

# Penicillins: Their Chemical History and Legal Disputes in New Zealand

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## Introduction

In 1928, Sir Alexander Fleming showed that *Penicillin notatum* inhibited the growth of *Staphylococcus* cultures,<sup>1-3</sup> and that it had antibacterial properties *in vitro* and did not appear toxic in rabbits and mice.<sup>4</sup> Despite this, the use of penicillins, as a practical aid in overcoming bacterial infection *in vivo*, was not considered for many years, despite the concept of antibiotics having been appreciated as early as 1887.<sup>5</sup> Real interest in penicillin did not come until the late 1930s<sup>4</sup> when academia and industry, *e.g.* Merck, became involved.<sup>5</sup> This led to the isolation and study of an impure form of penicillin in 1940 by Florey *et al.*,<sup>6</sup> who showed that its subcutaneous use was highly effective against streptococcal infection in mice. This demonstration revived interest in the possible therapeutic use of penicillin in humans,<sup>4</sup> and further work from these authors allowed for the mass production of penicillin in WWII and its general use from 1949.<sup>5</sup> Eventually, biosynthetic 6-aminopenicillanic acid (6-APA; **10** below) was isolated by the Beecham Group<sup>7</sup> in 1957 and now is a common precursor to semi-synthetic penicillins.<sup>8</sup>

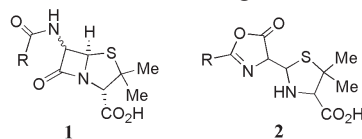
Florey's group at Oxford University did not patent their penicillin-related work, despite some members wanting it. In the 1950s, institutions such as Oxford lacked the facilities to progress intellectual property protection.<sup>5</sup> However, the Beecham company took full advantage of intellectual property rights, patented 6-APA, and have remained vigilant in its protection since. Over the fifty years since the initial patent, they have patented many variations, different semi-synthetic penicillins and related compositions.

This article provides a chemical history of penicillin, how it functions in biological systems, and how it has been developed since its initial discovery. It briefly expounds and comments on the patents relating to penicillin in NZ and the disputes that have arisen. Legal issues raised by penicillin are not fully explored; rather they have been used to provide a window into the patent-protected empire that can be built from a single discovery.

## The Chemistry of Penicillins

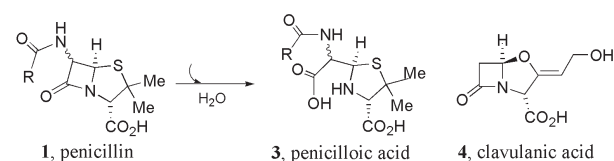
### What are Penicillins and How Do They Function?

When first isolated the structure of penicillin was uncertain. Beecham's Rolinson *et al.*<sup>9</sup> proposed the thiazolidine-oxazolone **2**, but it is now established<sup>1</sup> as the  $\beta$ -lactam **1** that carries a thiol ring and an amido side-chain.



Bacterial cells have a high internal osmotic pressure and maintain shape integrity avoiding lysis (cell bursting) by having rigid cell walls. These walls are constantly being rebuilt as they are continuously degraded by enzymes in the surrounding medium. Penicillin prevents bacterial cells re-forming, causes lysis and is assisted by the high internal pressure.<sup>1</sup> Most penicillins affect only Gram-positive bacteria due to the composition of the cell wall. To function, penicillin needs to pass the wall and enter the plasma membrane that surrounds the central cytoplasm.<sup>1</sup> Lower density Gram-positive bacteria have walls *ca.* 25 nm thick that consist of cross-linked peptidoglycans and a thin layer of extracellular teichoic acids that offer little protection to drug penetration. Comparatively, Gram-negative cell walls are denser, only 2-3 nm thick, and have an outer lipid bilayer and periplasmic space that surrounds the peptidoglycan cell wall; this makes drug penetration difficult.<sup>1</sup>

$\beta$ -Lactam antibiotics are able to diffuse through the outer membrane of Gram-negative bacteria whose porin channels (formed by proteins) allow the transport of such drugs. Once through the outer membrane, the drug must then diffuse through the periplasmic space that contains  $\beta$ -lactamases, which can inactivate the drug.<sup>1</sup> These  $\beta$ -lactamases, also produced by Gram-positive bacteria in their extracellular fluid, create  $\beta$ -lactam-resistant bacteria as they hydrolyze this ring to penicilloic acid (**3**), thus inactivating the penicillin (Scheme 1).<sup>1,3</sup>  $\beta$ -Lactamase inhibitors, such as clavulanic acid (**4**), are incorporated to overcome this.

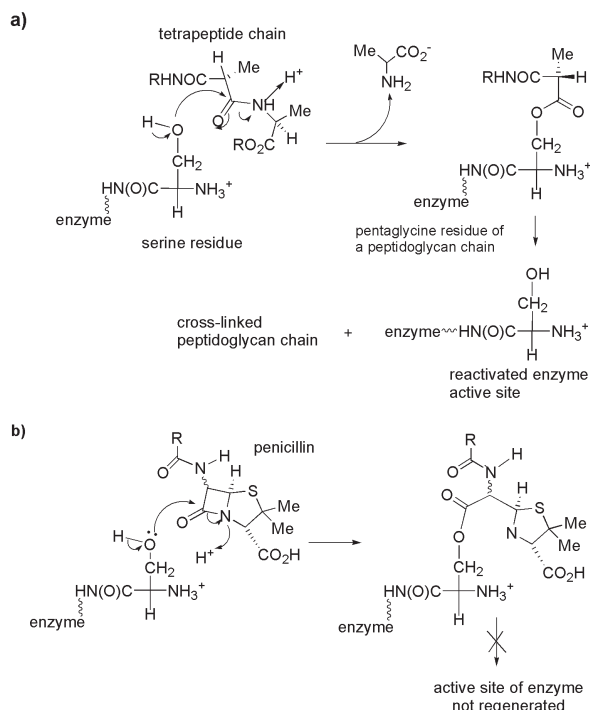


Scheme 1. Inactivation of penicillin by  $\beta$ -lactamase.

