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## One of These Things Is Not Quite the Same: A Comparison of the Patent Doctrine of Equivalents with Suitability for Filing an Abbreviated New Drug Application

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One of These Things Is Not Quite the Same:A Comparison of the Patent Doctrine of Equiv

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## Abstract

The doctrine of equivalents as applied to chemical patents is compared to the FDA's findings of bioequivalence in reviewing suitability petitions for filing Abbreviated New Drug Applications (ANDAs). The doctrine of equivalents provides the greatest flexibility early in the drug-development process, gradually diminishing as the product refinements become increasingly minor. Determinations of bioequivalence, however, exhibit the reverse trend as applied to analogous situations in the context of suitability petitions.

### I. Introduction

Similarity has long had an important role in the development of chemistry. From the abstract analogies inherent in the periodic table, to the concrete comparisons brought out in structure-activity relationship (SAR) data, many of chemistry's advances have stemmed from the substitution of a component with a different component expected or known to have similar functions or properties, just as the common law advances by analogy and interpolation.

Generally, law and chemistry advance independently. However, in a few discrete areas, these fields align. In patent law, the doctrine of equivalents is an equitable doctrine that allows a patent holder to exclude a competitor because, even though the competing product does not literally fall within the scope of the patent's claims, the competing product is so similar that it would be an injustice to the patent holder to permit the variant to escape his patent. A more recent development, Abbreviated New Drug Applications (ANDAs), permits a competitor to bypass much of the long and expensive drug approval process if the proposed product is so similar to an approved product that no further testing of safety and efficacy is needed.

Perhaps not surprisingly, these two areas of nexus are themselves interrelated. The filing of an ANDA is defined as an act of patent infringement.<sup>1</sup> From the patent holder's perspective, the range of similarities permitted for an ANDA is ideally narrower than that accorded by a patent, so that a competitor cannot at once evade both patent protection and expensive clinical trials by riding on the coattails of the original innovator. Accordingly, an innovator should draft patents of sufficient breadth to preclude this unwanted occurrence, and doing so requires an understanding both of the scope of the doctrine of equivalents and the conditions under which ANDAs are permitted. This paper presents an overview of these two areas, followed by a comparison that considers their similarities and differences from theoretical and practical perspectives.

## **II. FDA Treatment of ANDA Suitability Petitions**

### **A. The Statute**

The provisions relating to ANDAs were added to the FD&C Act in 1984 as part of the Hatch-Waxman Act, and were intended to make approval for minor changes to approved drug formulations faster, easier, and less expensive than preparing and processing a full NDA. Suitability for filing an ANDA is determined by comparison of a proposed drug product with an approved listed drug. The only deviations contemplated by Congress are found in §355(j)(2)(C) of the FD&C Act: a different active ingredient, route of administration, dosage form, or strength. The option for a different active ingredient is limited somewhat by the requirement that for drugs having only a single active ingredient, the ANDA must show identity of the active ingredient between the proposed and listed drugs,<sup>2</sup> and that for drugs having multiple active ingredients, any substituted active ingredient must also be listed.<sup>3</sup> In any event, the ANDA must demonstrate bioequivalence between

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<sup>1</sup>35 U.S.C. §271(\*\*\*)

<sup>2</sup>§355(j)(2)(A)(ii)(I).

<sup>3</sup>§355(j)(2)(A)(ii)(III).

the proposed and listed drugs.<sup>4</sup>

## B. FDA Decisions

### **Dosage and Strength**

The types of changes most readily accepted by FDA are those changing the strength of a dosage within established clinical guidelines, so as to eliminate the need to take two pills at once or to cut pills in half for children,<sup>5</sup> to change from a liquid injectable formulation to a dry or concentrated formulation that requires dilution before use (or vice versa),<sup>6</sup> or to vary between single-dose and bulk packages of injectables.<sup>7</sup> These changes are so obviously superficial as not to raise the most conservative eyebrow.

As superficial as such changes may typically be, deviation from the above parameters opens the door to rejection. The FDA has decided that a regimen of 15 mg tablets administered twice daily would require different safety and efficacy studies than were performed for the approved regimen of 10 mg tablets of cyclobenzaprine hydrochloride administered thrice daily.<sup>8</sup> Similarly, an increase in concentration from 2.5 mg/mL to 5 mg/mL fluphenazine hydrochloride was denied on the grounds that the more concentrated solution might cause muscle irritation, and would thus require its own safety study, and because the change in concentration might affect the absorption pharmacokinetics.<sup>9</sup> On the other hand, a change from 10 mg/ml to 20 mg/mL nalbuphine HCl was approved without comment, suggesting that there is no *per se* bar to

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<sup>4</sup>§355(j)(2)(A)(iv).

<sup>5</sup>For example, the FDA granted suitability petition 84P-0308/CP for use of a 0.5 mg estradiol tablet instead of a scored 1 mg estradiol tablet. In contrast, petition 86P-0243 was rejected, because the change from 356.4 mg to 224 mg aspirin would result in a per pill dosage below the lowest recognized effective dose.

<sup>6</sup>In a representative case, the FDA approved suitability petition 86P-0242/CP requesting the change from a 500 mg/vial lyophilized floxuridine (to be diluted to 5 mL) to a 500 mg/5 mL ready-to-use solution.

<sup>7</sup>The FDA approved suitability petition 85P-0221/CP for a 100 mL vial of 50 mg/mL fluorouracil injection instead of a 10 mL vial of the same solution, in an exemplary instance.

<sup>8</sup>Petition 86P-0386/CP.

