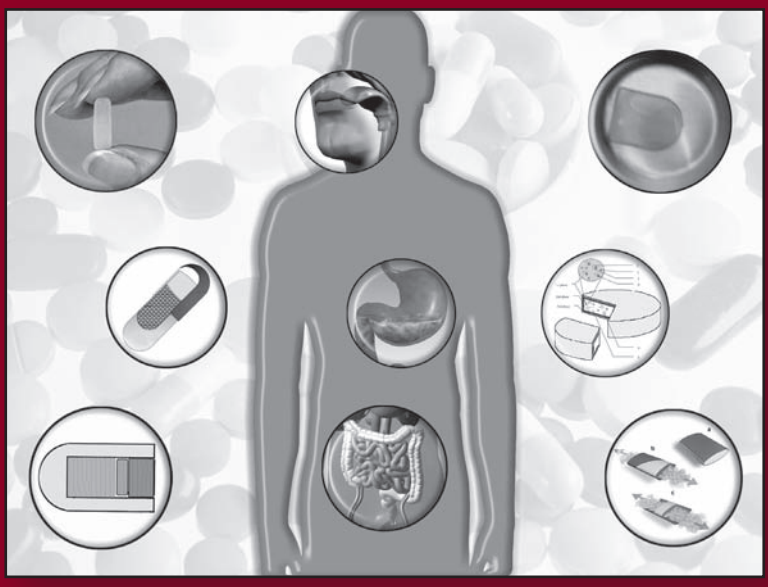
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 183

Modified-Release Drug Delivery Technology

Second Edition

Volume 1



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Modified-Release Drug Delivery Technology

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Modified-Release Drug Delivery Technology

Second Edition

Volume 1

edited by

Michael J. Rathbone
InterAg
Hamilton, New Zealand

Jonathan Hadgraft
University of London
London, UK

Michael S. Roberts
University of Queensland
Brisbane, Australia

Majella E. Lane
University of London
London, UK

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healthcare

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To my son Thomas

—Michael J. Rathbone

Preface

Optimizing drug therapy through delivery-system design is an ever-expanding area of pharmaceutical research. The first edition of *Modified-Release Drug Delivery Technology* remains the most comprehensive compilation of information on individual modified-release drug delivery systems. However, it must be recognized that this area is very dynamic. Therefore, we decided to produce this second edition, which expands and updates the previous collection.

The second edition has been divided into two volumes. Volume 1 addresses oral mucosal, oral, and gastrointestinal tract drug delivery, with targeting to the colonic and rectal sites. Volume 2 covers modified-release drug delivery technologies via injections and implants and the ocular, dermal nasal, vaginal, and pulmonary routes.

In both volumes, we have assumed that the reader is familiar with fundamental controlled-release theories. The volumes are divided into parts covering a particular route for drug delivery that begin with an overview written by a leader or leaders in that field. Each overview covers the anatomical, physiological, and pharmaceutical challenges of formulating a modified-release drug delivery technology for that drug-delivery route. It includes chapters written by experts in each technology that describe specific examples of the different approaches that have been taken to design and develop an innovative modified-release drug delivery system for those routes.

Our challenge in editing this book was to be comprehensive while acknowledging that no single work can expect to describe every modified-release drug delivery technology currently marketed or under development. This is because of both the vast and evolving nature of the field and the lack of available experts who are able to write a comprehensive and authoritative overview on a particular technology, usually because of the proprietary nature of their work. We hope that we have provided a representative selection of the technologies.

In the second edition, we chose to include not only relevant technologies from the first edition, but emerging technologies as well. We also offer insights into user perspectives and address the market requirements, intellectual property challenges, and regulatory requirements associated with the design and development of modified-release drug delivery technologies.

Volume 1 of *Modified-Release Drug Delivery Technology*, *Second Edition*, covers drug delivery technologies for the oral mucosal and gastrointestinal tract routes, as well as intellectual property and regulatory issues. Patrea Pabst expertly edits the topic of intellectual property in Part I. Her efforts provide an insightful summary of issues that, when understood and appreciated, add value to any developed modified-release drug delivery technology. Part II focuses on the oral cavity as the site of drug delivery. Sevda Şenel, Michael J. Rathbone, and Indiran Pather, together with invited coauthors, provide an overview of the issues relating to the development of modified-release drug delivery systems for the oral mucosal route. Many of the chapters included in this section describe innovative technologies being developed for specific regions of the oral cavity, including, sublingual, the buccal cavity, gingival, and the periodontal pocket. Rod Walker, the lead author for Part III, considers the oral route. Professor Walker provides an overview of the challenges involved with this popular route for modified-release drug delivery. The introduction to Part III is followed by chapters that provide the reader with insight into the novel and varied approaches, ranging from microparticles to novel manipulations of tableting technologies (including geometric designs and osmotically driven technologies) to three-dimensional printing and the use of lipids. In Part IV, Clive Wilson and Hardik Shah have compiled chapters that describe several diverse approaches that are used to target compounds to various regions of the gastrointestinal tract. Finally, Part V addresses the topic of regulatory issues relating to modified-release drug formulations. Part leader Michael Roberts brings together contributions from Europe, Japan, the United States, Canada, Australia, and New Zealand.

We would like to express our thanks to each of the lead authors for each part, who spent so much time identifying technologies, writing informative overviews, and editing the chapters associated with the routes of drug delivery that are their areas of expertise. We would also like to thank all of the contributors. Their individual, innovative, research activities have contributed significantly to the current modified-release drug delivery technology portfolio that exists today. We thank them for taking the time to share their experiences and work.

Michael J. Rathbone
Jonathan Hadgraft
Michael S. Roberts
Majella E. Lane

Contents

Contributors

Christine Andersen Egalet a/s, Vaerlose, Denmark

Jong Bark Protherics, PLC, Salt Lake City, Utah, U.S.A.

Scott D. Barnhart ARx, LLC, a Subsidiary of Adhesives Research, Inc., Glen Rock, Pennsylvania, U.S.A.

Abdul W. Basit The School of Pharmacy, University of London, London, U.K.

Daniel Bar-Shalom Egalet a/s, Vaerlose, Denmark

Andrew Bartholomaeus Drug Safety Evaluation Branch, Therapeutic Goods Administration, Canberra, ACT, Australia

Brain J. Bellhouse Medical Engineering Unit, University of Oxford, Oxford, U.K.

A. Bernkop-Schnürch Department of Pharmaceutical Technology, Leopold-Franzens University Innsbruck, Innsbruck, Austria

Jörg Breitenbach SOLIQS Drug Delivery Unit, Abbott GmbH & Co. KG, Ludwigshafen, Germany

Bianca Brögmann Degussa Pharma Polymers GmbH, Darmstadt, Germany

Catherine Castan Flamel Technologies, Vénisieux, France

George Costigan Medical Engineering Unit, University of Oxford, Oxford, U.K.

David C. Coughlan Merrion Pharmaceuticals PLC, Trinity College Dublin, Dublin, Ireland

Steve L. Durfee Drug Delivery Research, Cephalon Inc., Salt Lake City, Utah, U.S.A.

Thomas J. Dürig Aqualon, a Business Unit of Hercules Incorporated, Hercules Research Center, Wilmington, Delaware, U.S.A.

Kirk D. Fowers Protherics, PLC, Salt Lake City, Utah, U.S.A.

Sultan Ghani Drugs and Health Products, Health Canada, Ottawa, Ontario, Canada

Florence Guimberteau Flamel Technologies, Vénisieux, France

Janet A. Halliday Controlled Therapeutics (Scotland) Limited, East Kilbride, Scotland, U.K.

Ehab Hamed Formulation Development, CIMA LABS INC., Brooklyn Park, Minnesota, U.S.A.

