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## **THE IMPACT OF THE USPTO'S PROPOSED RULE CHANGES ON THE PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES**

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### ABSTRACT

*The abstract will go here.*

### INTRODUCTION

¶1 One of the articles in the 2008 Symposium Series is an excellent paper by Andrew T. Spence setting forth the United States Patent and Trademark Office's (USPTO's) August 21, 2007 final rules on continuing application practice and the examination of, and limitations on, claims in patent applications.<sup>2</sup> Mr. Spence's paper provides a detailed discussion of the new rules that will not be repeated herein. In addition to the rules discussed by Mr. Spence, the USPTO has promulgated new rules on information disclosure statement (IDS) practice. These proposed new rules are discussed below.

¶2 The focus of this paper, however, is not the USPTO rules per se. Rather, this paper will focus on the potentially adverse affects of the new rules on companies in the pharmaceutical and biotechnology industries. As noted by Mr. Spence, one member of the pharmaceutical industry is currently challenging the proposed rules in court.<sup>3</sup>

### I. BACKGROUND

¶3 Patents and intellectual property play an important role in pharmaceutical industry and the biotechnology industry. The issuance and expiration of patents affect the market valuation of pharmaceutical and

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<sup>2</sup> Andrew T. Spence, The USPTO Final Rule Governing Continuing Applications and Claim Quantities Up in the Air, *publication forthcoming with DLTR* (2008).

<sup>3</sup> *SmithKline Beecham Corp. v. Dudas*, No. 1:07cv1008 (E.D.Va. filed Oct. 9, 2007).

biotechnology companies to a greater extent than in other industries. Indeed, commentators have noted that the pharmaceutical, chemical and biotechnology industries are industries where “the patent virtually equals the product”.<sup>4</sup> The annual sales of blockbuster patented drugs, e.g. Lipitor®, can reach billions of dollars, and then decline quickly after the end of the patent term.

¶4 In other industries, many technologies are patented prior to, or in conjunction with, reaching the market. Outside the pharmaceutical and biotechnology industries, however, patents are often cross-licensed among companies. Major electronics/information technology companies routinely cross license hundreds of patents. “Microsoft, Apple, and Intel may fight like an army of tigers against having to share their hard-earned profits with the patent trolls, but patent cross-licensing provides a sort of country club of mutual accommodation enabling the haves to preserve the harmonious status quo among themselves.”<sup>5</sup> In contrast, although licenses are common in the biotechnology and pharmaceutical industries, product exclusivity is closely guarded and patented products are generally marketed by a single company.

#### *A. An Overview of the Drug Discovery Process*

¶5 One reason for the different treatment of patents in the biotechnology and pharmaceutical industries results from the nature of research and development in these industries, and the regulatory processes that exist to approve products prior to marketing. It has been reported that the costs of developing an innovative new drug can be as high as \$800 million dollars,<sup>6</sup> although some commentators have challenged this number as too high. Nevertheless, pharmaceutical and biotechnology companies routinely spend millions of dollars annually in research and development.

¶6 In a typical process, a market, or potential market is identified. Company scientists and researchers review scientific papers and journals to gain information about prior research in the area. From this review, or upon further research, a biological target may be identified. For example, research indicates that neuronal nicotine receptors regulate nervous system activity relating to diseases such as Alzheimer’s.<sup>7</sup> As treatment of Alzheimer’s disease as a large and expanding market, a pharmaceutical

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<sup>4</sup> Bruce A. Lehman, *The Pharmaceutical Industry and the Patent System*, (2003) (Mr. Lehman is a former Commissioner of Patents and Trademarks, and a former President of the International Intellectual Property Institute)

<sup>5</sup> Jay Sandvos, Bromberg & Sunstein LLP -- Electronic Business, 9/19/2007

<sup>6</sup> Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, (October 2006).

<sup>7</sup> See, e.g. [www.targacept.com](http://www.targacept.com)

and/or biotechnology company may conduct research to develop small or large molecules that interact with the target receptor.