Once at the plasma membrane, the penicillin binds to the transpeptidases (and other proteins) involved in cell wall synthesis and blocks their action from an interaction with its four-membered  $\beta$ -lactam ring.<sup>1</sup> It is thought that the glycopeptide transpeptidase needed for the final step of the cross-linking is inactivated due to the structural similarity of the amido carbonyl group adjacent to the terminus of the natural tetrapeptide chain with the carbonyl group of the  $\beta$ -lactam unit of penicillin.

The final step of cross-linking is believed to occur when a serine hydroxyl of the catalyzing enzyme (glycopeptide transpeptidase) attacks the carbonyl group next to the end of a tetrapeptide chain and displaces the terminal alanine (Scheme 2a). The enzyme is then displaced by the

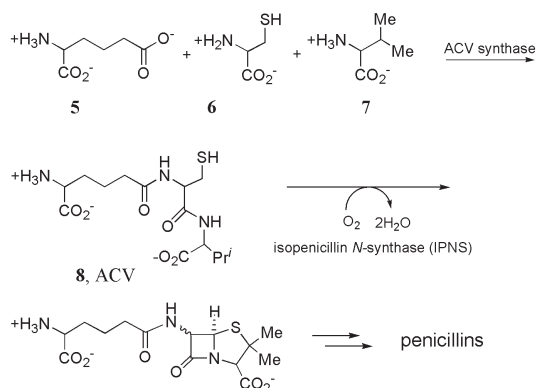
pentaglycine peptide bridge from another tetrapeptide chain, regenerating the enzyme (Scheme 2a).<sup>1,10</sup> However, in the presence of a highly reactive penicillin, this hydroxyl attacks the  $\beta$ -lactam carbonyl instead and forms a covalently bound acyl derivative that is slow to hydrolyse (Scheme 2b),<sup>1,10</sup> the 1,3-thiazolidine ring appears to prevent pentaglycine-induced enzyme-acyl bond cleavage. The active site of the enzyme is thus deactivated.<sup>1</sup>



Scheme 2. a) Normal cross-linking process in bacteria, b) penicillin intervention - see ref. 1

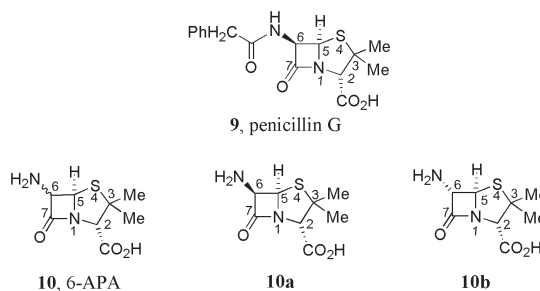
## Synthesis of Penicillins

**Penicillin biosynthesis in nature**—Penicillins are secondary fungal metabolites, often isolated from *Penicillium chrysogenum*.<sup>10,11</sup> The fused lactam-thiazolidine rings are thought to be biosynthesized from L- $\alpha$ -amino adipate (**5**), L-cysteine (**6**) and L-valine (**7**). These three peptides together (with the ACV synthase catalyst) form L- $\delta$ -( $\alpha$ -amino adipoyl)-L-cysteinyl-D-valine (ACV, **8**), an acyclic tripeptide (Scheme 3). The bicyclic  $\beta$ -lactam is then formed from ACV by catalysis with isopenicillin N-synthase (IPNS), a non-heme Fe(II) enzyme. The side chain of  $\beta$ -lactam antibiotics formed from natural biosynthetic cyclization is L-amino adipoyl and it can be epimerized to the D-form naturally.<sup>10</sup>



Scheme 3. Biosynthesis of penicillins.

**Side-chain modification**—*Penicillium chrysogenum* can produce more than one type of penicillin that differs only in the acyl side-chain of the  $\beta$ -lactam ring.<sup>12</sup> In the late 1940s, the identity of the side-chain resulting from the mould fermentation could be altered by adding requisite precursors to the brew, e.g. phenylacetic acid incorporates a benzylic group into the side-chain giving penicillin G (**9**).<sup>12</sup> Such modification continued throughout the 1940-50s but failed to provide<sup>12</sup> anything superior to penicillin G, until the discovery of 6-aminopenicillanic acid (**10**, 6-APA) in the late 1950s.



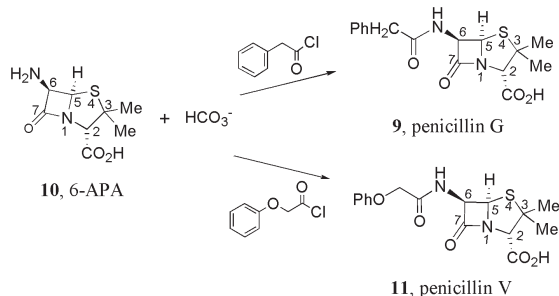
**The discovery of 6-APA**—Batchelor *et al.*<sup>11</sup> were the first to isolate, identify and appreciate the value of 6-APA (**10**). The molecule lacks the pendant acyl group of the fermentation products, and the UK patent application for it was made in 1957. While there is evidence that others<sup>13</sup> had previously stumbled across 6-APA, none had established its structure and assessed its possible use as a penicillin precursor.

