active compounds can be made by replacing the naphthalene ring with a benzene ring or by substituting the pyridazine ring or fusing a benzene ring to it. To make sure that all active compounds are claimed in a patent, the scientists and their patent attorney devise a Markush structure with the scope represented by Formula II (Figure 4).

Although a patent claiming all compounds of Formula II would provide strong protection for the new serotonin antagonist and all of the analogs contemplated by the inventors, no patent will be granted unless all of the compounds described by Formula II are, in fact, new. After a patent application is filed, a patent examiner will search the scientific literature to confirm that none of the compounds claimed in the patent application has been described in the prior art. The patent examiner will find that

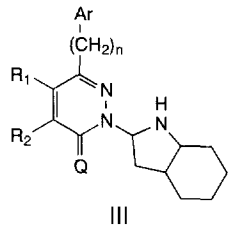


II

Ar = benzene or naphthalene ring, optionally substituted by halogen, lower alkoxy, lower alkyl or CF_3
n = 1, 2 or 3
Q = O or S
R_1 and R_2 = independently, H or lower alkyl, or, together, form a fused benzene ring

Figure 4. *Hypothetical claim scope, including the compound in Figure 3.*

US patent 3,813,384 describes a genus of compounds, shown in Figure 1, that overlap with the proposed claim scope, and will reject the claims. If the inventors or a patent information specialist were to perform a patentability search before filing the patent application, they would find this prior art reference early enough to revise the claim scope by deleting the fused benzene ring required in the compounds of the prior art reference. Assuming that no other overlapping references were found, the revised claim scope might define the generic structure shown in Figure 5.



III

Ar = benzene or naphthalene ring, optionally substituted by halogen, lower alkoxy, lower alkyl or CF_3
n = 1, 2 or 3
Q = O or S
R_1 and R_2 = independently, H or lower alkyl

Figure 5. *Revised claim scope including the compound in Figure 3.*

It may not be necessary to forego patent coverage of valuable new drugs when the prior art lacks a specific teaching of the chemical, physical and pharmacological properties of the new compounds. In such cases, the patent specification can include data showing the nonobvious properties of the claimed compounds or their claimed use, and arguments in support of their patentability can be made during prosecution of the patent application. Patents claiming pharmaceutical compositions or new therapeutic uses for prior art compounds can often be obtained even when the compounds themselves are unpatentable.

When the inventors and their attorney are aware of prior art references that might interfere with the granting of a patent, they have the opportunity to modify the patent specification and claims so that they define a patentable invention, but if the patent application is to be filed in the United States they also have an obligation to notify the US patent examiner about the prior art. US law imposes 'a duty of candor and good faith' upon anyone involved in the filing of a patent application – any prior art that would be important to the examiner's evaluation of the application must be reported in an Invention Disclosure Statement[13].

Searching the prior art

There are literally thousands of databases and paper-based data repositories that contain chemical and pharmacological information[14–18]. It would be impossible to search all of these databases to confirm the patentability of each new drug in development; therefore, the searcher must select the databases or other sources of information that promise the most efficient use of time and resources. The traditional place for patent practitioners to search is at the Patent Office public search room, where classified collections of patent documents are available, whereas the usual place for scientists to search is in the scientific libraries of their research institutions. The standard reference series such as Beilstein and Gmelin have been collecting data since the dawn of the chemical literature, while abstracting services such as Chemical Abstracts Service have been collecting summaries of journal articles, patents and conference presentations for most of this century. Fortunately, it is no longer necessary to perform painstaking manual searches of these data sources, because scientists or information specialists can now search most of the major data compilations in computerized databases, either on commercial search services or on local area networks. The abstracting services and the patent offices also make their files available through commercial services like STN International, Questel, Orbit, Dialog and DataStar (Box 1), and more and more information is becoming available via the Internet.

Because drug development depends upon finding new pharmaceutically active molecules or finding new uses for known pharmaceutically active molecules, most patentability searches need to use a database that indexes chemical compounds according to their chemical structure. The best of these index large numbers of scientific documents, as well as all of the compounds described in those documents, and have records collected over many years. However, these databases vary in several ways:

- The rules used for the selection of compounds to be indexed.
- The documents from which the compounds are indexed.
- The indexing systems by which the chemical structures are stored and retrieved.
- The way that chemical structures of indexed compounds are related to the nonstructural information in the literature.