<sup>9</sup>Petition 85P-0019/CP.

increasing the concentration of injectable solutions.<sup>10</sup> Moreover, such changes are generally more acceptable for non-injectable dosage forms. A proposed change from a 2% miconazole nitrate cream to a 4% cream was granted by the FDA despite a proposed change in therapeutic protocol from a 3-day regimen to a 24-hour regimen - a change that appears to lack “bioequivalence” on its face in terms of safety *or* efficacy.<sup>11</sup>

## Dosage Form

Approval also follows reliably on changing dosage form without changing the route of administration. Thus, topical formulations such as ointments, creams, topical solutions, towelettes, and lotions are generally interchangeable.<sup>12</sup> Still, certain changes result in rejection. For example, one suitability petition was rejected because the subject nitroglycerine patch controlled the delivery of the drug by the construction of the patch itself, whereas for the listed patch, delivery was controlled merely by the rate of absorption by the skin.<sup>13</sup> Tablets, capsules, and oral syrups, powders, and liquids were originally treated as largely interchangeable.<sup>14</sup> However, the change from a tablet to a liquid formulation, often used to treat children, for ibuprofen, a drug not approved to treat children, led the FDA to reject it under the reasoning that no warning label would be sufficient to deter its administration to young children.<sup>15</sup> Similarly, the proposed change from an indomethacin capsule to a tablet was rejected because of the known gastrointestinal toxicity of indomethacin.<sup>16</sup> Also, changes to sustained-release dosage forms with concomitant reduction in dose frequency

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<sup>10</sup>Petition 92P-0224/CP.

<sup>11</sup>Petition 84P-0398/CP.

<sup>12</sup>The switch from a triamcinolone cream to a lotion was approved in petition 87P-0019/CP, and the switch from a topical chlorhexidine gluconate solution to a moist towelette was approved in petition 88P-0295/CP, for example.

<sup>13</sup>Petition 84P-0302.

<sup>14</sup>Suitability petition 85P-0543/CP, requesting a change from acetaminophen/codeine tablets to soft gelatin capsules was approved, as was 86P-0055/CP, requesting a change from tablets to an oral suspension of spironolactone. Similarly, petition 88P-0061/CP, requesting a change from hydrocodone bitartrate/homatropine methylbromide syrup to a chewable capsule was approved.

<sup>15</sup>Petition 88P-0291/CP2.

<sup>16</sup>Petition 85P-0025/CP.

met with resistance,<sup>17</sup> as might be expected given FDA's position on increased dosages at reduced frequency for ordinary oral dosage forms noted above. In 1994, Pfizer challenged the ease with which the FDA granted petitions of this type, when the rates of absorption can be significantly affected by the particular oral dosage formulation selected.<sup>18</sup> Subsequently, the FDA seemed to take a much harder look at these types of changes, and has denied a substantial proportion of these petitions.<sup>19</sup>

Changes of dosage form are also rejected on occasion for very practical reasons. One petition was rejected by the FDA because the change from a 5 mg diazepam tablet to a 10 mg/mL oral solution would result in a product too difficult to administer in accurate doses because of the difficulty measuring volumes less than a milliliter.<sup>20</sup> Similarly, the FDA argued that because metoclopramide hydrochloride is dosed depending on the patient's weight, the proposed single-dose formulation would have precluded appropriate variations in dose.<sup>21</sup>

Changing the route of administration in addition to the dosage form, though, invites denial of the petition. As one example, a proposed vaginal sponge delivering metronidazole was denied by the FDA as being too different from the listed IV and oral dosage forms to rely on the safety and efficacy data gathered for those products.<sup>22</sup> On a closer case, the FDA denied permission to file an ANDA for a hydrocortisone rectal suppository in place of approved rectal creams and other topical formulations.<sup>23</sup> The decision was driven by the finding that the suppository would be placed past the sphincter, and the dosage that would be received

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<sup>17</sup>For example, the FDA denied petition 88P-0365/CP, which proposed a change to a 0.2 mg extended-release formulation from a 0.1 mg formulation administered twice as often. On the other hand, petition 86P-0129/CP was granted, in which the proposed change was from an immediate-release to a controlled-release propranolol hydrochloride formulation, and the petition showed graphs of serum levels obtained using the listed products and the proposed product showing significantly different profiles, although the proposed formulation gave serum levels within the range of those produced by the listed products. For other examples, see petitions 85P-0181/CP and 85P-0180/CP (denied), and 86P-0129/CP and 85P-0197/CP (granted). No clear rationale appears to distinguish the approved petitions from those denied.

<sup>18</sup>Washington Drug Letter, 11/8/1994, pp. 4-5.

<sup>19</sup>The FDA summarily denied the following suitability petitions shortly after the Pfizer protest: 94P-0119/CP1 (change from terfenadine tablets to chewable tablets), 96P-008/CP1 (change from cimetidine tablet to effervescent tablet), 96P-0365/CP1 (change from delayed-release diclofenac sodium tablet to delayed-release capsule).

<sup>20</sup>Petition 85P-0075/CP.

<sup>21</sup>Petition 86P-0015/CP.

<sup>22</sup>Petition 85P-0117/CP.

<sup>23</sup>Petition 85P-0088/CP.

by the areas before the sphincter, where the cream would be applied, could not be predicted, and thus trials would be required to demonstrate efficacy.

## **Combinations**

Changes to combination drugs, those which have two or more active ingredients, make up a world unto themselves. Typically, the FDA will grant a petition if one active ingredient is substituted for another ingredient in the same pharmacologic class in an equivalent dose. Thus, the FDA approved the change from pseudoephedrine sulfate to phenylpropanolamine hydrochloride.<sup>24</sup> Other drugs which are often found interchangeable are aspirin and acetaminophen, codeine, oxycodone bitartrate, dihydrocodeine bitartrate, and hydrocodone bitartrate, and dexbrompheniramine maleate, chlorpheniramine maleate, and brompheniramine maleate. The bar is often set high. A switch to chlorzoxazone from meprobamate was denied because “[n]o comparable experience and scientific knowledge [relative to acetaminophen and aspirin] exists with regard to substitution between chlorzoxazone and meprobamate.”<sup>25</sup> The FDA even denied a proposed switch between hydrocodone bitartrate and dihydrocodeine bitartrate, on the grounds that no dose equivalency had been established between the two drugs.<sup>26</sup>

Even for drugs generally recognized as interchangeable, the FDA applies relatively strict standards. For example, replacement of acetaminophen for aspirin was denied because the FDA decided that acetaminophen and methocarbamol in combination would require their own preclinical teratology studies and subacute toxicity studies.<sup>27</sup> Similarly, a change from clotrimazole to miconazole nitrate was rejected despite recognition

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<sup>24</sup>Petition 85P-0492/CP.