Additionally, Batchelor's Beecham group discovered that **10** could be formed from penicillins by enzyme-catalysed hydrolysis in numerous micro-organism media with removal of the penicillin side-chain.<sup>14</sup> This was very important because the original isolation of **10** by fermentation was from a difficult process and in relatively poor yield.<sup>4</sup> The isolation of **10** from *Streptomyces lavendulae* and *Escherichia coli* (*E. coli*), as well as from *Penicillium chrysogenum*, was also demonstrated.<sup>14</sup> In March 1959, Beecham made patent application for the deacylation of phenoxymethylpenicillin [penicillin V (**11**) that they had also isolated] by *Streptomyces lavendulae*. Enzymatic hydrolysis in *Alcaligenes faecalis* also gives **10**, and small quantities have been isolated from *Aerobacter cloacae*, *Bacillus subtilis*, *Micrococcus lysodeikticus*, and *Mycobacterium phlei* by a Bristol Laboratories group<sup>15</sup> who showed that both **9** and **11** reverted to **10** on hydrolysis.

**Semi-synthetic variations**—The discovery of side chain-free **10** was ground-breaking as it provided a penicillin directly usable as a precursor for semi-synthetic derivatives in a simple procedure without need for synthesis of the bicyclic lactam moiety.<sup>3,4,11</sup> For these reasons, **10** has been termed *the penicillin nucleus* that allowed research into this most important groups of antibiotics.<sup>12</sup> Prior to this 1957 discovery of **10**, **9** and **11** were the only penicillins of clinical relevance; following its discovery some twenty derivatives had entered clinical use by the end of 1970.<sup>12</sup>

In itself, **10** has antibiotic properties but its activity is much below than of the modified **9**,<sup>11</sup> which, unlike **10**, is not inactivated by penicillinase, a specific type of  $\beta$ -lactamase.<sup>11</sup> This increased potency, resistance and sta-

bility to enzymatic attack has allowed the spectrum of antibacterial activity to be broadened by systematically varying the side-chain through semi-synthetic modification employing **10**, and screening the products for desired traits.<sup>10</sup> Scheme 4 illustrates the ease by which *N*-acylations can be effected; Batchelor *et al.*<sup>11</sup> provided **9** and **11** with excess acid chlorides but they are hydrolyzed by  $\beta$ -lactamase.<sup>11</sup> A selection of synthetic analogues obtained from **10** and their properties appear in Table 1.



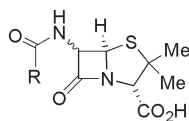
Scheme 4. Acylation of 6-APA.

Methicillin (**12**) was introduced in 1960 at a time when staphylococci had become seriously penicillin resistant.<sup>5</sup> It is effective against certain penicillin G-resistant bacteria<sup>16</sup> but its sensitivity to acid required it to be used subcutaneously rather than orally.<sup>5</sup> By 1961, strains of methicillin-resistant staphylococci had appeared!<sup>17</sup> Oxacillin (**13**), also introduced in the early 1960s<sup>4</sup> is more active against penicillinase than methicillin and it exhibited high levels

of protein binding in cell plasma.<sup>18</sup> It was followed by ampicillin (**14**; 1961), which had short term use against some Gram-negative bacteria until their resistance increased.<sup>4</sup> In 1964, amoxycillin (or amoxicillin; **15**) appeared from use of enantiomerically pure  $\alpha$ -amino-*p*-hydroxyphenylacetic acid (**19**) with **10**.<sup>19,20</sup> All six stereo- and regioisomers of  $\alpha$ -amino(hydroxyphenyl) acetylated **10** were tested, but the (6*R*)-amoxycillin (**15**) was the most effective.<sup>21</sup> It showed oral absorptions three times greater than its *m*-hydroxy regioisomer.<sup>19,20</sup>

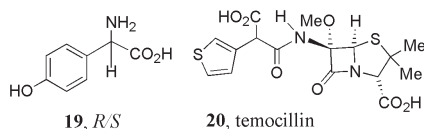
The greatly improved oral absorption of **15** *in vivo* required lower dosages than other penicillins<sup>19,20</sup> and made it the most widely prescribed antibiotic in clinical practice.<sup>12</sup> It is not known why its oral absorption is *ca.* twice that of ampicillin (**14**)<sup>19,20,22</sup> given that the structures differ only in a *p*-hydroxy substituent, but it is not due to differences in stability, in lipid or aqueous solubility, or  $pK_a$  values.<sup>4</sup> Moreover, the two penicillins behave similarly *in vitro*; only *in vivo* is there a difference.<sup>4,23</sup> A further advantage of amoxycillin in its reproducibility of oral absorption with little variation between patients.<sup>4</sup> The discovery of **15** led to worldwide patent disputes in no less than fourteen countries (see below) including NZ, which is usually free from disputes because of its small market. Carbenicillin (**16**), introduced in 1967, was the first  $\beta$ -lactam antibiotic effective against *Pseudomonas aeruginosa*, a Gram-negative bacterium. The 1970 thiophene-containing ana-

Table 1. Different forms of penicillin - see ref. 9.