For example, structural records may be stored in a separate registry file, or combined with summaries of physical,

chemical, biomedical and bibliographic data from the literature. In addition, chemical structures may be stored as connection tables and searched by topological retrieval systems or stored as collections of chemical fragments and searched as Boolean combinations of fragments. The most familiar databases are those that index specific compounds discussed in journal articles or patents. A database such as this can be searched for substructures as well as for fully defined compounds, but the only compound records that can be retrieved from these databases are specific, fully defined compounds. A search that retrieves only compounds with full chemical and physical descriptions in the literature is essential for a patentability search, but it is not a complete search of the prior art, because patents define compounds in generic Markush structures. A comprehensive patentability search cannot be achieved by searching for a single compound in a file of single compound records, as many millions of compounds have been disclosed only generically within patents. A reliable patentability search therefore requires the capability both to search the Markush structures from patents and to use a Markush query structure to search files of specific compounds. These requirements limit the available databases to a relative handful.

Structure-searchable databases

Beilstein

The Beilstein registry (Box 1) of organic compounds contains over seven million records for compounds published in the chemical literature since 1779. It contains the chemical structure and information about the physical and chemical properties of the compounds, their salts and isomers, along with data derived from the major chemical journals and, in earlier years, patents from major countries. The records in the database are based on the chemical compounds, not on the literature itself; each compound has a record with a Beilstein registry number, and new data is added to the compound record as it appears in the literature. Records for pharmacologically active compounds note only that the compounds have biological activity; the precise nature of the activity is not considered to be worth indexing in a chemical database.

Until recent years, Beilstein was published in German, searchable by molecular formula, German chemical name, and a specialized organizational system that determined the location of chemical compounds in the many volumes of the printed Beilstein Handbook. This esoteric indexing system discouraged its use in ordinary searching by English-speaking chemists. However, Beilstein has now been reborn as an English language electronic database, searchable by chemical structure online using STN and Dialog or in-house using the Beilstein CrossFire database[19–21]. Because Beilstein is a properties database, charges for online searches are based upon the amount of physical and chemical data printed from the file. There is no surcharge for chemical structure searching, so this is a relatively inexpensive resource for patentability searches that involve new compounds; if the compounds are not in the Beilstein registry, the search is quite inexpensive.

Chemical Abstracts and MARPAT

The Chemical Abstracts Service (CAS) (Box 1) has been indexing chemical compounds in the chemical literature since 1907. The information in articles from a broad selection of chemical journals and patents from most industrialized countries is indexed according to the compounds described, their reactions and their physical, chemical and biological activities. The CAS chemical compound registry and the CAS bibliographic database can be searched as text on nearly all of the commercial search services. The CAS registry has records for over 16.5 million compounds that have been described in the journal literature, books and patents since 1956. However, this number cannot be compared with the number of compound records in Beilstein, as separate registry numbers are assigned to each salt, isomer, and mixture, both organic and inorganic compounds are indexed, and biopolymers are included. The CAS registry file is structure-searchable on STN and Questel, allowing retrieval by means of topological representations of exact chemical structures, substructures with unlimited substituents, or Markush structures with defined substituents. In addition, the CAS registry identification numbers of the compounds can then be cross indexed into the bibliographic database and searched in combination with controlled index terms and, using STN, with the text of the abstract.

Since the late 1980s, CAS has also provided topological searching of generically described compounds in the MARPAT database, which is available only on STN. Searches using MARPAT retrieve the bibliographic CAS records of the patents from which the generic structures were indexed. Both MARPAT and the CAS registry can be searched with a single chemical structure query, resulting in duplicate records for patents with both generic structures and specific compounds; STN facilitates deletion of duplicate records by allowing the search to be performed in a merged file system called CASLINK (Ref. 22).