<sup>25</sup>Petition 85P-0071/CP.

<sup>26</sup>Petition 86P-0243/CP.

<sup>27</sup>Petition 85P-0102/CP.



that these ingredients are in the same pharmacologic class.<sup>28</sup> The FDA reasoned that because miconazole had not been approved for any combinations, it might be susceptible to as-yet-unknown drug-drug interactions, thus requiring trials for safety and efficacy in combinations with other drugs. Even a switch from aspirin and acetaminophen to ibuprofen in combination with oxycodone bitartrate was disallowed, because the FDA insisted on clinical testing of fixed dose combinations of non-steroidal anti-inflammatory drugs in combination with narcotics.<sup>29</sup>

## Other Modifications

Swapping of active ingredients is permitted only for combination drugs, and not drugs with a single active ingredient.<sup>30</sup> Two listed drugs cannot be joined in combination,<sup>31</sup> new active ingredients cannot be added to a listed combination,<sup>32</sup> nor can an element of a listed combination simply be removed.<sup>33</sup> Certain changes are simply not considered by the FDA as appropriate subjects for ANDAs. Changes of indication, for example, are summarily denied.<sup>34</sup> This change, like the replacement of the active ingredient in formulations with only one active ingredient, does appear to be beyond the scope of Congress' grant of authority, even if

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<sup>28</sup>Petition 84P-0398/CP.

<sup>29</sup>Petition 85P-0141/CP.

<sup>30</sup>One early petition, 85P-0334/CP, was denied because the listed drug was pseudoephedrine hydrochloride, while the proposed drug contained pseudoephedrine polisterex - essentially a different salt of the same active compound. A contemporaneous petition, 85P-0258/CP, proposing a change from metronidazole to benzoylmetronidazole, was rejected, even though the latter compound was approved in Europe and is converted to the metronidazole in the body. Similarly, the FDA rejected petition 84P-0161/CP despite recognizing that the listed drug, ergocalciferol (vitamin D2), and the proposed drug, cholecalciferol (vitamin D3), are transformed to the same active compounds in the body. Although the FDA recognized that some literature sources referred to "no practical difference" between the two compounds, the FDA relied on the fact that each compound had a separate monograph in the U.S. Pharmacopeia and alleged scientific uncertainty as to whether both compounds are converted to the same active compounds *in the same proportions* in the body.

<sup>31</sup>See petition 84P-0325/CP, denying a new combination of diatrizoate meglumine and lidocaine hydrochloride.

<sup>32</sup>See petition 85P-0571/CP, denying an attempt to add propranolol hydrochloride to a listed combination of hydrochlorothiazide and triamterene.

<sup>33</sup>See petition 86P-0040/CP, rejecting the omission of codeine from a new combination relative to a listed combination.

<sup>34</sup>As one example, petition 88P-0265/CP, proposing a change from a 75 mg phenylpropanolamine hydrochloride tablet to a 150 mg patch, in part because the patch was intended for appetite suppression, an indication recognized by physicians, but not approved by the FDA.

bioequivalence could reasonably be demonstrated.

## Summary

On the whole, the FDA's approach to suitability petitions - which do not ensure the acceptance of an ANDA, but only make it possible - has been quite conservative. While in many instances, the FDA can safely assert that bioequivalence would be impossible for the proposed change, in other instances, a company is not even allowed to make a case even though the possibility of bioequivalence logically exists. Only truly small variations with highly predictable consequences appear to consistently pass muster in the FDA's eyes. As to the other cases, apparent inconsistencies may arise from policies that change over time or are simply not evenly applied by the various agents who review these petitions, or from actual scientific/biological distinctions that are evaluated in the decision-making process but are not elucidated in FDA correspondence.

## III. Chemical Patents and the Doctrine of Equivalents

### Historical Origins

The doctrine of equivalents<sup>35</sup> originated in the case of Winans v. Denmead<sup>36</sup> as a way of protecting a patent holder from fraud, although no clear standard for assessing equivalence was provided. Perhaps the

<sup>35</sup>A number of limitations to the application of the doctrine of equivalents exist, most notably prosecution history estoppel. Such limitations will not be considered in any depth here, both because these limitations say little about what an equivalent is and because a pending Supreme Court decision, Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., argued on January 8, 2002, is likely to alter the application and severity of prosecution history estoppel as recently restated by the Federal Circuit. Accordingly, several of the cases discussed below were reversed on appeal, but are considered because the reversal was predicated on the application of estoppel, rather than a finding of non-equivalence.

<sup>36</sup>15 U.S. 330, 14 L.Ed. 717 (1853).

earliest formulation of chemical equivalence was decided by the Supreme Court in 1868:<sup>37</sup> “This term ‘*equivalent*,’ when speaking of machines, has a certain definite meaning; but when used with regard to the chemical action of such fluids as can be discovered only by experiment, it only means *equally good*.” (emphasis in original). Following this lead, the court in Chadeloid Chemical v. Frank S. De Ronde Co.<sup>38</sup> found equivalency between acetone (Me<sub>2</sub>CO) and ethanol (MeCH<sub>2</sub>OH) in the making of paint and varnish removers, despite the defendant’s contention that ethanol reacted with other components during use, whereas acetone merely evaporates. The court was satisfied in that both removers underwent gelatinization after application, acetone was a “recognized chemical equivalent” for alcohols in paint and varnish removers, and that the chemistry behind the process was irrelevant.

The first modern restatement of the doctrine was in Graver Tank.<sup>39</sup> The Supreme Court there held that manganese silicate was equivalent to alkaline earth metal silicates, such as magnesium silicate, in the context of welding compositions, again because such silicates were understood to be interchangeable by experts in the field and the two products were found to be “substantially equivalent.” Little clear guidance was given as to how equivalency should be ascertained for chemicals, although the Court did point out that “[c]onsideration must be given to the purpose for which an ingredient is used in a patent, the qualities it has when combined with the other ingredients, and the function which it is intended to perform.”<sup>40</sup>

## Modern Applications

Currently, two alternative tests are used to determine equivalence. The first is known as the triple identity or function-way-result test: “if two devices do the same work in substantially the same way, and accomplish

<sup>37</sup>Tyler v. City of Boston, 74 U.S. 327, 19 L.Ed. 93, 7 Wall. 327 (1868).