R	Name	Category	Properties
PhCH <sub>2</sub>	Pen G <b>9</b>	Narrow spectrum penicillinase-sensitive	Poor acid stability $\beta$ -lactamase sensitive
Ph-O-CH <sub>2</sub> -CH <sub>3</sub>	Pen V <b>11</b>		Good acid stability $\beta$ -lactamase sensitive
	Methicillin <b>12</b>	Narrow spectrum penicillinase-resistant	Both penicillinase resistant due to bulky side chains causing misalignment with $\beta$ -lactamase active sites. High resistance to hydrolysis.
	Oxacillin <b>13</b>		
	Ampicillin <b>14</b>	Broad spectrum amino-penicillins	Orally active, good bioavailability. But, penicillinase sensitive. Active against Gram-negative bacteria
	Amoxycillin <b>15</b>		
	Carbenicillin <b>16</b>	Broad spectrum anti-pseudo-monal	Increased penetration into porins. Can be administered intravenously.
	Ticarcillin <b>17</b>		
	Piperacillin <b>18</b>	Extended spectrum	Increased activity against certain bacteria. Can be administered intravenously.

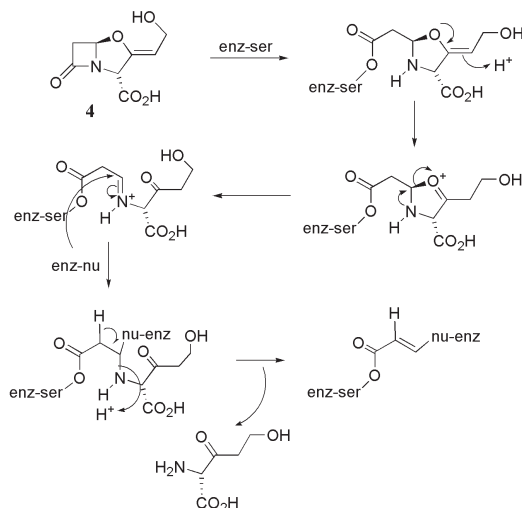
logue, ticarcillin (**17**),<sup>12</sup> was even more active against this bacterium.<sup>4</sup>



As use of penicillins increased, the resistance caused by  $\beta$ -lactamases continued to rise<sup>4,24</sup> demanding new  $\beta$ -lactamase-resistant penicillins – temocillin (**20**) became available in 1981. Stable against many  $\beta$ -lactamases including wide-spectrum derivatives, its clinical use has recently increased.<sup>12</sup>

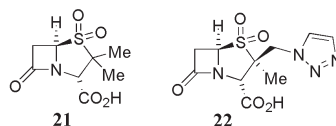
### $\beta$ -Lactamase Inhibitor—Clavulanic Acid (**4**)

In the 1950s, it was suggested that  $\beta$ -lactamase inhibitors could increase the efficacy of penicillins.<sup>10</sup> However, only with the discovery of clavulanic acid (**4**; Scheme 5) by the Beecham Group did a successful example exist.<sup>25</sup> Acid **4** is one of the most important  $\beta$ -lactamase inhibitors and remains in use thirty years after its discovery. It is a  $\beta$ -lactam enol ether from *Streptomyces clavuligerus* and it specifically targets serine-based  $\beta$ -lactamases<sup>10</sup> as a mechanism-based inhibitor. It is a suicide substrate of  $\beta$ -lactamase, thereby protecting the penicillin  $\beta$ -lactam from hydrolysis. The enol ether moiety in **4** weakens the  $\beta$ -lactam carbonyl bond and makes it more prone to attack by the active serine-OH than in penicillin (Scheme 5). Subsequent fragmentation and rearrangement gives an acylated enzyme that is not easily hydrolyzed and is thus deactivated.<sup>10</sup>



Scheme 5. Inactivation of  $\beta$ -lactamases.

In itself, **4** is not a strong enough antibiotic for sole use. Rather it is used in conjunction with other penicillins where it sacrifices itself and allows the penicillin to reach the plasma membrane. Commonly used is **4** with amoxicillin (**15**) – Augmentin<sup>TM</sup> – that has broad spectrum activity, is effective against a wide range of pathogens and makes a significant contribution to the fight against penicillin-resistant bacteria.<sup>26,27</sup> Augmentin<sup>TM</sup> is one of the most dominant anti-bacterial pharmaceuticals on the world market;<sup>28</sup> Timentin<sup>TM</sup>, a combination of ticarcillin (**17**) and potassium clavulanate, is another.<sup>27</sup> Two other comparable  $\beta$ -lactamase inhibitors are sulbactam (**21**) and tazobactam (**22**), which are effective against serine-based  $\beta$ -lactamases.<sup>10</sup>



## The Legal Position of Penicillins in NZ

### A Short History

As mentioned earlier, Florey and Chain's group did not patent their pioneering penicillin-related work<sup>5</sup> but, in 1941, Chain indicated that their penicillin isolation should be patented with any accrued benefits put to further research.<sup>29</sup> Other members of the group, including Florey, regarded profiting from discoveries as unethical, a view common to academia in that era; patenting rather than publishing was looked upon unkindly.<sup>3,5</sup> This was the case when Moyer, a US collaborator with Florey, later tried to patent his developments; animosity remained between the associates for years.<sup>3</sup>