Derwent World Patents Index

Derwent Information Ltd (Box 1) has been indexing the chemical structures of pharmaceutical patents from industrialized countries since 1963, when Farmdoc, the earliest forerunner of the World Patents Index, was founded. Gradually, the scope of the database was expanded to include agricultural patents, polymer patents, other chemical patents and eventually nonchemical patents. Moreover, the number of countries or patent-issuing authorities covered has increased from 14 to 40. Derwent indexes the technical content of the first patent covering a particular invention, which it designates as the basic patent, and adds subsequent patents to a family record. The Derwent World Patents Index database (DWPI) is available on the Dialog, Orbit, Questel and STN search services, but searching for chemical structures is restricted to companies with subscriptions to the Chemical Patents Index service. Specific compounds and Markush structures are both indexed using a fragmentation code that defines common substructures and, to some extent, the spatial relationships among the groups. For patents indexed since 1972, each ring system has a unique code[23,24]. Searching is accomplished by combining the codes with Boolean logic, resulting in answer sets that refer directly to the bibliographic record and abstract of the indexed patent. Since 1987, topological searching has also been available from the World Patents Index Markush (WPIM) database on Questel by means of the Markush DARC indexing and retrieval system. Searches in WPIM generate sets of compound numbers, some relating to specific compounds and others to generic structures unique to a single patent, and the compound numbers are transferred to the bibliographic DWPI database in order to retrieve the bibliographic records.

Derwent Drug File

Pharmaceutical literature is indexed structurally in the Derwent Drug File, formerly known as Ringdoc[25]. Compounds from journal articles and conference abstracts have been indexed with a fragment code since 1964. The database and Ring Code were devised by the Pharma-Documentations ring, a consortium of European pharmaceutical companies, and given to Derwent for commercial production; additional structure search terms were added to the indexing system in 1983. The Derwent Drug File is available online on DataStar, DIMDI, Dialog, Orbit and STN. Although originally available only to subscribers, the database has now been made available to nonsubscribers with subscriber-only access to the chemical structure search fields. Named compounds appearing at least twice in the Derwent Drug File or the Derwent Veterinary Drug File are indexed in the Derwent Drug Registry companion file; thus, a structure search must be performed in both the Derwent Drug File database and the Registry to be sure of retrieving literature covering all relevant compounds. The STN version of the Derwent Drug Registry is also searchable topologically.

GENESEQ

GENESEQ, produced by Derwent Information Ltd, contains biosequence indexing from the patents covered in the DWPI (Ref. 26). Although specific biosequences from the literature have always been available in databases such as GenBank®, and are now widely available via the Internet[27], only GENESEQ contains indexing for the generically defined polypeptides and polynucleotides that appear in patents. GENESEQ is available on STN or via Bionet with the IG Suite software (Oxford Molecular, Oxford, UK).

PHARMSEARCH

PHARMSEARCH is the chemical patent database of the French patent office, l'Institut National de la Propriété Industrielle (INPI) (Ref. 28, Box 1). It consists of a bibliographical database, with patent abstracts and controlled indexing in French and English, available through Questel and Orbit, and MPHARM (the companion structurally searchable database available through Markush DARC on Questel). PHARMSEARCH indexes both specific and generically described compounds in patents from a limited number of countries. Older patents are being added to the database over time; series of French Medicament patents issued in the 1950s and 1960s is searchable along with patents published during the 1980s and 1990s, and access to the chemical structure indexing is not limited to subscribers.

CLAIMS

The CLAIMS Uniterm and Comprehensive Databases (Box 1), produced by IFI/Plenum Data Corp., contain chemical structure indexing for United States patents from 1950. Compounds and generic structures from the claims and examples are indexed with a fragmentation code[29] but, unlike most other fragmentation code systems, the CLAIMS system generates new terms for new functional groups when no appropriate code exists. The version of the

fragmentation code used in the Comprehensive Database, which is restricted to subscribers, is more precise than the version used in the Uniterm Database, which may be searched by nonsubscribers for a limited amount of time each year. Nonheterocyclic compounds indexed at least five times are given specific compound numbers, which can be found by searching a companion file and then used to search as alternatives to the fragment codes. The CLAIMS databases are available on the Dialog, Orbit, Questel and STN search services.