<sup>38</sup>146 F. 988 (C.C.N.Y. 1906).

<sup>39</sup>Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605, 70 S.Ct. 854, 94 L.Ed. 1097, 85 U.S.P.Q. 328 (1950).

<sup>40</sup>Id., 339 U.S. at 609-610, 70 S.Ct. at 857.

substantially the same result, they are the same, even though they differ in name, form or shape.”<sup>41</sup> The second test, which sprang from situations for which the function-way-result test is ill-suited to the nature of the invention, is simply whether the accused product is “insubstantially different” from the claimed product,<sup>42</sup> a test not unlike that used in Graver Tank. Under either formulation, evidence that two components are recognized as interchangeable in the art tends to support a finding of equivalency.

In Parmlee Pharmaceutical Co. v. Zink,<sup>43</sup> Parmlee’s product was a tablet coated with shellac, while the patent’s claim was limited to tablets coated with cellulose acetate or cellulose nitrate. The court held that even though the coatings performed the same function, so many different coatings were known prior to the patent’s filing that it would be inequitable to expand the scope of the claim beyond the two listed substances. In light of the prior art, the court held that “the proper range of equivalents for this patent is a narrow one and... is of insufficient breadth to include a substance” other than the two recited in the claim.<sup>44</sup>

However, the partial replacement of methyl cellulose with hydroxypropyl cellulose in a whipped cream product was found infringing, because the latter was a chemical and functional equivalent of methyl cellulose and methyl ethyl cellulose, and satisfied the function-way-result test.<sup>45</sup> The claim itself read “cellulose substituted with alkyl groups comprising not more than two carbon atoms and at least a part of such groups being methyl.” Although the hydroxypropyl cellulose satisfies the latter portion of this phrase, propyl comprises three carbon atoms. Nevertheless, the court concluded that if substitution of 1/6 of the methyl cellulose with the hydroxypropyl variant would avoid the patent, “form would be elevated over substances, and literalness would triumph over fairness and good sense.”

In Chemical Cleaning, Inc. v. Dow Chemical Co.,<sup>46</sup> a cleaning product including a compound prepared by

<sup>41</sup>Union Paper-Bag Machine Co. v. Murphy, 97 U.S. 120, 125, 24 L.Ed. 935 (1877).

<sup>42</sup>Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co., 520 U.S. 17, 39, 117 S.Ct. 1040, 1054, 137 L.Ed.2d 146 (1997).

<sup>43</sup>285 F.2d 465 (8th Cir. 1961).

<sup>44</sup>285 F.2d at 473.

<sup>45</sup>Rich Products Corp. v. Mitchell Foods, Inc., 357 F.2d 176 (C.A.N.Y., 1966).

<sup>46</sup>379 F.2d 294 (C.A.La., 1967).

condensing formaldehyde and thiourea was accused of infringing a claim to a cleaning product incorporating thiourea. The court found equivalence because, under conditions of use, the accused product underwent dissociation to liberate thiourea. This sort of manipulation is a textbook example of a situation where the defendant's clever manipulation of the claimed product to avoid the literal scope of the claims would have permitted it to take advantage of the patentee's invention, were it not for the doctrine of equivalents.

A claim to a zinc coating comprising "partially hydrolyzed tetraethyl orthosilicate" was found to be infringed by a product containing completely hydrolyzed ethyl silicate and/or partially hydrolyzed ethyl silicate.<sup>47</sup> Tetraethyl orthosilicate has the chemical formula  $\text{Si}(\text{OEt})_4$ . When it is hydrolyzed, one or more of the OEt groups is replaced by a hydroxyl, which can further react with other molecules of tetraethyl orthosilicate. In this way, dimers, oligomers, and polymers can form. The court correctly found that commercially available products such as ethyl silicate and ethyl silicate 40 are simply lower grades of tetraethyl orthosilicate which have already been subjected to some amount of hydrolysis, and determined that the coating composition as a whole met the function-way-result test.<sup>48</sup>

A complex and significant case invoking the doctrine of equivalents arose when Ziegler, the inventor of an important new catalytic polymerization reaction, accused Phillips Petroleum of infringing two patents relating to his process.<sup>49</sup> Phillips' process for polymerizing butadiene was asserted to infringe the first patent. The court construed the claim as being directed to a catalyst for the polymerization of ethylene,<sup>50</sup> and determined that Phillips' catalyst for polymerizing butadiene was not equivalent. The court considered evidence

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<sup>47</sup>Carboline Co. v. Mobil Oil Co., 301 F.Supp. 141 (D.C. Ill. 1969).

<sup>48</sup>This analysis, of course, would differ under the doctrine as presently applied. The all-elements rule now requires that equivalency be determined on an element-by-element basis, so the proper question is not whether the composition *as a whole* meets the test, but whether the hydrolyzed ethyl silicate is equivalent. No doubt the result would have been the same, as the plaintiff's product was found to be 87% hydrolyzed tetraethyl orthosilicate, while the defendant's product was 89% hydrolyzed.

<sup>49</sup>Ziegler v. Phillips Petroleum Co., 483 F.2d 858 (5th Cir. 1973).