It could be that the Oxford work would have failed patent criteria as the 1941 *Lancet*<sup>30</sup> publication equated to public disclosure thereby removing novelty from the discovery.<sup>5</sup> Moreover, patents for compounds alone were not granted in most countries in 1941,<sup>31</sup> and the processes of manufacture and extraction were not new.<sup>5</sup> Pharmaceutical protection itself began in the UK in 1950 but not until 1955 in NZ.<sup>31</sup>

By 1955, however, Florey's position had changed and he much regretted having no patent for the penicillin extraction process.<sup>5</sup> This was not for personal reasons but because of the Anglo-American fight over penicillin ownership that the lack of a patent caused; some accused the US of stealing penicillin from Britain. When the US joined WWII in 1941, British researchers freely shared their penicillin results with the allies who subsequently transferred the research to the commercial interests of Merck, Squibb and Pfizer.<sup>5</sup> Penicillin was then mass produced by these companies using a *deep culture* process that was patented.<sup>3</sup> British producers used this (included the Ministry of Supply who had manufactured during the war) and a formal licence fee and royalties were expected.<sup>5</sup> An inquiry by the US Carnegie Institution found that no British firms had actually paid royalties but they had been charged for the know-how of the deep culture process.<sup>5</sup>

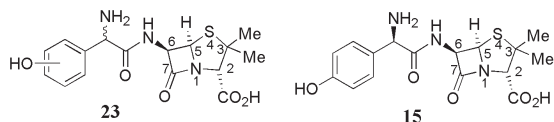
In today's world patenting by academia is common,<sup>32</sup> as evidenced by the approach taken with the anti-bacterial cephalosporins (ring-fused  $\beta$ -lactams, not dealt with here), discovered in the mid-1950s in another Oxford-led project. The patents for these [under the 1949 Patents Act (UK) that provided patents for substances] had provided the National Research Development Corporation, on behalf of Oxford University, substantially over £100 M by the late 1970s.<sup>5</sup>

### Some of the Beecham Penicillin Patents

As well as the original patents for the isolation of **10**<sup>33</sup> and its acylation,<sup>34</sup> Beecham have been diligent and expedient in protecting the spin-off inventions and synthetic derivatives from **10**. A simple search under the Intellectual Property of NZ (IPONZ) for *penicillin* and *Beecham* provides eighteen different patents.<sup>29</sup>

A patent that covered an extensive class of  $\alpha$ -amino acid-derived penicillins comprising various aminoacyl substituted **10** (*the amino patent*) was registered in 1959.<sup>35</sup> Because many  $\alpha$ -amino acids are chiral, the patent included the optically active (*R/S*) forms as well as the racemic mixture. A *patent of addition*<sup>36</sup> was made four years later for  $\alpha$ -amino(phenyl)penicillin, which was produced from racemic  $\alpha$ -phenylglycine. Separation of the diastereoisomers led to (*R*)- $\alpha$ -amino- $\alpha$ -phenylpenicillin, which became known as ampicillin (**14**).<sup>37</sup>

In 1962, a further patent of addition was included in the UK<sup>38</sup> (but not NZ) for the preparation of all three regioisomeric phenol derivatives/variants of  $\alpha$ -amino- $\alpha$ -phenylpenicillins (**23**) from the corresponding *o*-, *m*- and *p*-hydroxyphenyl- $\alpha$ -amino acids; three pairs of epimers (diastereoisomers) ensued as a result of using the racemic aminoacids. This patent is known as the OMP patent as it claimed all three epimeric pairs; amoxycillin (**15**) is the (*R*)- $\alpha$ -amino-*p*-hydroxyphenyl isomer. The specification of this patent also divulged results from tests of the (*R*)- and (*S*)- $\alpha$ -amino-*m*- and -*p*-substituted forms in mice using oral and subcutaneous administration. The results showed the compounds to be more active than ampicillin (**14**) against two Gram-negative bacteria, with the *m*-isomers the most potent.



In 1969, Beecham filed for a patent for amoxycillin (**15**) in NZ.<sup>21</sup> It was referred to in the specification as *a development of our [Beecham's] British patent No 978178* (the OMP patent). To form the pure (*R*)- $\alpha$ -amino epimer, **15** was made from enantiomerically pure  $\alpha$ -amino-*p*-hydroxyphenylacetic acid and 6-APA (**10**; cf. Scheme 4).

Beecham's subsequent discoveries on the use of naturally occurring  $\beta$ -lactamase inhibitors in conjunction with the semi-synthetic derivatives of penicillin have also been attentively patented. In 1984, a combination of **15** with **4** was introduced and Beecham gained multiple NZ patents covering different processes for the preparation of **4**, its salts, and its use with penicillins, such as amoxycillin. Beecham subsequently patented<sup>39</sup> different compositions of amoxycillin with clavulanic acid (**4**) and has continued to patent methods of producing salts of acid **4**; the IPONZ database lists twenty different patents for Beecham and clavulanic acid.<sup>29</sup> Of all the Beecham penicillin-related patents, the most controversial in NZ is that for amoxycillin.

### The Amoxycillin Case

The Bristol-Myers Company was not pleased with the world-wide amoxycillin applications that extended Beecham's property rights for the compound. In 1969, the NZ amoxycillin patent was disputed on the grounds of novelty and obviousness (lack of inventive step) because of the OMP patent filed in the UK in 1962 and subsequently published in NZ. The UK OMP patent ran from 1962–1976 and the amoxycillin patent from 1968–1982, thus extending protection by six years. OMP was not

patented in NZ but amoxycillin was covered, to a point, by the 1959 amino patent (1959–1973 protection). The amoxycillin patent in suit would extend protection by ten years to 1983.