Aiman H. Hommoss Department of Pharmaceutical Technology, Biopharmaceutics, and Nutricosmetics, The Free University of Berlin, Berlin, Germany

Jette Jacobsen Department of Pharmaceutics and Analytical Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, Copenhagen, Denmark

Cornelia M. Keck Department of Pharmaceutical Technology, Biopharmaceutics, and Nutricosmetics, The Free University of Berlin, Berlin, Germany

Susanne Keitel European Directorate for the Quality of Medicines (EDQM), Strasbourg, France

Richard A. Kendall The School of Pharmacy, University of London, London, U.K.

Janez Kerč Lek Pharmaceuticals d.d., Sandoz Development Center Slovenia, Ljubljana, Slovenia

Peter Klusmann Hoffmann-Eitle, Munich, Germany

B. Kombi Remfry & Sagar, New Delhi, India

Evdokia Korakianiti European Medicines Agency (EMEA), London, U.K.

Roger Kravtzoff Flamel Technologies, Vénisieux, France

David Lee Drugs and Health Products, Health Canada, Ottawa, Ontario, Canada

Thomas W. Leonard Merrion Pharmaceuticals LLC, Wilmington, North Carolina, U.S.A.

Jon Lewis SOLIQS Drug Delivery Unit, Abbott GmbH & Co. KG, Ludwigshafen, Germany

Kenneth Lundstrom Flamel Technologies, Vénisieux, France

Juan A. Mantelle Noven Pharmaceuticals, Inc., Miami, Florida, U.S.A.

Patrick J. Marroum Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, U.S.A.

Emma L. McConnell The School of Pharmacy, University of London, London, U.K.

Rémi Meyrueix Flamel Technologies, Vénisieux, France

Rainer H. Müller Department of Pharmaceutical Technology, Biopharmaceutics, and Nutricosmetics, The Free University of Berlin, Berlin, Germany

Gour Mukherji Jubilant Organosys Ltd., Noida, India

Sudaxshina Murdan The School of Pharmacy, University of London, London, U.K.

Naomi Nagai Pharmaceuticals and Medical Devices Evaluation Center, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan

Jerneja Opara Lek Pharmaceuticals d.d., Sandoz Development Center Slovenia, Ljubljana, Slovenia

Edel O'Toole Merrion Pharmaceuticals PLC, Trinity College Dublin, Dublin, Ireland

Patrea L. Pabst Pabst Patent Group LLP, Atlanta, Georgia, U.S.A.

S. Indiran Pather California Northstate College of Pharmacy, Rancho Cordova, California, U.S.A.

Margrethe Rømer Rassing Copenhagen, Denmark

Michael J. Rathbone InterAg, Hamilton, New Zealand

Ramesh C. Rathi Protherics, PLC, Salt Lake City, Utah, U.S.A.

Michael S. Roberts School of Medicine, University of Queensland, Princess Alexandra Hospital, Brisbane, Queensland, Australia

Steve Robertson Controlled Therapeutics (Scotland) Limited, East Kilbride, Scotland, U.K.

Carolyn Rolls Mallesons Stephen Jaques, Melbourne, Victoria, Australia

Sevda Şenel Department of Pharmaceutical Technology, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey

Hardik K. Shah Biovail Technologies (Ireland) Ltd., Dublin, Ireland

Wilfred Aubrey Soskolne Department of Periodontology, Hebrew University-Hadassah Faculty of Dentistry, Jerusalem, Israel

H. N. E. Stevens Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, Scotland

John A. Tessensohn Shusaku Yamamoto Patent Law Office, Osaka, Japan

Satoshi Toyoshima Pharmaceuticals and Medical Devices Evaluation Center, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan

George Wade European Medicines Agency (EMEA), London, U.K.

R. B. Walker Faculty of Pharmacy, Rhodes University, Grahamstown, South Africa

Wang Wang Lee AstraZeneca, Macclesfield, U.K.

Neena Washington Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, Scotland, U.K.

M. Werle ThioMatrix GmbH, Research Center Innsbruck, Innsbruck, Austria

Clive G. Wilson Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, Scotland, U.K.

Iris M. Ziegler Pharmaceutical Development, New Therapeutic Entities, Grünenthal GmbH, Aachen, Germany

Part I: Intellectual Property Rights

1

Patent and Other Intellectual Property Rights in Drug Delivery

Patrea L. Pabst
Pabst Patent Group LLP, Atlanta, Georgia, U.S.A.

INTRODUCTION

Advancements in drug delivery technology are often achieved only through a substantial investment of industrial, academic, and governmental resources. Patenting these technological advancements is frequently used to recoup that investment, to create profits that are used in part to develop new or improved products, and to enhance a competitive commercial edge. Other forms of intellectual property protection, such as trade secrets, copyrights, and trademarks may also be used to further protect and exploit drug delivery processes, products, and services.

One of the most frequently asked questions is why we need to go to the trouble and expense of patenting a composition or method. The most common reason is that protecting a new composition or method of manufacture or use provides a means for obtaining the revenue required to develop a new drug or medical treatment. With the cost of developing and obtaining regulatory approval for a new drug approaching $200 million dollars in the United States, patent rights are essential to recovering expenses. For small companies that spend more time raising money then selling products, patents and patent applications represent only tangible assets they can show to potential investors. For universities and other nonprofit research institutions, patents and associated know-how and, in some limited cases, trade secrets can be used to obtain royalties from license agreements, from, in many cases, sponsored research, and from equity in new companies that have been started for the purpose of exploiting the technology.

Patents and other intellectual properties are valued in many different ways. For example, a process for manufacture typically would be licensed for 2% to 3% of the gross selling price of a product of the process. This price would be decreased if multiple licenses had to be obtained to use the process. Patents claiming compositions tend to have a greater market value, e.g., between 5% and 10% of the gross selling price, due to the perception that they are easier to enforce than process patents.

Enforcement, however, is a risky business. A good patent strategy is to obtain patents that claim a product, methods of manufacture, and methods of use, broadly and specifically, so that a patentee is able to assert multiple patents against an alleged infringer. Patents with broad claims generally will be easier to invalidate than more specific patents. Faced with the prospect of fighting several patents, most parties will opt for settlement. The alternative of litigation is extraordinarily expensive for both parties and can result in the patents being invalidated, or the infringer being liable not only for damages for infringement, but also attorney's fees and punitive damages.

PROPRIETARY RIGHTS IN THE UNITED STATES

The importance of patent protection is clear. To protect and enable innovation, one must seek protection in all areas where the invention will be manufactured, distributed, or used. In the pharmaceutical area, one typically looks to patents to exclude competitors engaged in the manufacture and/or distribution of drugs. It is difficult or impossible to enforce patents *against* patients or the health care providers, and is a disaster in public relations.

Therefore, in determining how and when to patent an innovation, especially in the pharmaceutical area, one focuses on protecting methods of manufacture and novel drugs or drug formulations. Novel chemical entities are far rarer than new formulations. New formulations are typically based on new routes of administration (pulmonary instead of oral, topical instead of systemic); regional instead of systemic delivery; delivery regimes (escalating dosages, delayed release, extended delivery, pulsed release); combinations with other drugs; administration via a new route, form, or dosage to a different class of patients or a different disease or disorder to be treated.

As the following chapters demonstrate, the requirements for patentability and the breadth and enforceability of claims vary dramatically depending upon the country in which protection is sought. The United States has always been "friendlier" to the pharmaceutical industry than a country such as India, which still provides only limited protection despite its own rapidly expanding and powerful generic drug industry. Japan has limited its protection in recent years, making it extremely difficult to obtain broad patents and patents in the absence of detailed working examples.

While creative lawyers in the United States have tried to expand protection of patent rights through the use of patents that define products by their general functional language (a dosage regime or release profile), the European Patent Office has made it clear that such claims do not meet the requirements of European patent law.