<sup>50</sup>The claims at issue were clearly directed to the catalyst as a composition of matter, albeit of as a product by process. The court recognized this, yet refused to allow the claim to embrace the catalyst for "all uses." Nowhere did the claim recite any feature of the reaction or the intended substrate, yet the district court read such a limitation into the claim and this construction was retained on appeal. No doubt such a construction would not be upheld by the Federal Circuit today. Nevertheless, the analysis of the doctrine of equivalents as it relates to the court's construction, however faulty, is relevant to the subject of this paper.

that the catalyst taught by Ziegler performed poorly at polymerizing butadiene, and also noted that Phillips prepared the catalyst *in situ*, making it difficult to ascertain what catalyst was actually present in the reaction. Expert testimony was also presented that butadiene can be polymerized to a variety of polymers having significantly different physical characteristics, and the court seized on the fact that it could not have been predicted which of these polymers would result from use of Ziegler's catalyst. Experts also testified that butadiene differs significantly from ethylene in terms of structure and reactivity. Finally, concluding that no infringement under the doctrine of equivalents could be found, the court noted that an additional component not mentioned<sup>51</sup> in the claim was added to form Phillips' catalyst.<sup>52</sup>

The second patent also had claims directed to catalysts,<sup>53</sup> and was asserted to cover Phillips' process for polymerizing propylene. This time, the court agreed and overturned the district court's ruling, finding that ethylene and propylene do not differ significantly in terms of reactivity. The court noted that this patent, unlike the first, expressly contemplated the polymerization of other lower alkene monomers like propylene, and that the catalyst disclosed in the patent was known to work for such purposes.<sup>54</sup> Ultimately, the Phillips catalyst was found to perform the same function, in the same way, just better than the Ziegler catalyst. Clearly contributing to this outcome was the determination that Ziegler's patents were "pioneer" patents, and were thus entitled to a broader construction of equivalents than would be true of an average patent.<sup>55</sup>

Another of Ziegler's patents, one directed to a method of polymerization rather than to a catalyst *per se*, was

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<sup>51</sup>The patent also allegedly taught away from this component.

<sup>52</sup>Both the scientific analysis and the legal reasoning employed in this opinion are unusually poor. In spite of this, the result is at least not unreasonable.

<sup>53</sup>The claims included strict composition of matter claims and product-by-process claims, and the court similarly balked at an "all uses" construction across the board.

<sup>54</sup>Sadly, the court was also moved by the fact that the title of the first patent included the word "ethylene," while the title of the second patent mentioned no substrates at all, and that large industrial companies polymerizing propylene had taken licenses to the second patent. On the other hand, the court construed "consisting essentially of" as allowing the addition of substances that would make a material difference in the catalyst, and overlooked the fact that, again, the exact identity of the catalyst in the reaction mixture was unknown. Thus the old adage, "In my youth, I lost many cases I should have won. When I was older I won many cases I should have lost. All in all and on the average, justice was done."

<sup>55</sup>That broad construction is due to pioneer patents was determined early in the history of the doctrine of equivalents. Westinghouse v. Boyden Power Brake Co., 170 U.S. 537, 561-562, 18 S.Ct. 707, 718, 42 L.Ed. 1136 (1898).

at issue in Studiengesellschaft Kohle mbH v. Eastman Kodak Co.<sup>56</sup> This court began by noting that slight changes to a catalyst can dramatically change its reactivity. In finding non-equivalence between the claimed and accused catalysts, the court pointed to the addition of an extra ingredient to the catalyst (BuLi), the use of a different titanium salt,<sup>57</sup> different ratios of the components, the different temperatures and pressures of the reaction, and the unexpected properties of the product.<sup>58</sup> Taken together, the court concluded that the claimed process “produces a different result through means that are different and by an operation that is different.”<sup>59</sup>

*In Atlas Powder,*<sup>60</sup> claimstoanexplosivecompositionwereatissue.Whilethepatentclaimsrequireda“water-in-oiltypeemulsifyingagent,”theaccused

*E.I. Dupont*<sup>61</sup> requiredthecourttodeterminetheequivalenceofanaccusedpolymertoaclaimedpolymerdefinedintermsofitsphysicalproperties.Theclaim

*Ontheotherhand,anexperttestifiedthatpolymerswithdensitiesintherangesof0.9525wereequivalenttotheclaimedpolymers,makingthelessdensepolymer*

The question of equivalency between patented norgestrel and accused norgestimate was the subject of Ortho Pharmaceutical Corp. v. Smith.<sup>64</sup> Norgestimate is a structural analog of norgestrel, in which the ketone of norgestrel has been converted to an oxime, and the alcohol has been acetylated. In the body, however, these changes are rapidly undone,<sup>65</sup> resulting in blood and urine levels of norgestrel and norgestrel

<sup>56</sup>616 F.2d 1315 (C.A.Tex. 1980). Although the court was not as entangled by the science as its predecessor, the first patent at issue in Ziegler was found not to cover polymerization of propylene because the specification showed no contemplation of the polymerization of propylene with the disclosed catalysts. Such contemplation, of course, has never been a requirement for finding equivalence, as is amply demonstrated by several other cases already considered.

<sup>57</sup>The salt disclosed was titanium tetrachloride, while titanium trichloride was used by Eastman. While it is true that these two compounds show substantially different reactivity, the court strangely (or perhaps tellingly) pointed out that the former is a clear liquid, while the latter is a violet crystalline substance. Also, the patent clearly contemplated the use of titanium trichloride in the claimed process.

<sup>58</sup>In all salient respects, the claims at issue did not differ substantially from the first patent at issue in Ziegler. The ratios of components, the temperature and pressure of the reaction, the specific titanium catalyst, any characteristic of the product – none of these were specified in the claim. The substrate was mentioned, but so generally as to include ethylene, propylene, and higher terminal olefins. A strict construction of the claim would *literally* read on the accused process.

<sup>59</sup>616 F.2d at 1332. Note, however, that the court viewed the process as a whole, rather than determining equivalency in an element-by-element analysis.

<sup>60</sup>Atlas Powder Co. v. E.I. Du Pont de Nemours and Co., 588 F.Supp. 1455 (D.C.Tex. 1983).

<sup>61</sup>E.I. DuPont de Nemours & Co. v. Phillips Petroleum Co., 711 F.Supp. 1205 (D.Del. 1989).

<sup>62</sup>The court, however, explicitly pointed out that this statement did not create estoppel, but merely evidenced a distinction.

<sup>63</sup>Interestingly, after determining equivalence of each limitation, the court proceeded to consider the equivalence of the polymers as a whole.

<sup>64</sup>1990 WL 121353 (E.D.Pa. 1990).

<sup>65</sup>Such modifications are often used in medicinal chemistry to arrive at compounds that have improved bioavailability or processing characteristics, yet are converted to a known active compound under physiologic conditions. Such reversibly modified

acetate, both of which were claimed, and only minimal levels of norgestimate itself.<sup>66</sup> An expert testified that from the blood levels of the various derivatives, the norgestrel and norgestrel acetate were primarily responsible for the pharmacologic activity. Not surprisingly, the court found that norgestimate satisfied the function-way-result test of equivalency.