Fragmentation codes and topological search systems

Until the introduction of topological search systems in the 1980s, fragmentation codes provided the only means for retrieving chemical compounds from databases[30–33]. The earliest databases were supplied to subscribers for mounting on their computers, but these databases have since been mounted on commercial search services, and topological search systems have been added to some of the subscription services. However, patentability searching cannot be restricted to recent publications simply because the newer art is easier to search, and it would be impossible to re-index the millions of patents published before topological systems were introduced. Hence, subscriptions are still necessary for access to this large segment of the prior art. To date, only the CLAIMS Uniterm coding has been made available to nonsubscribers.

The fragmentation codes greatly complicate the process of searching. Each database that uses fragmentation codes has a different system for fragmenting molecules and different symbols for the codes. Applying the appropriate codes is much less straightforward than drawing a structure for topological searching. Furthermore, because fragmentation codes leave some aspects of chemical structures undefined, the searches usually result in significant amounts of 'false drop' records that have the desired structural units connected in the wrong ways. Modifications of Derwent's fragmentation codes require the inclusion of time-ranging in retrieval strategies. Unfortunately, topological systems for retrieval of Markush structures do not eliminate the problems of structure definition and inexact retrieval. Markush structures are defined in terms of functional groups and ring systems listed as alternative structural units. This requires that they be indexed and searched by means of generic terms, just as they are with traditional fragmentation codes. The chemical structures disclosed in pharmaceutical patents are never simple, and there is no obvious system for indexing or retrieving the structures. Needless to say, there is no substitute for appropriate training in the use of these retrieval systems.

Searching for nonstructural information

Although most inventions in the pharmaceutical sciences are related to the discovery and use of therapeutically useful molecular entities, others are not limited by the chemical structures of the compounds under development. Some are directed to methods for conducting research, including methods and apparatus for use in chemical synthesis or analysis. These include methodology, apparatus and computerized systems for molecular modeling, combinatorial chemistry[34] and high-throughput screening. Others are directed towards therapies employing a particular mechanism of action, where the active drug is not limited by its chemical stucture[35]. Although such patents usually contain information about compounds that are specifically exemplified in the body of the disclosure, the essential features of the inventions are described in the text or graphically in drawings. Chemical structure indexing is of little use in retrieving these references. In addition, prior art descriptions of developments in computational and combinatorial chemistry are often reported in the gray literature, which is not included in commercial databases. Searching for prior art in these areas must rely upon controlled indexing, or on searches of the text of scientific publications or their abstracts, and upon manual searches in collections of gray literature.

Thesauri of controlled index terms are provided by the producers of many pharmaceutical and patent databases, and these are extremely helpful in identifying relevant publications[36]. Computerized searches using free text terms are less reliable because the language used by the authors is uncontrolled. The best results in searches of these fields are often obtained by reading the publications of scientists or institutions known to be working in the field and following trails of cited and citing references.

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In short...

Visible Genetics Inc. (VGI) (Toronto, Canada) announced it has formed an international collaboration between leading HIV researchers to carry out human clinical trials with the company's genotyping kits for the human immunodeficiency virus (HIV). The research will be based in four sites in the USA and two in Canada, and may expand to additional sites. The trials group will advise VGI on clinical protocols and kit formulations to meet the new U.S. Food and Drug Administration (FDA) DNA diagnostics regulations. John Stevens, CEO of VGI, said, 'our company had anticipated the FDA's decision in late November to regulate gene-based diagnostics, and we had already begun to assemble a strong trials group for our HIV product line, as well as to apply Good Manufacturing Practices (CGMP) procedures to the production of our reagents and instruments'.

The US Food and Drug Administration (FDA) have approved an Investigational New Drug application (IND) for **Phytopharm** (Godmanchester, UK) to proceed with clinical trials of its first botanical product – Zemaphyte, for the treatment of atopic eczema. The study will be carried out by Parexel International and will recruit patients with severe cases of the disease from 20 centers in the USA. Chief executive of Phytopharm, Dr Richard Dixey, said of the approval that 'it confirms our strategy of focusing on the development of Botanicals as prescription medicines and endorses the investment we have made in the raw material supply, manufacture and clinical development of these products'.