Drug screening methods and patents on long product lists obtained from high throughput screening or genomic libraries have become harder to obtain in the United States, and are more expensive, and more difficult to enforce. Trade-secret protection for constantly evolving data bases and drug libraries can provide more cost effective and enforceable protection than is obtainable with patents.

Enforcement actions are extremely expensive, especially in the United States. Typical litigation costs run $3 to $10 million and can be higher. Approximately 60% to 80% of litigations are settled. Creative settlements that provide for the sale of "authorized" generic drugs or that delay entry into competition with the brand owner are, despite opposition by the U.S. Justice Department, increasingly common. Alternative proceedings, especially oppositions or invalidation trials in Europe, Australia, and Japan, are significantly faster and less expensive and are being used to narrow the issues and create incentives to settle prior to litigation in the United States. Absent exclusive rights, however, drug companies cannot ensure the profits required to drive the continued development of new drugs and drug formulations.

In summary, patents and other forms of proprietary protection continue to be of crucial importance to the pharmaceutical industry, even as the apparent scope of protection has narrowed, especially outside of the United States.

PATENTS

Patents are used to exclude competition, not to "protect" a product. A patent is a limited monopoly granted to an inventor by a government entity in exchange for public disclosure of the invention. The limited monopoly permits the inventor to exclude others from making, using, selling, offering to sell, or importing into a geographical area (such as the United States) the invention, which may be a composition, method of manufacture, or method of use, defined by the claims in the patent, in exchange for teaching the public how to make and use that which is claimed. The patent system is based upon the public policy objective of fostering the collective advancement of technology and science through the sharing of individual achievements. The limited monopoly (limited by geography, by the country or region granting the patent, and in time to a period of years) conferred by a patent provides the incentive for inventors to publicly reveal their technological development.

PATENTABILITY REQUIREMENTS

Patents have basically the same requirements throughout the world, although, as emphasized in the following sections, they vary in scope and subject matter. In the United States, the requirements for obtaining and asserting a patent are defined by Chapter 35 of the United States Code (U.S.C.). Patents are governed exclusively by federal law.

In the late 1990s, this law in the United States was subject to a considerable number of changes. When the United States entered into the General Agreement on Trade and Tariffs (GATT) in December 1994, major changes in effective U.S. patent term resulted. Ongoing efforts to change the U.S. Patent and Trademark Office from a government agency to a governmental corporation, primarily to avoid further diversion of patent office fees to other government agencies, and harmonization with the Patent Laws of other jurisdictions, has resulted in even more changes to the U.S. patent law.

Further changes to the requirements for obtaining a patent, and in the enforceability of method of medical treatment claims, have resulted from reactionary changes in the laws following unpopular court decisions. This is especially true in the biotechnology area. The late 1990s were known for swift and drastic decisions by the Court of Appeals for the Federal Circuit, invalidating biotechnology patents on the grounds the claims were not enabled by the specifications. Fortunately, more patents have recently been upheld under 35 U.S.C. § 112 based on challenges to enablement and lack of written descriptions, with prior art considerations playing a greater role in validity determinations.

Patentable Subject Matter

In general, patentable subject matter includes composition, method of manufacture, and method of use (1). Composition may include, for example, biodegradable polymeric microparticles containing a therapeutic agent, or a bioadhesive compound useful for targeted drug delivery within the body. A method of manufacture may be directed to, for example, a process for creating a unique drug delivery device. A method of use may entail a method for the administration of a therapeutic composition, or a surgical implantation of, for example, a synthetic tissue matrix containing implanted isolated cells that secrete insulin.

Although the law provides for patenting of compositions, methods of manufacture, and methods of use, biotechnology can present a problem under U.S. patent law when the subject matter moves away from the realm of the artificial, or "things engineered by the hand of man," to a blend or chimera of "artificial" and "natural" (2). An example is blending cells and a matrix to form a cell-matrix structure that is then implanted into a patient. Then, the matrix degrades to leave only implanted cells, and/or the patient's

own tissue grows into an implanted matrix structure, which then degrades. At what point do these materials "become" the patient and not patentable subject matter? Ethical issues may arise because of the overlap between patient material and traditional subject matter, particularly in those cases involving dissociated isolated cells, biodegradable matrices for implantation, polymeric materials for altering cell/cell interaction (such as adhesion or restenosis), and materials for implantation that are designed to remain in the body, such as stainless-steel hip replacements or cryopreserved pig valves.

Outside the United States, methods of treatment for humans or other animals are generally not patentable subject matter. For example, although surgical instruments, drugs, or devices used in surgery are patentable, surgical treatments are not considered patentable subject matter. Therefore, one cannot obtain a patent on a method for surgically treating a patient. Typically, however, while surgical treatment is not patentable, the compositions and methods of manufacture for use in treating patients are patentable subject matter. Claims may be obtained to the composition *per se*, which is to be implanted. In Europe, claims can be obtained to a first, or even a second, use of the material when the material itself is known. However, the patentability is quite limited in individual countries and in the European Patent Office for policy and ethical reasons. Generally, patent offices in Asian countries are far less flexible than the European Patent Office in this matter. As a result, patent attorneys have adopted a number of strategic approaches to obtain protection that is equivalent to the protection available in the United States. For example, one may draft claims directed to methods of manufacture of such materials, as well as to methods of use that are defined by the composition rather than the method of use steps.

Novelty

The second requirement for patentability is novelty (3). Novelty, in the simplest terms, means that no one, including the applicant, has publicly used or described (orall, in writing, or presented) that which is being claimed before the patent application is filed. In the United States, an exception is made when the publication occurs less than one year before the patent application is filed. The publication can be "removed" as prior art if the applicants are able to demonstrate that, prior to publication, they conceived and diligently reduced to practice what they are claiming.

What constitutes a publication? Generally, a publication is any oral, written, or physical description that conveys to the public that which applicant would like to claim. It may be a talk at the proceedings of a society (including any slides presented), an article in a scientific journal, a grant application that is awarded, a thesis, or even an offer for sale or a press release. A critical requirement is that the publication must be enabling, that

is, it must convey to one of ordinary skill in the art how to make and use that which is being claimed. Public use means more than using the composition or method in one's laboratory. However, it can include even a single patient study reported during clinical rounds or at a presentation where a drug company or surgical supply representative is present. In many cases, the courts have had to interpret what it means to be publicly available. A frequent question is when a student's thesis is available as prior art. U.S. courts have held that once the thesis is cataloged, it is publicly available because it has been entered into a computer database so that anyone searching the database will be able to access it (4). Accordingly, the publication date of a thesis is the date on which the thesis is cataloged, not the date on which it is defended or signed by the thesis committee. This rule is not applicable outside of the United States, however, where an earlier date may constitute the date of publication. Slides that are not distributed, but are instead shown at an oral presentation, are considered to be publications, particularly if the meeting is attended by those skilled in the art, who would be able to understand and use the information in the slides.

A disclosure to another party under the terms of a confidentiality agreement is not a publication. Uses that are strictly experimental may not be public disclosures, if, among other aspects, they are designed to determine whether what is to be claimed will work and if other involved parties are clearly informed that the studies are experimental in nature. If something is an announcement that does not enable one of ordinary skill in the art to use or make that which is claimed, then the disclosure is not a publication. For example, an announcement could be a statement made to the press that researchers X and Y have discovered a cure for cancer. Since the announcement does not tell one of ordinary skill in the art how to cure cancer, it is not enabling. However, sufficiency of enablement can be difficult to prove, and standards may change over time. One example is the court case in which the question of whether a publication related to the development of a transdermal patch for delivery of nicotine was enabling (5). The court found that a prior publication referring to transdermal patches for drug delivery mentioned that transdermal patches containing nitroglycerin for the treatment of heart disease could be replaced with nicotine to help patients quit smoking. The court held that the article disclosed or made obvious the transdermal patch for delivery of nicotine claimed by the applicant, because the applicant merely took the transdermal patch described in the article, put nicotine in it, and then demonstrated that the nicotine was delivered and would work exactly as predicted based on delivery of the heart disease drug. Even though there was no information relating to the exact dosage or schedule or to how the drug was to be incorporated into the transdermal patch, the publication was enabling because one of ordinary skill in the art would be able to determine the dosage and how to put the nicotine in the transdermal patch without undue experimentation.