In Zenith Laboratories,<sup>67</sup> Bristol-Myers asserted that the Zenith's compound, cefadroxil hemihydrate, was converted in the body to the claimed compound, cefadroxil monohydrate.<sup>68</sup> This time, however, no conclusive data supported that contention,<sup>69</sup> yet the court found that such was the case. Although the district court thus found *literal* infringement, this finding was reversed on appeal, because at trial, Bristol-Myers compared the accused compound not to the claim, but to the Bristol-Myers's product, and several characteristics recited in the claim were not addressed by Bristol-Myers. Left only with the doctrine of equivalents, the Federal Circuit concluded that the *function* of the monohydrate was not the treatment of disease,<sup>70</sup> but the improved behavior in the formulation process. Thus, any monohydrate formed in a patient's stomach would not perform this function, and would thus not satisfy the function-way-result test.

The recent landmark case of Warner-Jenkinson<sup>71</sup> also considered chemical subject matter. The claimed subject matter was a filtration process performed at a pH between 6 and 9. Warner-Jenkinson's accused process often operated at a pH of 5. Expert testimony that the claimed process would operate at a pH of 5 and that the process would achieve the same result at even lower pH led the court to find that the accused

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compounds are often referred to as prodrugs.

<sup>66</sup>It is unclear what intrinsic potency as a hormone norgestimate possesses, or even whether such a measurement is physically possible.

<sup>67</sup>Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418 (Fed.Cir. 1994).

<sup>68</sup>As the names suggest, the monohydrate form includes one molecule of water per molecule of cefadroxil, while the hemihydrate has one molecule of water per two molecules of cefadroxil. It should be noted that the FDA approved suitability petition 99P-5449/CP1 for cefadroxil hemihydrate, apparently based on bioequivalence with the monohydrate form. From statements in the court opinion, it appears that Zenith and Bristol-Myers fought a second battle in the FDA over that issue.

<sup>69</sup>Indeed, proof of such conversion would likely require recovering partially digested drug from a patient's stomach and performing X-ray diffraction studies on selected contents – an unlikely occurrence at best.

<sup>70</sup>The court apparently took into account the prior expiration of a patent to cefadroxil generally.

<sup>71</sup>Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co., 62 F.3d 1512 (Fed.Cir. 1995).



process infringed the claim under the doctrine of equivalents.<sup>72</sup>

Nylon membranes were the subject of comparison in Pall.<sup>73</sup> The claim at issue required a nylon having a ratio of methylene to amide groups within the range of about 5:1 to about 7:1, while the ratio in the accused membrane was 4:1. While the court noted that the 4:1 nylon did have certain properties that differed from those within the claimed range, it recognized that membrane's functional performance in the claimed assay was insubstantially different, and met the function-way-result test as well.<sup>74</sup>

Another process, one for alkylating amines, was the subject of Tanabe Seiyaku,<sup>75</sup> which raised the question of whether acetone ( $\text{CH}_3\text{C}(=\text{O})\text{CH}_3$ ) was equivalent to butanone ( $\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{CH}_3$ ) as a solvent for the reaction. The defendant presented evidence that duplicating examples from the patent with butanone instead of acetone often gave poor results, although in one case, the result with butanone was better. Also, a good deal of experimentation was performed by the defendant while optimizing the reaction for large scale, from which the court inferred that the defendant had designed around, rather than copied, the patented method, and that butanone and acetone were not truly interchangeable. As a result, the court upheld the FTC's determination that the function-way-result test was not met by the accused process.

In Upjohn Co. v. MOVA Pharmaceutical Corp.<sup>76</sup> a pharmaceutical formulation was accused of infringing a claim requiring at least 70% spray-dried lactose, where the accused product<sup>77</sup> contained about half spray-dried lactose and half 'Starch 1500.' MOVA introduced evidence that the two types of excipients were not recognized as equivalent in the field. Additionally, one expert testified that Starch 1500 acts by disintegration

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<sup>72</sup>The subsequent Supreme Court opinion reviewing this decision, 520 U.S. 17, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997), reinforced the requirement that equivalence be determined on an element-by-element basis, and provided new guidance on the application of prosecution history estoppel.

<sup>73</sup>Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211 (Fed.Cir. 1995).

<sup>74</sup>The court also pointed out that while the 4:1 nylon was known at the time the patent was filed, *membranes* of that nylon were not commercially available. Thus the unnecessarily narrow restriction on the nylon membrane merely reflected the commonly available membranes at that time.

<sup>75</sup>Tanabe Seiyaku Co., Ltd. v. U.S. Intern. Trade Com'n, 109 F.3d 726 (Fed.Cir. 1997).

<sup>76</sup>31 F.Supp.2d 211 (D.Puerto Rico 1998).

<sup>77</sup>The remaining cases were all triggered by the filing of an ANDA, indicating that the corresponding suitability petitions had been accepted by the FDA.

upon ingestion, while spray-dried lactose merely dissolves, i.e., the modes of action of the two excipients were different. Accordingly, the court held that the MOVA formulation did not satisfy the function-way-result test of equivalence, and this decision was upheld on appeal for the same reasons.<sup>78</sup>

A generic form of Zantac<sup>®</sup> was at issue in Glaxo Wellcome v. Pharmadyne.<sup>79</sup> The claimed formulation required ethanol (CH<sub>3</sub>CH<sub>2</sub>OH), whereas the accused product contained propylene glycol (HOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH) instead. Pharmadyne argued that the propylene glycol was selected merely as a solvent for a preservative, but other evidence showed that much less was needed for this purpose than was present in the product, and that propylene glycol stabilized the active ingredient, as Glaxo had first discovered was true of ethanol. The court found that it was not necessary to prove that both solvents stabilized the active ingredient in the same way at the molecular level, and that it was enough to show that they had similar stabilizing effects and similar structures.<sup>80</sup> Between that and the court's view that Pharmadyne had spent little effort in arriving at its formulation other than testing various other alcohols to see which best replicated ethanol's stabilizing effects, the finding of equivalence was nearly guaranteed.