By the time the case reached Justice Cooke<sup>40</sup> (NZ Court of Appeal) corresponding disputes had been heard in thirteen other jurisdictions, but only in NZ and Australia was the protection that Beecham sought extended beyond oral use.<sup>20</sup> The claim was for amoxycillin itself and not just its oral use. This fact did not prevent Justice Cooke from finding that there was novelty and that the invention was not obvious; nor did the appearance of amoxycillin in the OMP patent interfere. However, because the inventive step was *found to lie in the exceptional oral absorption of amoxycillin*, the scope of the patent was required to be limited as such.

**Novelty (prior publication)**—Under the Patents Act 1953,<sup>41</sup> patent applications can be opposed if the claims have been published previously. Bristol-Myers argued that the OMP patent was prior publication of amoxycillin. The issue was whether it published amoxycillin *so far as claimed in any claim of the complete specification*.<sup>20</sup> The OMP patent clearly included amoxycillin, as it covered both *R/S*- $\alpha$ -amino epimers of all three (*o*-, *m*-, *p*-hydroxyphenyl) regioisomers of  $\alpha$ -amino(hydroxyphenyl)penicillin (**23**). Furthermore, the OMP patent stated that the isomers could be prepared and isolated according to the methods described in the amino patent, although it did not give a full and explicit method for preparing the (*R*)- $\alpha$ -amino-*p*-hydroxy isomer in its optically pure form. Specifically, it failed to disclose how the side-chain acid was initially resolved prior to reaction with **10**. However, it was agreed by both parties that a normally skilled chemist would be able to do this without any invention, though some trial and error would be required.<sup>20</sup>

In making its decision, the Court of Appeal rejected a literal approach to the prior publication test *preferring* a more direct approach as to whether the invention claimed had been *published* previously in NZ, in relation to semi-synthetic chemical compounds: *If such a compound has not been made before, its properties often cannot be predicted with confidence; and where that is the case [as the Court found] one cannot consider that the invention claimed can fairly or accurately be described as published, even if a skilled chemist would realize that to make the compound by routine means would be practicable. A making of the compound and a discovery of its properties is necessary before the invention has occurred and can be published.*<sup>20</sup> Thus, whether or not the OMP gave explicit instructions as to how to make the (*R*)- $\alpha$ -amino-*p*-hydroxy isomer was not the decisive factor. Rather, novelty was found because the isomeric form had not actually been made and tested before, even though disclosed. If a chemical compound has not been made, it cannot be held to be known or used just because it is predicted as a theoretically possible compound.<sup>20,42</sup>

This conclusion leads to the situation that *there can be no invention in particular penicillins before they have been actually produced, so as to enable their therapeutic*

*characteristics to be ascertained.*<sup>20</sup> Bristol-Myers further contended that Beecham had already made amoxicillin before they applied for the OMP patent as it was one of the isomers in the *p*-hydroxy mixture. This argument was rejected, as the compound had not been separately made or isolated.<sup>20</sup>

Finding novelty in an epimer apart from its existence in a pair of diastereoisomers is somewhat contentious. However, because a pair of diastereoisomers have different chemical and biochemical properties from each other and from their (*R/S*) mixture, the Court of Appeal's finding is understandable and supportable on a scientific level. That the court found that the invention was not obvious is more controversial.

**Non-obviousness**—In addition to novelty, claimed inventions also must be either non-obvious or involve an inventive step. Non-obviousness differs from novelty in that it is qualitative rather than quantitative. The non-obviousness standard is used to distinguish patent-worthy inventions from routine or slight advances to the prior art.<sup>43</sup> If there is no inventive step, relative to that published or used before the priority date of an application, an application can be opposed.<sup>41</sup>

There are several good reasons for the conclusion to the claim that amoxicillin as a compound was obvious, and lacking in any inventive step.<sup>44</sup> Firstly, the (*R*)- $\alpha$ -amino-*p*-hydroxyphenyl isomer was already divulged in the OMP patent. Secondly, its possible clinical use was apparent given that the OMP patent showed that the three epimeric pairs had desirable properties against Gram-negative bacteria, and that *p*- and *m*-hydroxy (*R/S*) mixtures showed greater activities than their predecessor, ampicillin.<sup>20</sup> Thirdly, counsel for Beecham made it clear that they were not contending whether the actual making of amoxicillin involved an inventive step.<sup>20</sup> Fourthly, it is commonly known that a pure isomer is likely more efficient than its racemic mixture, and the OMP patent had made this clear with respect to  $\alpha$ -amino(hydroxyphenyl)penicillin.<sup>20</sup>

The Court of Appeal found that it was obvious to try the (*R*)- $\alpha$ -amino-*p*-isomer in the search for generally better penicillins, and that this isomer had not yet been singularly made and tested. This was supported as both Beecham and Bristol-Myers independently tested it.<sup>20</sup> However, the Court of Appeal came to the conclusion that there was an inventive step because the unexpected higher oral absorption of amoxicillin over ampicillin and the other isomers of  $\alpha$ -amino(hydroxyphenyl)penicillin.<sup>20</sup> The OMP patent had expounded no such finding, nor had it inferred it. The Court stated that:<sup>20</sup>

The search for medical advance is to be encouraged. It can be long, expensive and fruitless. The pursuit of one of a number - perhaps many - obvious lines of research may produce a signal or particularly valuable discovery. In deciding on patentability it would seem to us regrettable, and not in accord with a primary purpose of patent law, to have to rule this out automatically in the name of obviousness. We think that the pursuit of an obvious line of research, in the synthesising and testing of a new chemical compound, may be held to culminate in an invention which is not obvious and does involve an inventive step, if a sufficiently distinctive advantage is discovered. It is a question of degree ...