Nonobviousness or the Inventive Step

The third requirement for patentability is that the claimed method or composition must be nonobvious to those of ordinary skill in the art from what is publicly known (6). This is usually referred to outside of the United States as a requirement for an inventive step. In the 1960s, the U.S. Supreme Court carefully analyzed nonobviousness and the factors to be considered in determining whether that which is claimed is obvious from the prior art (7). This analysis is a fact-based determination, involving not only the elements that are claimed, but also the level of skill in the art and the expectation that the claimed method or composition will perform as predicted, its actual success in the marketplace, the long-felt need for it, and whether there are unexpected results. If there is no better than a 50-50 chance that a particular method will work, and the method does work, it is, arguably, not obvious, although it may be obvious to try. If one tries something and the results are vastly different from what was expected, then the results are not obvious. For example, if one administers two drugs each in the dosage known to yield a particular effect, and the combination yields a substantially greater effect than the sum of the individual effects of each drug , resulting in the ability to use a much lower dosage of each drug than expected, then one would have unexpected results or "synergy." If the prior art teaches away from what the applicant has done, this result would support a finding of nonobviousness. For example, if the prior art states that one cannot administer drugs transdermally using ultrasound except at a very high frequency, then it may be nonobvious if the patent applicant finds that the same or better results are obtained using a very low frequency. Many other considerations factor into whether a claimed composition or method is obvious in view of the prior art.

In May 2007, the U.S. Supreme Court (8) again addressed the issue of obviousness, overturning the general requirements developed by the Court of Appeals for the Federal Circuit (CAFC) over the past 20-plus years. The CAFC had issued a series of decisions in which patents were determined not to be obvious over the prior art if the prior art failed to disclose the claimed elements and the motivation for one skilled in the art to combine the elements as the inventor had done with a reasonable expectation of success. The Supreme Court broadened the prior art that could be used in determining obviousness, and stated that the motivation to combine could be apparent to one skilled in the art and did not have to be explicit in the prior art. This decision has called into question the validity of many issued U.S. patents.

However, the Supreme Court also affirmed their previous decision that nonobviousness can be found when there is long standing but unmet need, commercial success, and/or unexpected results, or any of the other criteria articulated in *Graham v. John Deere Co*. Patents containing data

showing greater efficacy, cost efficiency, fewer side effects, or manufacturing benefits should still be valid and enforceable.

Requirements of 35 U.S.C. § 112

To obtain a patent, the patent application (also referred to as the specification) must satisfy the requirements of 35 U.S.C. § 112, first paragraph. This part of the statute has three separate requirements: (1) the specification must contain a written description of the invention; (2) the written description must describe the manner and process of making and using the invention; and (3) the specification must describe the best mode contemplated by the inventor of carrying out the invention at the time the invention is filed (9). These three requirements are generally referred to as the written description requirement, the enablement requirement, and the best mode requirement. Although the written description requirement and the enablement requirement are related to each other, the Court of Appeals for the Federal Circuit has repeatedly held that the two requirements are separate and distinct (9).

Written Description

The purpose of the written description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification" (9,10). The written description requirement of a patent specification serves a teaching function, as a "quid pro quo" in which the public is given "meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time" (11). Thus, in the specification the applicant must describe what is being claimed in sufficient detail to "establish that [the applicant] was in possession of the . . . claimed invention, including all of the elements and limitations" (9,12).

In *Univ. of Rochester v. G.D. Searle*, 358 F.3d at 930, the Court of Appeals for the Federal Circuit held that to satisfy the written description requirement, method claims reciting a specific compound or class of compounds must be supported in the patent specification by written disclosure of examples of such compounds or class of compounds. U.S. Patent No. 6,048,850 ("the '850 patent") claimed methods for selectively inhibiting cyclooxygenase COX-2 by administering a nonsteroidal compound that selectively inhibits activity of the PGHS-2 [COX-2] gene product to a human host in need of such treatment. Although the patent specification described methods for screening for compounds that selectively inhibit COX-2, the patent specification did not disclose a single compound that selectively inhibited COX-2. Selective inhibitors of COX-2 were unknown at the time the application resulting in the '850 patent was filed.

On the day the '850 patent issued, the University filed an infringement action against several defendants collectively referred to as Pfizer for the

selling the COX-2 inhibitors Celebrex® and Bextra®. Pfizer moved for summary judgment arguing that the '850 patent was invalid for failing to satisfy the written description and enablement requirements. The district court ruled in favor of Pfizer, concluding that the '850 patent disclosed "nothing more than a hoped-for function for an as-yet-to-be-discovered compound, and a research plan for trying to find one" (9: 926–27).

The University appealed to the CAFC which upheld the decision. Although the claims do not require the exact wording as found in the specification to satisfy the written description requirement, the claims must have sufficient written description so that one of ordinary skill in the art would recognize what was claimed (9: 922–23). "Even with the three-dimensional structures of the enzymes such as COX-1 and COX-2 in hand, it may even now not be with in the ordinary skill in the art to predict what compounds might bind to and inhibit them, let alone have been within the purview of one ordinary skill in the art in the 1993–1995 period in which the applications that led to the '850 patent were filed" (9: 925).

Enablement

To satisfy the enablement requirement, the applicant must describe the invention with appropriate methods and sources of reagents or other materials or equipment, to enable one of ordinary skill in the art to make and use the invention being claimed. This sounds far simpler than it actually is in practice. In many cases, particularly when it is coming out of a university study or a start-up company, the invention that an applicant would like to claim is one that the applicant intends to develop over the next several years, based on a limited amount of data available at the time of filing. Particularly in the case of universities, where the applicant must publish or has submitted grant applications (which in and of themselves constitute prior art once they are awarded), the difficulty is in describing something that has not yet been done. The application must not only describe a specific limited example, but also must describe the various ways in which one intends to practice that which is claimed. Difficulties also arise where an applicant desires to protect the goal (e.g., a release profile), not the specific reagents used in one or two examples of formulations that achieved the desired profile.

The purpose of a patent is to exclude the competition from making and using that which is claimed, not to "protect" a product—a frequent misconception of patents. In order to exclude competition, one must describe and claim not only that which one intends to practice, but that which another party could practice in competition with the patentee. What does this mean in real terms? It means that the applicant for a patent must describe his preferred method, which is known as of the date of filing, the preferred embodiments

that he or his company intends to market, as well as any embodiments that a competitor could make and use in competition with the applicant's product.

"Invention" usually consists of two steps, "conception" and "reduction to practice." There are two kinds of reduction to practice: actual and constructive. Constructive reduction to practice means that the applicant has described in the application for patent *how* to make and use what is being claimed, but has not actually made and used it. This may be as simple as stating that although a biodegradable polymer such as polylactic acid-co-glycolic acid is preferred for making a matrix for drug delivery, other biodegradable polymers such as polyorthoesters or polyanhydrides could also be used. It may be less obvious that other drugs may be used when only one example showing reduction to practice of a type of drug is available. The rule of thumb in this case is the level of predictability. Therefore, in stating what kind of drugs one could deliver using the claimed technology, one might list a wide variety of drugs based on the data available with one type of drug. However, delivery of a peptide or a very hydrophobic compound, which usually are viewed as difficult to deliver, may or may not be possible to list based on data obtained with a drug that is "easy" to deliver, such as a sugar or small molecular weight dye. Being too predictive (i.e., engaging in extensive constructive reduction to practice), which includes "nonenabling" or nonenabled technology, may in some cases be a detriment during prosecution of subsequently filed applications, because the examiner may cite the earlier work as making obvious the applicant's subsequent work. (See also concerns regarding prosecution in Japan in subsequent section.) Patent attorneys frequently must play a balancing game in determining how far to go with constructive reduction to practice in order to exclude competitors while not eliminating the applicant's own ability to obtain additional, subsequent patent protection.