¶7 In the past, small molecules that could potentially interact with the target receptor were generated by ones and two's in an organic synthesis laboratory. These synthesized molecules were then tested in biological assays to determine the nature and extent of their interaction with the target. Currently most pharmaceutical companies use *in silico*<sup>8</sup> techniques to generate hundreds of thousands of potentially suitable molecules. These computer-generated molecules may also be tested for interaction with the target using computers to find the two-three hundred potential molecules that appear to have the highest affinity for the target. The 200-300 potential molecules may then be synthesized to create actual molecules that are screened for affinity for the target using biological assays and/or IC<sub>50</sub> values.<sup>9</sup> If the screening results are positive, a provisional patent application may be filed at this point in the process. The provisional application will likely describe a large genus of compounds that encompasses the molecules of interest, as well as several sub-genuses.

¶8 From the screening data, a small number of molecules of interest are selected. These molecules that may have the best combination of properties after screening may be designated as "candidate" or "pre-candidate" compounds. Often there is a primary candidate compound, and several back-up candidate compounds.

¶9 The candidate compounds are then subjected to pre-clinical animal studies to obtain preliminary efficacy, toxicity and/or pharmacokinetic information. If the results from these studies look promising, the candidate compounds may proceed through phase 0, I, II, III and IV clinical trials. In a phase 0 clinical trial, or human microdosing study, a single small sub-therapeutic dose of the compound is given to a small number of human subjects to determine whether the compound appears to act similarly in human as anticipated from the preclinical studies. The phase 0 results, if positive, also generate pharmacokinetic (PK) data that permits the selection of a single "candidate" compound, with several back-ups, for further Phase I, II, III and IV clinical trials.

¶10 Up until this point in the process, research on the molecules of interest has likely been conducted with small quantities of the molecules that can be synthesized in a laboratory setting. If a candidate compound is discovered through the research, larger quantities of the compound than can

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<sup>8</sup> "performed on computer or via computer simulation",  
[http://en.wikipedia.org/wiki/In\\_silico](http://en.wikipedia.org/wiki/In_silico)

<sup>9</sup> TransTech Pharma, Inc. is an example of a successful emerging pharmaceutical company that uses computers in the process of drug discovery. See, <http://www.ttpharma.com/technology.html>

be efficiently synthesized in an organic synthesis laboratory may be needed to complete additional clinical trials. Thus, the synthesis pathway may need to be “scaled up” to efficiently produce larger quantities of the compound for clinical trials, and at some point in the future, for commercial production and sale. This scale up process often generates additional intellectual property, and patent application filing(s), relating to methods for production of the compound. In addition, new intellectual property may be generated, and applications filed relating to the morphology of a candidate compound, and the pharmaceutical formulation used in the clinical trials.

¶11 As noted above, a first provisional patent filing is often made prior to pre-clinical and Phase 0 clinical trials. If completed by the one year due date for filing a utility and/or international application(s), information learned from the pre-clinical and clinical studies during that year may be added to the provisional for filing in the utility and/or international application(s). As noted above, the provisional application likely included a description of a large genus, and several sub-genuses, of compounds that encompassed the molecules of potential interest. At the time of filing the utility and international application(s), the application will generally include generic and sub-generic claims, as well as claims more narrowly drawn to compounds that have been identified as candidates for further clinical trials. In addition, the utility and/or international application(s) will also include disclosure and claims relating to pharmaceutical compositions, methods for producing the compounds and the pharmaceutical compositions, and methods for treating medical condition(s). As discussed more fully below, the new USPTO rules, if allowed to go into effect, will impact an applicant’s ability to include all of these types of claims.