A second Zantac<sup>®</sup>-related product was the focus of Glaxo Wellcome v. Ben Venue Laboratories.<sup>81</sup> This time, the claim limitation at issue was buffer salts stabilizing the pH in the range of 6.5 to 7.5. The accused solution listed sodium acetate, hydrochloric acid, sodium hydroxide, and water.<sup>82</sup> The court found that this particular combination of ingredients would only be an effective buffer at a much lower pH, and thus would not perform substantially the same function as the buffer recited by the claim.

Another recent decision evaluated the infringement of a diltiazem capsule.<sup>83</sup> The claimed capsule required

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<sup>78</sup>225 F.3d 1306 (Fed.Cir. 2000).

<sup>79</sup>32 F.Supp.2d 265 (D.Md. 1998).

<sup>80</sup>Interestingly, Pharmadyne's original position was that propylene glycol was a polyol but not an alcohol. It is a fine line between bravery and foolishness. Their own expert conceded that, as all polyols are necessarily alcohols, propylene glycol was generally recognized as being both an alcohol and a polyol.

<sup>81</sup>1998 WL 965993 (N.D. Ohio 1998).

<sup>82</sup>This is, of course, a rather odd list, in that hydrochloric acid and sodium hydroxide would immediately react to form salt and water. It may be that the hydrochloric acid was actually complexed with the active ingredient.

<sup>83</sup>Biovail Corp. Intern. V. Andrx Pharmaceuticals, Inc., 158 F.Supp.2d 1318 (S.D.Fla. 2000).

diltiazem in admixture with a wetting agent that maintained the solubility of the diltiazem. In the accused product, the diltiazem was admixed only with ethylcellulose and povidone, both of which Biovail conceded are not wetting agents, and this mixture coated a sucrose sphere, sucrose being a wetting agent within the meaning of the claim. In finding non-equivalence of this formulation to the admixture, the court pointed to evidence that sucrose *in a mixture* helps the mixture break apart and dissolve because of its high solubility, while the sucrose *core* would be of little or no assistance in breaking up the shell coating it. Indeed, the evidence showed that, once dissolved, sucrose exhibits *anti-wetting* properties. Accordingly, the court concluded that the sugar core acted primarily as a support, thus having a different function, acting in a different way, and providing a different result than in the claimed formulation.

Oral contraceptives were the subject of Bio-Technology General v. Duramed Pharmaceuticals.<sup>84</sup> One disputed claim, a method of contraception, required that a woman take estrogen pills on a certain few days of a cycle, and a progestin on most of the remaining days. Another claim covered a package of pills including an “initial” set of estrogen pills and a “follow-up” set of progestin pills. The court found that the accused pills did not infringe the latter claim because a package contained two 28-day courses of pills, arranged to begin with progestin pills, followed by estrogen pills, thus contradicting the initial/follow-up elements of the claim.<sup>85</sup> In considering equivalence, the court pointed out that by reversing the placement of the pills, a different result is obtained – that is, the first pill of one system has a different effect on the female body than the first pill of the other.<sup>86</sup> Thus, a judgement of no infringement was entered.

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<sup>84</sup>174 F.Supp.2d 229 (D.N.J. 2001).

<sup>85</sup>Indeed, the only apparent difference is at what point in a particular package of pills menses occurs. With the plaintiff’s product, menses occurs at the first pill, whereas with the defendant’s product, menses occurs around the 22<sup>nd</sup> pill – the only difference is the arbitrary choice of timing between “Day One” and menses. It was undisputed that the only significant differences between the two products were the colors of the pills and the order the pills were arranged in the package.

<sup>86</sup>This statement is particularly bold, following a citation to a case holding that the doctrine of equivalents was satisfied by a two-part product that, instead of having a positive dopant in one part, had a negative dopant in the complementary part to achieve the same effect. Corning Glass Works, 868 F.2d 1251 (Fed.Cir. 1989) Greater elevation of form over substance is difficult to imagine.

## Summary

Although the formal test of equivalence is generally uniform in the cases, particularly since the Federal Circuit came on the scene, outcomes remain a little bit unpredictable. No doubt this is in part because equivalence is based in fact rather than in law, and juries, or even different district court judges, may be more or less generous in applying the doctrine. The Federal Circuit can only overturn the cases of clear error,<sup>87</sup> leaving a middle ground of cases in which a clear demarcation of the doctrine cannot be discerned. Also, the fundamental question is so closely intertwined with the way in which a claim is drafted that similar cases have different outcome solely because of the exact reading of the claim. Nevertheless, some patterns emerge which will be considered in the next section.

## IV. Comparative Analysis

The first type of claim that is typically sought in the quest for a new drug is a composition of matter claim that defines the subject compounds by structure. The doctrine of equivalents often provides protection for compounds outside the literal scope of the claims, as was true in Chemical Cleaning. An ANDA, however, cannot be filed for any such change. In fact, the attempted switch from ergocalciferol (vitamin D2) to cholecalciferol, denied by the FDA, is conceptually quite similar to the facts of Ortho, since in each case the active metabolites in the body are the same regardless of which of the two compounds is administered. Thus, at least for single active compound drugs, a patentee can expect to be protected against competitor ANDAs for the life of the patent.

Because equivalency is determined on a limitation-by-limitation basis, a similar scope of equivalents should

<sup>87</sup>Such as, one hopes, Bio-Technology v. Duramed.

be available for each element of a patented combination drug. Of course, the FDA has some leeway for substitution here as well. The FDA, however, is pretty rigid in requiring known interchangeability of the two components – the very sort of data that makes it easy for a court to find equivalence, as in Glaxo Wellcome v. Pharmadyne. Accordingly, a patentee of a combination can also expect to be well protected against competitor ANDAs, particularly if the patent explicates the functional attributes desired of each component.

Although there are no apparent cases relating to patents directed to new indications for old drugs, the fact that the FDA does not permit ANDAs for new indications means that such patentees have little to fear.