Best Mode

In the United States, there is a requirement to disclose the best mode for practicing that which is claimed at the time of filing the application. No similar requirement exists outside of the United States. Because most applicants file the same application in the United States and outside of the United States, U.S. applicants frequently disclose their best mode in foreign-filed applications. As a result of the American Inventor's Protection Act, U.S. patent applications are now published eighteen months after their earliest priority date unless a request for nonpublication is filed (13). Part of the request for nonpublication includes a certification that the invention disclosed in the application has not been and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication after filing. If the applicant subsequently decides to file the same application in a country that publishes patent applicants, the request for nonpublication must be rescinded

before filing the counterpart application or a notice of foreign filing must be submitted to the U.S. Patent Office no later than 45 days after the filing date of the counterpart application to avoid abandonment of the application.

In some circumstances it may be desirable to file a nonpublication request if the patent application will not be filed abroad. In rapidly evolving technologies, e.g., computer software, where a publication of the invention will permit competitors to begin designing around or improving the technology before a patent issues, it may be prudent to forego foreign patent protection and file a nonpublication request. Although an applicant has certain remedies if the claims that ultimately issue in the U.S. patent are substantially the same as the claims in the published patent application, these remedies may not be as commercially valuable as being first to market.

35 U.S.C. § 112, Paragraph 4

Recently a relatively unremarkable aspect of Section 112 became the unlikely focus of a patent infringement case concerning the blockbuster drug, Lipitor®. 35 U.S.C. § 112, fourth paragraph provides:

> Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

35 U.S.C. § 112, fourth paragraph requires that a properly drafted claim further limit the subject matter of the claim from which it depends.

In early 2003, Pfizer filed four complaints against Ranbaxy Pharmaceutical, Inc. ("Ranbaxy") alleging infringement of one or more claims of U.S. Patent No. 4,681,893 ("the '893 patent") and 5,273,995 ("the '995 patent") in response to Ranbaxy's filing of an Abbreviated New Drug Application (ANDA) to market a generic version of Lipitor before the expiration of the '893 and '995 patents (14). Ranbaxy responded that the '893 and '995 patents were invalid, not infringed, and/or unenforceable for various reasons, including anticipation, obviousness, and inequitable conduct.

Prior to trial, Pfizer decided to limit its infringement allegations with respect to the '995 patent solely to claim 6, which claimed atorvastatin calcium (i.e., the hemicalcium salt of atorvastatin acid). Claim 6 and the claims from which it depends (claims 1 and 2) are shown below:

1. Atorvastatin acid or atorvastatin lactone or pharmaceutically acceptable salts thereof.
2. The compound of claim 1, which is atorvastatin acid.
6. The hemicalcium salt of the compound of claim 2.

In its opinion, the U.S. District Court held that the '893 patent was valid and enforceable. With respect to the '995 patent, the Court found that the meaning of claim 6 was clear and unambiguous: the hemicalcium salt of atorvastatin acid. However, the Court recognized that there was a "technical problem in the drafting of claim 6" because it improperly depends from claim 2 (14: 508). Claim 6 depends from claim 2 and is directed to the hemicalcium salt. Claim 2, however, is directed to atorvastatin acid. Claim 6 does not further limit the scope of the subject matter recited in claim 2 from which it depends (14). In fact, claim 6 actually recites different and non-overlapping subject matter. Accordingly, claim 6 violates 35 U.S.C. §112, fourth paragraph (14).

The District Court, however, understood 35 U.S.C. §112, fourth paragraph "to be limited to matters of form, rather than matters of substance" and concluded that 35 U.S.C. §112, fourth paragraph should not be used as the basis for invalidating a dependent claim (14). The CAFC disagreed. The CAFC held that invalidating an improper dependent claim under 35 U.S.C. §112, fourth paragraph "does not exalt form over substance" and is "consistent with the overall statutory scheme that requires applicants to satisfy certain requirements before obtaining a patent, some of which are more procedural or technical than others" (15). The CAFC went on to note that claim 6 could have been properly drafted as either a dependent or independent claim, but held that a Court "should not rewrite claims to preserved validity" (15). The CAFC did not decide the other defenses raised by Ranbaxy regarding the validity or enforceability of the '995 patent.

A unique aspect of U.S. patent law is that the claims of a patent are analyzed individually with respect to infringement and invalidity (unlike, e.g., under the European Patent Convention in which all claims stand or fall together). Since Pfizer only asserted claim 6 in the litigation, the other claims of the '995 patent are presumed valid in the absence of a Court's ruling to the contrary. In an effort to correct the technical problems in claim 6, Pfizer filed a reissue application with the United States Patent and Trademark Office (USPTO) on January 16, 2007. In its filing, Pfizer rewrote claim 6, as well as the other dependent claims that improperly depended from claim 2 (i.e., claims 4, 5, and 8–10), in independent form. This was one of the suggestions that the CAFC gave in its opinion for correcting claim 6.

PROVISIONAL APPLICATIONS

Provisional patent applications, while relatively new to the United States, becoming available June 8, 1995, have been utilized for many years in other countries, such as the United Kingdom and Australia. These applications are a mechanism for obtaining a filing date at minimal cost and with fewer requirements for completeness of the application and determination of the

inventive entity for a period of one year. The provisional application ceases to exist 12 months after the date of filing. If an application is filed as a provisional application, it can be converted to a standard utility application at anytime during the twelve months period after filing. Alternatively, it can serve as a basis for a claim to priority in a subsequently filed utility application, if the utility application is filed prior to the expiration of the one year life of the provisional application.

Although touted as a great benefit to the small entity or individual applicant, provisional applications have the same requirements for disclosure as a standard utility application. Failure in the provisional application to completely disclose and enable that which is subsequently claimed in an utility application can result in a loss of the claim to priority to the provisional application, if what is claimed is not enabled or supported with written description in the provisional application. Merely filing a journal article manuscript that will be published or presented in order to avoid loss of foreign rights usually will not comply with the enablement and written description requirements, and therefore will not serve as an adequate basis for priority. It is essential that applicants who file provisional applications based on a manuscript augment the description to encompass multiple embodiments of the invention and to provide the basis by which one of ordinary skill in the art can practice that which is ultimately claimed. Application sections that are not required for enablement, which are typically included in a utility application, include the background of the invention, the problems that the claimed invention addresses, and the claims. These sections can be omitted from the provisional application, thus saving time and money in preparing the application. In many cases, fairly standard language can be used to expand or broaden the description in a manuscript in order to meet the enablement requirements, providing a means for those with limited amounts of time or money to protect that which they are disclosing with minimum risk and expenditure.

The World Intellectual Property Organization (WIPO), which implements the provisions of the Patent Cooperative Treaty (PCT) and the European Patent Office, has confirmed that U.S. provisional applications serve as an adequate basis for a claim to priority in corresponding foreign file applications. However, under the Paris Convention, all foreign applications that claim priority from an earlier filed application must still be filed within one year of the U.S. filing date or the filing date of the country in which the first application is originally filed.