¶12 Although a patent application has been filed at this point, the research and development process is far from complete. As noted above, up until this point, research may have identified a suitable candidate, and one or more back-ups to start actual clinical trials. Phase I clinical trials are the first full testing of a candidate compound in human subjects. Phase I clinical trials are generally designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a pharmaceutical composition comprising the candidate compound and may include dose-ranging to determine a most effective dose.<sup>10</sup> If the pharmaceutical composition comprising the candidate compound is shown to be safe by the results of the Phase I clinical trials, Phase II clinical trials may be conducted to assess how well the pharmaceutical composition comprising the candidate compound actually works. When the development process for a new drug fails, this

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<sup>10</sup> [http://en.wikipedia.org/wiki/Clinical\\_trial](http://en.wikipedia.org/wiki/Clinical_trial) (Feb. 18, 2008)

usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.<sup>11</sup>

¶13 If Phase II trials are positive, the pharmaceutical composition comprising the candidate compound may proceed to Phase III clinical trials involving a large number of patients where the pharmaceutical composition comprising the candidate compound is compared to a “best” existing therapy to determine which is better. Data generated in Phase III clinical trials is used to obtain approval from the appropriate regulatory agencies to market a drug in countries of interest. Generally, two successful Phase III clinical trials are required prior to regulatory approval.<sup>12</sup> Phase III clinical trials are generally the most expensive and time consuming of the clinical trials and may take years to design, conduct and analyze results from.

¶14 Phase IV clinical trials are conducted after market approval to monitor any long-term effects of a drug.

¶15 The discovery process is similar for large molecule pharmaceuticals/biotechnology therapeutics. In addition, although the regulatory process differs, biotechnology therapeutics follow a similar clinical regime to small molecule pharmaceuticals.

¶16 The entire clinical trial process through completion of the two Phase III clinical trials often necessary for regulatory approval can last many years, and a new therapeutic can fail at any stage. There may be adverse affects, or, even if safe, in order for a pharmaceutical composition or biotechnology therapeutic to be approved it must generally be “better” than an existing therapy.

¶17 The costs for clinical trials can range from \$15,000 to over \$26,000 per patient, depending on the Phase. The number of patients generally increases with each Phase, with Phase III clinical trials often involving thousands of patients. Thus, clinical trials for a new pharmaceutical composition, or biotechnology therapeutic, can cost millions of dollars.

¶18 The value of an approved pharmaceutical composition or biotechnology therapeutic relates directly to whether the composition or therapeutic is patented.<sup>13</sup> In the absence of patent protection, or after expiration of a patent, another company (e.g. a Generic Pharmaceutical Manufacturer) can piggyback on the prior approval process to introduce a competitive product.

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<sup>11</sup> Id.

<sup>12</sup> Id.

<sup>13</sup> FDA approval allows the submitter an exclusionary period to market a pharmaceutical, however the FDA exclusionary period is generally shorter than the remaining patent term on a patent covering the pharmaceutical.

¶19 As noted above, the first provisional patent application filed on a pharmaceutical composition or biotechnology therapeutic will generally be filed after bench top research, and before even pre-clinical studies. The following table presents a generalized timeline of the patent process and the development process through FDA approval.

Hypothetical Timetable for Patenting and FDA Approval of a New Pharmaceutical Composition or Biotechnology Therapeutic			
Time	Laboratory Process	Patent Process	FDA Process
0	Basic research and discovery of potentially valuable therapeutic	None	None
0.5 years <sup>14</sup>	Identification of potentially valuable genus of compositions, or biological therapeutic	Provisional Patent Application Filing on Genus/Sub-genuses (“Genus Prov.”)	None
0.5 – 1.5 years	Further research on specific compositions or therapeutics	Utility (“Genus US Util.”) and PCT (“Genus PCT”) applications filing within 1 year of Genus Prov. filing	Initiation of pre-clinical studies
1.5-3.0 years	Identification of candidate compound(s)/therapeutics; ongoing research on clinical trial design and in support of clinical trial(s); process scale up	Provisional Patent Application Filings on: 1) Process Scale-up (“Process Prov.”); 2) Isomers, crystalline structures, and other details on candidate; (“Morphology Prov.”) and/or 3) pharmaceutical product formulation (“Pharma Prov.”)	Phase 0, I and IIA clinical trials
3.0 years		National phase filings of “Genus PCT” in countries of interest <sup>15</sup>	
3.0 – 6.0 years	Ongoing research to support clinical trial(s); research on possible new indications for candidate compounds	Ongoing prosecution of Genus cases	Phase IIA, IIB, and III
	3.0 – 4.5 years	Potential Issuance of Genus application in US	
	4.0 years	US Util. and PCT Filings on Process, Morphology and/or Pharma	
	5.5 years	National phase filings on Process, Morphology and/or Pharma	
6.0 – 21.0	Continued research on new indications	Continued prosecution of Genus, Process, Morphology and/or Pharma applications, and/or their offspring	FDA Approval and Sale