The finding of non-obviousness in this case is somewhat dubious. It was held that the (*R*)- $\alpha$ -amino-*p*-isomer was obvious to try as a possible anti-bacterial agent and that no new methodology was required to create the isomer. Thus, the finding does not seem to stand on a scientific basis rather than on the end use of the claimed invention. Indeed, the finding of non-obviousness was influenced by amoxicillin being commercially very successful in NZ, which implies that the advantage given by amoxicillin over ampicillin entitles its inventor to protection.<sup>20</sup>

Because patents limit market competition, a founding principle to their grant is that they encourage innovation, which would otherwise not occur.<sup>45</sup> A further justification for the patent system is that it encourages inventors to divulge the information behind their inventions, rather than keeping trade secrets hindering the advance of science and technology.<sup>31</sup> The patent system is not intended to reward work;<sup>46</sup> such a role is ancillary. If the (*R*)- $\alpha$ -amino-*p*-isomer was an obvious compound to try, such that it did not involve much risk, and no new scientific information was obtained (no unknown compound or process was created), the finding of non-obviousness appears to go against the purposes of the patent system,<sup>46</sup> and purely rewards work. Thus, holding non-obviousness cannot be supported either scientifically or by the purposes of the patent system. There seems no good reason why Beecham were given further patent protection for a compound that they already had property rights for in their OMP patent, merely because they discovered properties previously unknown to them. That the properties were unexpected does not make the claimed invention fall into the purposes of the patent system, nor is it a very good or precise legal test.

**The scope of the patent**—A redeeming feature of this case is that the Court narrowed the scope of the claim for the invention. The 1953 Patents Act requires that every complete specification *[s]hall end with a claim or claims defining the scope of the invention claimed.*<sup>20,41</sup> Bristol-Myers argued that the patent claim should be limited to the oral use of amoxicillin - as in other jurisdictions such as the UK, where it had been limited to a pharmaceutical composition designed for oral administration.<sup>20</sup>

It was stated that *what is of direct concern ... is that a patent should not be granted and the public domain not restricted except to the legitimate extent of an invention. To put it tritely, a man should not have a patent for more than he has invented.*<sup>20</sup> The finding was made that it *[w]as artificial to try to define the scope of the invention ... without any linking or reference to the high oral absorbability in man which, in combination with high anti-bacterial activity, is said to give the compound its unique advantage and which ... enables the objection of obviousness and want of inventive step to be answered. Accordingly, ... any patent should be limited to the use of the compound in a composition for oral administration to human beings.*<sup>20</sup>

### **Ownership in Small Variations?**

Pharmaceutical companies commonly attempt to extend their patent rights over essentially the same compounds. This is often done by making small variations to existing drugs, or by creating new composition or dosage claims.

This *evergreening* has been said to occur (rather sceptically) by finely tuned planning before an application is made for the first patent.<sup>47</sup> Accordingly, information is split into multiple patents with applications staggered to lengthen the overall protection term.<sup>47</sup> Whether these variations are justified or not is beyond present scope, but the practice is prevalent with Beecham and their penicillins.

**Amoxicillin/clavulanic acid composites**—Beecham has had multiple patents for clavulanic acid (**4**) and its compositions. The IPONZ website shows four different such patents, one of which is still in force. In 2001, DSM NV sought to have one of these revoked for lack of novelty or for obviousness.<sup>48</sup> The patent was for a different weight ratio of amoxicillin (**15**) to **4** and a means of coating the tablet not previously published; it was held novel and not clearly obvious. DSM NV additionally challenged another **15/4** patent<sup>49</sup> with a different weight ratio that specifically targeted pediatric use. Again, it was found that obviousness had not been made out.

Should such patents be granted? Companies do invest large sums of money to formulate new compositions and usually these are more efficient or target a specific use. However, as patents are not a reward for work or investment, but for new information divulged to society, it is questionable whether the information obtained from new formulations are worthy of patent rights. Scientific research is directed to the discovery of previously unknown information; the presence of some new information behind an incremental invention should not automatically import patentability. Society should bear the costs associated with limited competition only if the information divulged in the patent is worthy and would otherwise not have been disclosed.

Interestingly, the US Federal Circuit is sceptical of strategies that prolong patent protection.<sup>50</sup> Recently, it invalidated a subsequently issued patent based on the parent<sup>51</sup> for Augmentin™ on the grounds of *double patenting*.<sup>52</sup> Augmentin patent protection was to lapse in the US in 2002. However, Beecham attempted to patent (temporarily succeeding) *new found* properties of Augmentin™ that extended protection until 2017. It was alleged that the work in question had been done in the 1970s.<sup>53</sup> In a summary judgement,<sup>54</sup> the Court held that the later application appeared to be a rewording of the previous patent.<sup>52,55</sup> And so Novartis brought an antitrust<sup>56</sup> action against Beecham in 2004 and Beecham agreed to pay \$US 92 M to direct and indirect purchasers, and third-party payers. Augmentin™ had global sales of > \$US 2 billion at that time.<sup>57</sup>

**Ampicillin trihydrate**—Another interesting NZ case was an attempt by Bristol-Myers to patent ampicillin (**14**) trihydrate following the lapse of the Beecham monohydrate patent.<sup>44</sup> Beecham opposed the application arguing that it was not new and obvious. The decision turned on whether ampicillin monohydrate had ever existed. Beecham denied that it had, argued that it was unlikely that they ever had penicillin monohydrate, and that at the time of their ampicillin patent, technology was not available to fully prove this. Evidence showed that the trihydrate was obtained when the method in the original patent was applied

at the time of the dispute. Bristol-Myers was not able to prove that Beecham had ever made ampicillin monohydrate or that the conditions of the experiment had changed to explain why the trihydrate was now formed. The case was decided in Beecham's favour.