INVENTORSHIP

The U.S. constitution provides that inventors have the exclusive right to their discoveries (16). An application for patent must be made by the inventor, or under certain circumstances (such as when the inventor is dead)

by persons on behalf of the inventor (17). When more than one person makes the invention, the inventors are required to file jointly, "even though they did not physically work together or at the same time, each did not make the same type or amount of contribution, or each did not make a contribution to the subject matter of every claim of the patent" (18). A patent may be invalidated if it names one who is not an inventor or if it fails to name an inventor; however, these errors may be corrected if they were not committed with an intention to deceive (19).

In a "nutshell," an inventor is one who conceives and reduces to practice the claimed invention, not at the direction of another. To determine who the inventors are, one must first ascertain that which is claimed. Second, one must determine what is already in the prior art; one is not an inventor if the claimed subject matter is already in the prior art. For example, if one is claiming a polymeric drug delivery device and the claim defines the matrix structure as formed from biodegradable polymer, then this particular element is probably already in the prior art and that element alone would not be the invention of any named inventor upon the application for patent. However, if the polymeric matrix were defined as having a particular structure or shape or composition that has not previously been defined, then the individual (or individuals) who determines that shape or structure or composition would be an inventor. In methods for manufacture, the person who is in the laboratory using the method may or may not be an inventor. If this person has been told by another to go and make composition X using steps A, B, and C, then the person who performs the method is not an inventor—even if there is some optimization of the concentration or selection of reagents or conditions under which they are combined. If, however, that person determines that it is essential to use a concentration ten times greater than what he has been told in order to make it work, then he may be an inventor of the method of use. A patent may name multiple parties as inventors. They do not all have to be inventors of each and every claim that defines the invention. One person may be an inventor of composition claims, another the method of manufacture claims, and yet another the method of use claims. Inventorship may need to be corrected following a restriction requirement or after cancellation or amendment of the claims.

Provisional applications differ from standard utility applications in that there is no requirement to name all, or even the correct, inventors; nor do the inventors have to file a disclaimer of inventorship stating they believe they are the correct inventors of the claimed technology. This is in keeping with the absence of a requirement for having claims defining what applicants think constitutes their invention.

Outside of the United States, patent applications frequently are filed by the assignee rather than by the inventors. Inventorship is not usually a basis for challenging a foreign patent.

DUTY OF DISCLOSURE

Another unique (although recently Australia, Canada and Israel have implemented similar provisions) requirement of the U.S. patent law is the duty of disclosure, described by Chapter 37 of the Code of Federal Regulations (C.F.R.), § 1.56. Applicants are required to submit to the examiner in the U.S. Patent and Trademark Office ("the Office") copies of all publications or other materials that may be determined by an examiner to be material to examination of the claimed subject matter (19). Failure to cite relevant material prior art to the Patent Office can result in a subsequent finding by a court of appropriate jurisdiction that the patent is invalid for fraud and violation of the duty of disclosure, also referred to as inequitable conduct.

INEQUITABLE CONDUCT

Inequitable conduct is an affirmative defense to infringement often pled in infringement law suits. Inequitable conduct can occur when an individual associated with the filing and prosecution of a patent application breaches the duty of candor and good faith imposed by the Office. 37 C.F.R. § 1.56 (a). The duty of candor and good faith includes a duty to disclose to the Office all information known to that individual to be material to patentability. "Material to patentability" is defined by the Office as information that is not cumulative to information already of record or being made of record in the application, and

1. establishes, by itself or in combination with other information, a *prima facie* case of unpatentability of a claim or
2. refutes, or is inconsistent with, a position the applicant takes in
   (i) opposing an argument of unpatentability relied on by the Office or
   (ii) asserting an argument of patentability (20).

Individuals having the duty of candor and good faith include the patent attorney or agent, the inventors, and every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

The CAFC recently explained that statements or omissions made to the Office during the prosecution of a patent application can be used to invalidate that patent if those statements or omissions are material to the patentability of the invention (21).

Purdue Pharma, L.P. et al. (collectively "Purdue") sued Endo Pharmaceuticals Inc. et al. (collectively "Endo") for patent infringement alleging that Endo infringed Purdue's patents covering an oxycodone formulation. The district court found that Endo's generic version of Purdue's

oxycodone product did infringe the claims of U.S. Patent Nos. 5,656,295; 5,508,042; and 5,549,912, but that the patents were unenforceable due to Purdue's inequitable conduct during the prosecution of the patent applications that matured into these patents. On appeal, the CAFC affirmed the finding of inequitable conduct, but on petition for rehearing remanded the case to the district court for additional fact finding relating the issues of materiality and intent. The CAFC noted that "inequitable conduct requires a special kind of balancing, weighing the level of materiality against the weight of the evidence of intent" 438 F.3d at 1126.

During the preparation of Purdue's patent applications the patent attorney wrote:

> It has now been *surprisingly discovered* that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold [range] (10 to 40 mg every 12 hours around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general.

438 F.3d at 1127 (emphasis in original and quoting the '912 patent, col. 3, 11. 34–41.) However, Purdue did not have any scientific data to support this statement. Although scientific results are not always required for patentability, the manner in which the invention is described to the Office is very important. Here, Purdue repeatedly argued to the Office that the 4-fold dosage range and more efficient titration process was the "surprising discovery" that distinguished the invention from the prior art. A declaration was even submitted during prosecution further leading one to believe that comparative studies had been conducted. In fact, an inventor testified at trial that the invention was based solely on his insight. Although the trial court agreed that Purdue never explicitly told the Office that clinical trials had been performed, the Court found that Purdue's representations during prosecution of the applications when considered together implied to the Office that the clinical trials had been performed to support the "surprising discovery." The actions by Purdue that resulted in the implication that scientific results supported the date included: referring to the 4-fold range as a "result"; emphasizing the clinical significance of the discovery; comparing the dosage range of controlled release oxycodone to that of other opioid analgesics in concise, quantitative terms (438 F.3d at 1131). Thus, the omission that the invention was predicated on insight was held to be material because the lack of scientific data supporting the discovery was inconsistent with Purdue's statements suggesting otherwise (438 F.3d at 1132).

The fact that Purdue failed to provide scientific proof supporting its "surprising discovery" was not why the Court found inequitable conduct. Inequitable conduct was found by the district court because Purdue failed to tell

the Office that the discovery was based only on the inventor's insight after suggesting during prosecution that the discovery was based on results of clinical studies (438 F.3d at 1133). On appeal, the CAFC agreed with the trial court that Purdue's omission was material to the patentability of the invention and therefore, should have been disclosed to the Office. However, the omission was not as material as an affirmative misrepresentation to the Office (438 F.3d at 1133). When materiality is relatively low, the level of intent must be proportionately higher to support a finding of inequitable conduct (438 F.3d at 1134).

PATENT TERM

A patent is awarded by individual government entities for a defined period of time. In most cases that period of time will run 20 years from the initial date of filing a nonprovisional application for patent. In some cases, term can be shortened, for example, by disclaimers of patent term in view of earlier issued patents, or lengthened, due to delays relating to appeals or regulatory approval. Provisional applications are useful for delaying the filing of a utility patent application, while simultaneously serving to establish priority over subject matter disclosed within the provisional application. However, provisional applications are not examined and will only result in a patent if a nonprovisional application is filed, which usually claims benefit of the earlier filed provisional application.