As illustrated by the foregoing table, the patenting process for a new pharmaceutical composition or biotechnology therapeutic generally proceeds in parallel with the FDA approval process. Many decisions, for example the decision to incur the costs of national phase PCT filings that may cost hundreds of thousands of dollars, however, need to be made prior to completion of even early stage clinical trials. These decisions, therefore, are often made, and costs incurred, for pharmaceutical compositions that ultimately fail in clinical trials.

¶20 As a result of the timeline for developing an approved product in the pharmaceutical and biotechnology industries, the new patent rules, if allowed to go into force, will have a disproportionately large impact on pharmaceutical and biotechnology companies.

## II. THE IMPACT OF THE PROPOSED RULES

¶21 One indication of the potential impact of the new rules on pharmaceutical companies is the lawsuit brought by SmithKline Beecham to enjoin implementation of the new rules.<sup>16</sup> Another indication is the number of comments received by the USPTO from pharmaceutical and biotechnology companies during the comment period on the new rules.<sup>17</sup>

### *A. Continuation Practice*

¶22 The new rules limit the number of continuation applications, including continuation-in-part applications, that can be filed by an Applicant without petitioning the Commissioner. As noted above, during development and regulatory approval of a pharmaceutical composition or biotechnological therapeutic, there are several situations that may lead to new patentable inventions related to the original discovery. Examples include inventions relating to process scale-up, pharmaceutical formulations and/or morphology. While Applicants will likely try to prepare such applications in a way that avoids a need to claim priority from an earlier filed application (i.e. a continuation-in-part application) under the prior rules, an Applicant had an option to claim priority. Under the new rules, such a priority claim will constitute the use of one of the limited number of continuing applications that may be filed.

¶23 Perhaps more burdensome is that the limitation on continuation applications will restrict the ability of an Applicant to re-file an application to obtain claims that may not have been pursued in the first filed application. At the time of filing of a first application on a pharmaceutical composition or biotechnology therapeutic, information relating to the clinical success of specific molecules is limited. Thus, most applications will rely on generic and sub-generic claims. Prior to the current rules, an Applicant could file a continuation application to obtain claims more

narrowly covering a candidate compound. This option will be limited under the new rules, and as a result it may be impossible for an Applicant to file a third or fourth continuing application to more specifically claim a back-up or second back-up composition should the first candidate fail at some point during clinical trials.

¶24 As noted by GlaxoSmithKline:

[A]n original patent application could be filed with claims that cover a genus of pharmaceutically active compounds. After the filing of the patent application, research and development efforts may identify two or more compounds within the genus that show particularly high activity such that they are designated as lead and back-up compounds for treatment of a particular disease. Before the issuance of the patent covering the genus, a first continuation application may be filed directed to the lead and back-up species. It may be discovered that one of the back-up compounds is a lead compound for treatment of another disease. If this discovery comes prior to the issuance of the first continuation, it will likely be desirable to file a second continuation application directed to the new lead compound species, thus providing for one patent that provides species protection for a first marketed compound and a separate patent that provides species protection for a second marketed compound.<sup>18</sup>

Genentech makes similar comments: “Continuation applications have long provided a mechanism for applicants in the biotechnology industry to pursue claims covering biologically active molecules that are first disclosed in an early application but that are found to be commercially important only much later.”<sup>19</sup>

¶25 Many of the parties submitting comments on the USPTO rules also noted that the system by which USPTO Examiners receive credit (disposition points) actually promotes the filing of continuation applications.