Companies often attempt to extend the patent protection for a new drug by filing follow-up patents directed to specific aspects of the final product, such as dosage or formulation. Such tactics are only effective, however, if they prevent a competitor from filing an ANDA. The patents at issue in the Zenith, Biovail, Upjohn, and Glaxo cases well illustrate the balance between the doctrine of equivalents and FDA ANDA practice. Of these cases, all but Zenith were triggered by the filing of an ANDA (subsequent to grant of a suitability petition), and all but the first of the Glaxo cases were decided in favor of the defendant. Why the difference? In Zenith, the change of hydrate form – particularly as an oral formulation – would be highly unlikely to alter its biological effect, because the drug ends up dissolving in the decidedly moist environment of the stomach or intestines, rendering the original ratio of water:drug irrelevant. It is no surprise that FDA would grant such a petition. The change is simply far less significant from a biological perspective than is a change of counterion, or the use of a prodrug form of an active agent. But from a patent perspective, Bristol-Myers' rationale for expanding the scope of the claim through the doctrine of equivalents to include the defendant's product would likely have ensnared forms of the compound for which patent coverage had expired. Courts routinely refuse to extend patent coverage in this way, and thus it is no surprise that such an expansive reading of the claim was rejected. Moreover, it is unlikely that this claim strategy could have borne fruit for

Bristol-Myers, for all the reasons described above. A claim to a particular hydrate form is necessarily narrow and not susceptible to a broad interpretation without encompassing the prior art, thus leaving competitors relatively wide berth for developing alternative products.

Biovail, Upjohn, and the Glaxo cases all turned on the particular excipients (or other additives) employed in the pharmaceutical. Excipients, like hydrates, present uncertain ground for expansive patent protection. This is partly because a large number of common excipients are available and recognized as safe, and partly because the FDA seems to be receptive to substitutions within the accepted class of excipients – at least as long as the change doesn't significantly affect the release rate of the drug. In terms of the doctrine of equivalents, it is the function prong that stands most ready to bar a finding of equivalency.<sup>88</sup> There are excipients that dissolve in vivo, and others that are chemically digested; some that help solubilize or stabilize the active ingredient, and others that are merely inert filler. To the extent that the patentable advance over the prior art derives from one of these functions, acceptable excipients that lack that function become fair game for competitors when the patent on the drug itself expires. And in most scenarios, some such function will play a role in this type of patent, because the idea of using *some* type of excipient – both from scientific and legal standards – is obvious the moment that a compound shows biological activity. In order to patent a particular formulation in most circumstances, some distinct advantage will need to be shown, whether it be improved stability, digestion, biocompatibility, or some other feature. In the other circumstances, where the point of novelty derives from some aspect other than the choice of excipient itself, the draftsman should take care to write claims that place no weight on the selection or function of the excipient, and should fill the specification with expansive lists of suitable excipients and additives having varying characteristics that undermine any claim to reliance on a particular functional attribute.

Finally, for the changes most readily accepted as equivalent by the FDA, such as changes of strength, dosage

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<sup>88</sup>And, indeed, the function prong stands ready to militate a finding of infringement when the function is retained, as in the first Glaxo case.

form, and concentration, patent protection is likely to be unavailable<sup>89</sup> or extremely narrow. Similarly, the additional scope afforded by the doctrine of equivalents would need to be similarly narrow to avoid ensnaring the prior art generally. Accordingly, claims should be drafted that *literally* encompass all foreseeable modifications, such as dosages throughout the clinically effective range, all preparations suitable for administration by a similar route, and the like. Failure to observe this minimal prognostication is likely to invite an unwanted ANDA by a competitor.

As a general rule, a pharmaceutical patentee receives the best protection against competitive ANDA's early in the development process, with a gradual atrophy as the refinements to the product grow increasingly refined. This result conforms to theoretical precepts of intellectual property protection generally. Theorists and courts generally agree that the importance of the patented technology, in terms of the significance of its advance over the state of the art, should be proportional to the scope of protection afforded, and thus "pioneering inventions" should receive the broadest protection.<sup>90</sup> In a very real sense, the stipulation that filing an ANDA is an act of infringement extends the breadth of patent protection. It follows, therefore, that the strength of this protection should begin to erode as the underlying patent which actuates this protection centers on increasingly subtle refinements of a pharmaceutical product.

The curious result – both in theory and in actual outcomes – is that when the doctrine of equivalents is at its zenith, bioequivalence for suitability petitions is at its nadir, and vice versa. Skillful patent drafting thus has its greatest effect near the fulcrum, where the doctrine of equivalents adds *some* breadth and bioequivalence is a close call. Patents relating to combination drugs and specialized formulations fall in this category.<sup>91</sup>

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<sup>89</sup>For example, for a compound to be administered by injection, it is equally obvious to supply it as a dry powder for subsequent dissolution as it is to provide it as a solution. Similarly, for an orally available compound, it is as obvious to provide it as a capsule, liquid, syrup, tablet, or other oral formulation. No special insight is necessary to arrive at this realization, and so any such patent would likely be obvious over the compound itself, absent highly particularized circumstances.

<sup>90</sup>See, for example, Augustine Medical, Inc. v. Gaymar Industries, Inc. 181 F.3d 1291 (Fed.Cir. 1999); Westinghouse v. Boyden Power Brake Co., 170 U.S. 537, 562, 18 S.Ct. 707, 718, 42 L.Ed. 1136 (1898); Edmund Kitch, Elementary and Persistent Errors in the Economic Analysis of Intellectual Property, 53 Vand. L. Rev. 1727, 1730-1731 (2000).

<sup>91</sup>In some situations, new strengths or dosage regimens might also be expected to fall in this category.

## **V. Conclusion**

In many situations, the outcome of the duel between the doctrine of equivalents and bioequivalence is a foregone conclusion. The patent drafter plays the most significant role for the applications that fall in the gray area in between. Because the function or behavior of the element that advances over the prior art tends to be outcome-determinative for the doctrine of equivalents, yet to have little effect on bioequivalence, the drafter should take especial care to consider this function broadly and define it expansively in the claims. Similarly, expounding upon alternatives that retain this function will also help ensnare the alternatives listed, as well as their equivalents. Gradually, the original patentee will cede ground to a generic competitor, but for an important drug the extra attention in drafting may be extremely rewarding.