Under the revised U.S. patent law that was enacted as a result of GATT, the term of a patent issuing on a pre-GATT (i.e., filed before June 8, 1995) is seventeen years from the issue date or twenty years from the original date of filing or the filing date of the earlier nonprovisional application to which priority is claimed, whichever is greater; for patents issuing on applications filed post-GATT, only the 20-year term is applicable. The one year period between filing a provisional application and filing a nonprovisional patent application is not included in the term of the patent. Applicants therefore have more incentive to prosecute all claims related to a single invention in a single application in order to minimize costs for prosecuting and maintaining the patent and maximize available patent term. Under the law in effect prior to June 8, 1995, the patent term was seventeen years from the date of issue in the United States. Divisional and continuation applications were a commonly used method to extend patent protection to encompass different aspects of the technology over a period of time much greater than 17 years. For example, an application would be filed in 1990, and a single inventive concept (e.g., the composition) would be prosecuted in the first application. Three years later, when those claims were allowable and a patent was to issue, a divisional application would be filed with another set of the claims that had been restricted out of the original application. This divisional application would be prosecuted for another two to three years, the claims would be determined to be allowable, the second patent would

issue with a 17-year term, and a third divisional application would be filed. The result is that patents on related technology would issue sequentially over several years, increasing the effective term of patent protection beyond twenty years. This is not possible under current law.

The GATT was signed into law in the United States on December 7, 1994, and the initial provisions affecting U.S. patent practice were implemented June 8, 1995. The most significant changes arising from enactment of that agreement, now called Uruguay Round Act, were changes in the patent term in the United States, the implementation of provisional patent applications, and the broadening of what constitutes infringement in the United States. The change in patent term has been discussed above. For those applications filed before June 8, 1995, the term of any issuing patent is seventeen years from the date of issue or twenty years from the filing date, whichever is longer. The term of any patent issued on an application filed June 8, 1995 or later is twenty years from the earliest claimed nonprovisional priority date. Extensions of terms are available upon delays in issuance arising from appeals or interferences. Additional extensions of terms are available for delays in obtaining regulatory approval by the Food & Drug Administration (FDA) for a device or a drug.

Patent Term Extensions

Delays in examination, with many patents now not being examined for more than three years after filing and more stringent examination proceeding under 35 U.S.C. §112 (enablement and written description) in the biotechnology area and prior art in the pharmaceutical area, have led to many patents not issuing for at least as many as five to seven years from the original priority date. The result is that a high percentage of biotechnology and pharmaceutical patents have a substantially shortened term compared to preGATT patent terms. Because a patent extension can still be obtained for delays due to regulatory issues involving the FDA, as well as for appeals to the Board of Patent Appeals and Interferences, those in the United States who believe that their patent rights will be limited in term due to delays in prosecution should avail themselves of the Patent Extension Act, if at all possible. One must bear in mind, however, that an extension for regulatory delays can only be obtained on *one* patent for any particular product or process; thus, the inventor or licensee with multiple, related patents clearly should choose the most important patent or the patent subject to the greatest increase in patent term, when facing such a situation. The patent that is to be extended must be brought to the attention of the FDA, immediately following FDA approval of the product.

The right to a patent term extension based upon regulatory review is the result of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355(b), (j), (l); 35

U.S.C. § 156, 271, 282) (Hatch-Waxman Act). The act sought to eliminate two distortions to the normal "patent term produced by the requirement that certain products must receive premarket regulatory approval" (22). The first distortion was that the patent owner loses patent term during the early years of the patent because the product cannot be commercially marketed without approval from a regulatory agency. The second distortion occurred after the end of the patent term because competitors could not immediately enter the market upon expiration of the patent because they were not allowed to begin testing and other activities necessary to receive FDA approval before patent expiration.

The part of the act codified as 35 U.S.C. § 156 was designed to create new incentives for research and development of certain products subject to premarket government approval by a regulatory agency. The statute enables the owners of patents on certain human drugs, food or color additives, medical devices, animal drugs, and veterinary biological products to recover some of the patent term lost while obtaining premarket approval from a regulatory agency. The rights derived from extension of the patent term are limited to the approved product [as defined in 35 U.S.C. § 156(a)(4) and (a)(5); see also 35 U.S.C. § 156(b)]. Accordingly, if the patent claims other products in addition to the approved product, the exclusive patent rights to the additional products expire with the original expiration date of the patent.

This issue was addressed by the CAFC in *Pfizer v. Dr. Reddy's Laboratories*, which involved the drug amlodipine. Pfizer owned two patents with claims directed to amlodipine and pharmaceutically acceptable salts thereof. Amlodipine is marketed as Norvasc®. Pfizer obtained FDA approval to market and sell the besylate salt of amlodipine. During the approval process, Pfizer submitted clinical data for both the besylate salt of amlodipine as well as the maleate salt. Ultimately, Pfizer decided to market the besylate salt due to its greater ease of tableting. Pfizer's patent on amlodipine was to expire in 2003, but under the Act, the patent term was extended to 2006.

Dr. Reddy's Laboratories, a generic pharmaceutical manufacturer, filed an Abbreviated New Drug Application (ANDA) proposing to market the maleate salt of amlodipine. A New Drug Application (NDA) is required when approval is being sought for a new chemical entity. In contrast, an ANDA is filed when the applicant is seeking to market a generic version of a drug that has already been approved by the FDA. The filer of the ANDA is allowed to rely on the clinical data submitted in the NDA to show safety and efficacy, thus dramatically reducing the cost and time associated with approval. In the case of amlodipine, Dr. Reddy's based its application on the clinical data that Pfizer submitted in its NDA for amlodipine besylate.

The question before the Court was whether the extension applied to all forms of amlodipine, or only to the form that Pfizer actually marketed and

sold (the besylate salt). Dr. Reddy's argued that the patent term extension applied only to the besylate salt of amlodipine and therefore, patent term for other salts of amlodipine, such as the maleate salt, expired in 2003. Pfizer disagreed and sued Dr. Reddy's for patent infringement, claiming that the patent term extension applied to all forms of amlodipine. The trial court agreed with Dr. Reddy's and dismissed Pfizer's lawsuit. The trial court's rationale was that the patent term extension was limited to amlodipine besylate because the act limits such extensions to "the product's first permitted commercial marketing or use."

Pfizer appealed to the CAFC. On appeal, Dr. Reddy's argued, in its request for an extension, Pfizer had identified the besylate salt as the approved product and therefore, the extension should apply to this product only. In contrast, Pfizer argued that the FDA's approval described the approved product as simply "amlodipine." Pfizer also argued that the commercial marketing and use are the same for the amlodipine maleate and that the choice of salt does not affect the activity of the active agent-amlodipine. It was Pfizer's position that if a change in the salt removes amlodipine from the Act's term extension benefit to the patent owner, it also removes it from the Act's counterpart benefits to the generic manufacturer. Thus, Dr. Reddy's could not rely on Pfizer's clinical data for FDA approval. The appellate court took notice of the fact that Dr. Reddy's ANDA relied on Pfizer's clinical data for both salts. The CAFC held that the active ingredient is amlodipine and therefore the drug is the same regardless of the salt. The CAFC said that the purpose of the Act is to strike a balance between preserving the innovation incentive by allowing for patent term extension and facilitating generic entry into the marketplace when that extended term expires. Thus, giving Dr. Reddy's the benefit of the Act, while denying the corresponding benefit to the patent owner, would defeat the intent of the Act. The Court reversed the dismissal of Pfizer's patent infringement claim.

35 U.S.C. § 271(e) provides that it shall not be an act of infringement to make and test a patented human or animal drug solely for the purpose of developing and submitting information for an ANDA. 35 U.S.C. § 271(e)(1). See Donald O. Beers, Generic and Innovator Drugs: A Guide to FDA Approval Requirements, Fifth Edition, Aspen Law & Business, 1999, 4.3[2] for a discussion of the Hatch-Waxman Act and infringement litigation. Congress provided that an ANDA cannot be filed until five years after the approval date of the product if the active ingredient or a salt or ester of the active ingredient had not been previously approved under section 505(b) of the Federal Food, Drug and Cosmetic Act. 21 U.S.C. 355(j)(4)(D)(ii) (23,24).