Under this system, examiners have a production goal and only receive credit for First Actions on the Merits (FAOM) and disposal, abandonment, allowance, or examiner’s answer. This system provides a perverse incentive for examiners to (i) issue final rejections at an early point in prosecution; (ii) refrain from working with patent applicants to come to agreement on claims of commensurate scope with the applicant’s invention; and (iii) encourage applicants to file RCEs.<sup>20</sup>

Thus, it was suggested that changing the “points” system for Examiners was more appropriate than limiting the number of continuation applications.

¶26 Although the new continuation rules will likely have an adverse impact on pharmaceutical and biotechnology companies, the impact of other new rules may be worse.

### *B. Divisional Application Practice*

¶27 The new rules change divisional application practice. Under the new rules, a divisional application may only be filed if the parent application has received a restriction requirement and a divisional may only claim priority to the parent application. As a result, any divisional to be filed must be filed before the parent application is patented or abandoned. It is fairly common for pharmaceutical or biotechnological applications to receive restriction requirements dividing an application into more than two groups. The author's personal record is an application that was divided into 39 different groups by the Examiner, and divisions into 10 or more groups are routine.

¶28 As a result of the single parent rule change, if an Applicant wants to pursue the restricted out claims/inventions all 10 – 39 divisional applications must be filed at relatively the same time prior to patenting or abandoning the parent case. Further, this time period occurs relatively early in the development/regulatory approval process as an initially filed patent application will likely be in condition for allowance within two to three years from filing. In addition, the costs of multiple divisional filings will be significant, particularly for smaller, emerging pharmaceutical or biotechnology companies.

¶29 As noted by Amgen:

The proposed rules are particularly onerous on smaller, less capitalized companies, as financial constraints will make filing and prosecution multiple divisional applications impracticable. Amgen shares the concerns of less capitalized biotechnology companies and relies on the value that is created by their innovations, including developing patent portfolios, through joint development agreements or other business relationships. Thus, less capitalized companies will be forced to pick and choose aspects of inventions to pursue in divisional applications, typically at an early stage in product development, long before commercial embodiments are known.<sup>21</sup>

Although perhaps particularly harsh for smaller, less well capitalized companies, the costs of multiple divisional filings will also impact the budgets of larger companies, forcing money into patent filings that could be used for additional research.

### *C. Limitation on Claims*

¶30 Although the changes to the rules for continuation and divisional practice will likely adversely impact pharmaceutical and biotechnology companies, the adverse impact will be even greater if the new rule limiting the number of claims that may be presented is implemented. Under the new rule, an application can contain a maximum of twenty-five claims and no more than five independent claims. Further, this limitation applies not only to a particular application, but also to all of the claims in co-pending, commonly owned applications without a patentably distinct claim. Even further, the rule, if implemented in its current form, will be applied retroactively to most pending applications.

¶31 As noted above, the nature of a small molecule pharmaceutical composition discovery process generally results in the discovery and development of a genus of molecules having desirable characteristics (e.g. affinity for a target site). Such a genus may contain hundreds of thousands of potential compounds. Generally, for patent filings, subgenres are defined. In addition, data may be presented for hundreds of different molecules. At the point of initial filing, all of the molecules are possible clinical candidates, although certain molecules are generally chosen as “lead” molecules for pre-clinical testing. Patent applications will generally contain one or more independent genus claims, several subgenus claims, and sub-subgenus claims on the molecules of interest. In addition, the initial patent application may include claims for pharmaceutical compositions comprising the molecules of interest. As a result, many pending applications in the pharmaceutical industry contain well over 25 claims, and well over 5 independent claims.