35 U.S.C. §156 also provides for interim extension of a patent where a product claimed by the patent was expected to be approved, but not until after the original expiration date of the patent. Public Law 103-179, Section 5.

An application for the extension of the term of a patent under 35 U.S.C. § 156 must be submitted by the owner of record of the patent or its agent within the 60-day period beginning on the date the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use [see 35 U.S.C. § 156(d)(1)]. The USPTO initially determines whether the application is formally complete and whether the patent is eligible for extension. The statute requires the Director of the Patent and Trademark Office to notify the Secretary of Agriculture or the Secre-tary of Health and Human Services of the submission of an application for extension of patent term which complies with 35 U.S.C. § 156 within sixty days and to submit to the Secretary a copy of the application. Not later than thirty days after receipt of the application from the Direc-tor, the Secretary will determine the length of the applicable regula-tory review period and notify the Director of the determination. If the Director determines that the patent is eligible for extension, the Director calculates the length of extension for which the patent is eligible under the appropriate.

INFRINGEMENT

In addition to changes in patent term and creation of provisional patent applications, passage of the GATT changed the definition of infringement in the United States. One who, without authority, makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefore, infringes the patent (24). In the United States, a claim for infringement cannot be made until after issuance of the patent. In some other countries, including the European Patent Convention countries, translated claims can be filed prior to issuance of the patent and damages can be backdated to the date of filing the translated claim, once the patent issues.

A party who believes that an issued U.S. patent is not valid may file a request for re-examination, citing art that was not made of record during the prosecution of the patent. If the patent is asserted against the party, that party may go into federal district court and ask for a declaratory judgment that the patent claims are invalid or that they are not infringed. In Europe, and in many other countries, there is a postgrant opposition proceeding available. In the European Patent Office, there is also a process whereby one may file observations during the prosecution of an application, which is public, unlike in the United States. Third party observations can be used as a means to bring relevant prior art, mischaracterized prior art, or problems relating to enablement to the attention of the European patent examiner, and may result in revocation. In the United States, a party can file a request for re-examination to bring additional art to the attention of the Patent

Office. There is also a limited procedure available during prosecution for a third party to submit prior art.

As is now evident, intellectual property rights help increase the value of technology. This is easiest to place in perspective and understand in relation to patents. Patents give the patent owner the right to exclude competition. This is accomplished by asserting the patent against third parties who are marketing a product or service which falls within the scope of the claims. Referred to as "infringement," the criteria are totally different from the criteria for obtaining a patent, referred to as "patentability." In simple terms, a patent claim consists of "elements" in a defined relationship. Certain phrases expand or limit the scope of the claim. For example, the term "comprising" can be translated as "including at least," while "consisting" means "including only" If a claim reads

Composition comprising:
A,
B, and
C,

then the claim would cover any composition including A, B, C and any other component. Use of the term "consisting" would restrict the claim to a composition including *only* A, B and C. In determining infringement, one must look to the claims of the patent. Claims may be clear on their face, or require reference to the specification, or description, of the patent. Claims also may be limited by amendments or arguments made during prosecution, a doctrine referred to as "file wrapper estoppel." For example, if the prosecuting attorney argues that the claims distinguish over the prior art on the basis that the prior art does not disclose a particular feature that the attorney argues is essential to the claims in the patent, then the claims will be construed to require that limitation, even if not explicitly recited in the claims as issued.

TRADE SECRETS, COPYRIGHTS, AND TRADEMARKS

Other types of intellectual property that may have applicability to drug delivery technology include trade secrets, and to a lesser degree copyrights and trademarks. Trade secret protection of an invention may be an appropriate alternative to patent protection for an invention or discovery, in certain competitive circumstances. Copyrights and trademarks, which do not protect ideas or inventions, may have value in protecting other facets of a business related to the drug delivery technology. These three types of intellectual property are only briefly described below.

Trade Secrets

Trade secrets can be compositions or methods of manufacture or even uses that are maintained in secrecy. Most companies that have optimized

methods for manufacture (e.g., methods for processing polymers to impart the most desirable physical and chemical properties) keep them secret. Trade secrets are unlimited in term but must be actively protected; they are lost if another party independently derives the same method or composition that is being maintained as a trade secret. Unlike patents, trade secrets are defined by and enforced pursuant to state laws. Trade secrets may be protected by asserting laws relating specifically to trade secrets, as well as unfair competition and business practices.

In order to maintain the process or product as a trade secret, one must (*i*) not disclose the process or product in public and (*ii*) must take affirmative steps to protect the information from public disclosure. This duty includes informing parties who may accidentally become aware of the technology, as well as those who are intentionally informed regarding the technology, that the material is a trade secret and is to be maintained in confidence. Laboratory notebooks describing processes or products that are considered proprietary should be maintained in designated areas labeled confidential or restricted access. Employees involved in the use of the trade secrets should be informed that the material is to be maintained as confidential and that breach of any agreement with the company by disclosing the trade secrets to a third party could result in irreparable harm and therefore be subject to injunctive relief. Trade secrets cease to be trade secrets upon public disclosure, as discussed above, or when they are independently developed by another party. If a third party independently develops the trade secret, the original holder of the trade secret has no recourse unless he can prove that the secret was acquired by theft, fraud, or other improper means. Unlike patents, which have a defined term during which the patentee can exclude others from competition, trade secrets are subject to no similar limitation. One of the most famous trade secrets is the formula for the original Coca-Cola® which has been kept in secret for decades and is enormously valuable, demonstrating that it is not just patents that have value as an asset to a company.

Copyrights

Copyright protects original works of authorship fixed in any tangible medium of expression (25). Unlike patent and trade secret law however, copyrights do not protect an idea, rather only the expression of that idea. Copyright protection may extend, for example, to visual depictions of products, or to advertising material associated with the use and sale of products. Also, copyright may protect computer software programs, publications, protocols, or other materials. In many cases where the author is employed or engaged as a consultant, the copyrights will be owned by the party contracting with the author, the journal publishing the work, or the employer. Copyrights, which also can be extremely valuable, are

transferable and enforceable under U.S. law and in many foreign jurisdictions, as a result of international agreements relating to copyrights.

Trademarks

Trademarks typically are associated with the sale of goods or services and are used to denote the origin of the goods or services. Advantages of trademarks are that they are not limited in term and rights arise upon use in either intra- or interstate commerce. One very well-known trademark is Coca-Cola®, which has been in continuous use for over 100 years. The company has used the trademark in combination with retaining the formula as a trade secret to create enormous value for the company. A company name, as well as a product name, can be a trademark. A trademark can be a name design or combination thereof. The trademark cannot be generic or totally descriptive of the product, and it must be distinct enough from other trademarks in a similar field of use or similar good or service to avoid any likelihood of confusion as to the origin of the good or service among the consumers of the trademark good or service. Trademarks can be protected under either state or federal law. An applicant for a trademark registration must show that the trademark has been used in *intra*state commerce for a state registration and *inter*state commerce for a federal registration. A federal "intent to use" application can be used to preserve the right to use a trademark prior to actual use in commerce. This provides for an initial determination of the registerability of the trademark, i.e., that the mark is not already in use by another in a way that would be confusingly similar to the applicant's use, and that the mark is not generic or descriptive, and not contrary to the public interest.

SUMMARY

Intellectual property rights provide a means for the owners of technology to recover their investment in the technology and, in some cases, to make a profit. More importantly, intellectual property rights provide a means for financing the incredibly expensive research and development and testing required for commercialization of new products and processes in the medical and biotechnology field. When the intellectual property rights have been lost or given away by publication, many times it is not possible to obtain the money required to see a product or process reach the clinic and benefit those for whom it is intended. It is only by protecting the technology that it can be used to help those who need it the most.

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