¶32 As will be appreciated from the discussion herein however, the initial patent filings correspond with the early stages of development of a potential pharmaceutical composition or biotechnology therapeutic which creates a conundrum for a company over which claims to pursue. Broad generic claims provide patent protection, but are the most subject to being invalidated by prior art whose existence may not be known until after a patent issues. Narrow claims provide an opportunity for a competitor to design around the product and introduce a competing product to the marketplace. Further, the limitation on the number of claims applies to continuation applications and other related applications that, in do not have a patentably distinct claim. Thus, the impact of claim limitation rules is increased by the change in the continuation practice rules.

### *D. Information Disclosure*

¶33 In a separate rulemaking from the rules discussed so far, the USPTO has also promulgated new rules relating to Information Disclosure

practice. Among the more relevant proposed changes the addition of a requirement that an Applicant provide an “explanation” of the relevance of a submitted reference if the reference is over 25 pages in length or if the total number of submitted references exceeds 20. The “explanation” must include an identification of the particular information of relevance in the reference and a correlation of that information to a pending claim in the application.<sup>22</sup>

¶34 This proposed rule is also likely to have significant impact on pharmaceutical and biotechnology companies. The scientific, and often academic, nature of pharmaceutical and biotechnology research results in inventors often having reviewed more than 20 references as part of the discovery process. In addition, the existence of patent portfolios with multiple US and foreign patents around a discovery, results in numerous additional references that need to be disclosed to the Patent Office.

¶35 Under the existing rules, assembling the references and creating an information disclosure statement can be a time consuming task. The additional requirement to provide an explanation for each reference will increase the amount of time, and cost, for preparing and filing the information disclosure statement.

### III. ALTERNATIVE APPROACHES

¶36 In addition to explain the hardship that will be created if the new rules are implemented, many in the pharmaceutical and biotechnology community suggested alternative approaches to achieve the USPTO’s objectives, particularly as these objectives are likely not to be achieved by the proposed rules. Among the more often suggested alternative approaches are: changes to the Examiner production system; worksharing with other patent offices; delayed examination; and graduated fees for continuation applications.

¶37 As noted above, under the current system the metric for determining Examiner productivity is a point system that encourages, rather than discourages, the filing of continuation applications. It has been suggested that this metric change to measure the quality of the examination.<sup>23</sup> Similarly, worksharing with the European and Japanese Patent Offices has been suggested to assist with the Examination of cases.<sup>24</sup>

¶38 The idea of delayed examination, wherein an application is filed to establish priority, but not examined until a request for examination is filed, is a practice utilized by several patent offices outside the U.S. (e.g. Japan). As stated by Novo Nordisk:

Novo Nordisk believes that the current PTO examination system, which calls for immediate substantive examination for all patent

applications, is not consistent with the reality of the different ways in which US patents are used. Academic research in the field has repeatedly shown that only a very small fraction of patents ever become licensed or are associated with a marketed product, and an even significantly smaller fraction of such patents are ever litigated. In view of these facts, Novo Nordisk believes that PTO resources would be best used on examination of patent applications where a rigorous, substantive examination is of most benefit to applicants and society, regardless of the number of continuing applications required for the patent applicant and the PTO to reach resolution as to the patentability of the applicant's claims. Indeed, Novo Nordisk believes that such patent applications frequently embody the type of invention that requires two or more continuing applications for the PTO and the applicant to reach an acceptable resolution regarding patentability.<sup>25</sup>

¶39 Another suggested approach to be used with the foregoing approaches, or alone, in the absence of the proposed rules in the concept of graduated fees for continuation applications. Under this approach, each additional continuation application would have an increased fee. The cited advantages of this approach include an economic incentive for an Applicant to be efficient in prosecution. In addition, the additional fees could be used to attract and retain Examiners.

#### CONCLUSION

¶40 Although the discussion herein focuses on the pharmaceutical and biotechnology industries, the new rules, if implemented, will affect all patent applicants. Given that there is general agreement that something needs to be done to increase the efficiency of the USPTO and the quality of patents, the proposed rules by the USPTO, and the lawsuit in response, are likely opening salvo's in a longer discussion.