Whether ampicillin trihydrate had been previously published or not should not determine novelty. The trihydrate is the most stable form, but the active component is **14** itself. Furthermore, as the trihydrate is the more stable form, were the monohydrate actually made, it would have taken up moisture and transformed into the trihydrate. Controlling the moisture content of the environment to maintain the monohydrate would be impractical. Consequently, the inference that the different content of water could make a new invention is flawed.

### **The Beecham Penicillin Empire**

Beecham's tight grasp on penicillin is not surprising given they owned the patent for 6-APA (**10**) that began the evolution of semi-synthetic penicillins. A flaw of the patent system is that the 20 year protection given to encourage innovation can, in fact, stifle it by preventing other groups from working with the invention and creating spin-offs. It explains why Beecham continues to dominate the penicillin market with new semi-synthetic variants and new dosage forms. Amoxicillin, first patented in NZ in 1969, remains in the patent system. Over this 40 year period, Beecham has had some 23 patents relating to it and they attempted to get the NZ term extended.<sup>58</sup> This was opposed by Pacific Pharmaceuticals Ltd.,<sup>59</sup> but the outcome is not clear as the IPONZ cases were not substantive.<sup>60</sup>

Beecham did extend their original NZ patent for clavulanic acid (**4**) by eight years as represented *lost years* between the initial application and patent approval.<sup>26</sup> In their extension application, the relatively high notional royalty rate of 17.5% was deemed reasonable because of the merit of the invention. The invention was considered an *exceptional case* due its great public benefit and that it was discovered through many difficulties. Equivalent patents were also extended in Australia, South Africa and Ireland.

Augmentin™ was ranked 4<sup>th</sup> in global anti-bacterial sales for 2007,<sup>28</sup> reaping £530 million,<sup>61</sup> even though the individual patents for amoxicillin and clavulanic acid, and the initial composition, have lapsed. The NZ pharmaceutical market is difficult to compare with others because Pharmac's decision *to subsidize or not* has a major impact. However, Augmentin™ remains the only amoxicillin/clavulanic acid composition subsidised by Pharmac,<sup>62</sup> despite generic versions on the global market.

### **Concluding Remarks**

The discovery of penicillin and the nature of its nucleus are among the most important made by mankind.<sup>63</sup> Penicillin-related pharmaceuticals are in daily use and have saved many lives. Determining exactly how they function *in vivo* took time but assisted research into combating  $\beta$ -lactam-resistant bacteria. That much study is still conducted on penicillins measures their importance to society, and their continued patent protection demonstrates

their unremitting monetary value to the pharmaceutical industry.

The empire that Beecham has built over their patent of 6-APA (**10**) is likely a model that others would wish to follow. Fifty years after their original patent, the Group continues to dominate the penicillin-related market and the intellectual property protection for such pharmaceuticals in NZ. Since the initial discoveries of **10** and **4**, it is arguable that no *new* inventions have been made, but that Beecham is riding the waves of its previous ingenuity. We have not sought to resolve whether the aims of patent law are met by allowing patents for such *inventions*, but we suggest that perhaps they are not and that companies (such as Beecham) are gaining patent protection for minor variations that are scientifically routine and obvious.

No absolute conclusion can be drawn, but with the low inventive threshold that currently pertains, Beecham is likely to have patent protection for penicillin-related pharmaceuticals for some time to come. This is particularly true since SmithKline Beecham and Glaxo Wellcome merged in 2000 creating GlaxoSmithKline (SmithKline Beckman and Beecham merged in 1989,<sup>64</sup> and Glaxo and Wellcome in 1995<sup>65</sup>). It is now the largest company in the UK<sup>66</sup> and the largest pharmaceutical company worldwide.<sup>67</sup>

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## Dates of Note

*Stanislaw Cannizzaro* was born on 13 July 1826, while the following day marks the 75<sup>th</sup> anniversary of the death of *Marie Curie* and the 102<sup>nd</sup> of Sir *William Perkin*. 1973 Nobel Laureate in Chemistry Sir *Geoffrey Wilkinson* (with Ernst Fischer) was born on July 14, 1921 and *Emil Fischer* passed away 90 years ago on the 15<sup>th</sup>.

July 15 marks the 140<sup>th</sup> anniversary of patenting margarine in France by *Hippolyte Mège Mouriés*. He won the contest held by Emperor Napoleon III to find a substitute for butter used by the French Navy. His formula included a fatty component that mixed to a pearly lustre and so he named his product after the Greek for pearl - *margaritari*. His margarine was manufactured from tallow and it was not until Boudet patented a process for emulsifying it with skimmed milk and water (1872) that it became sufficiently palatable to be a commercial success.

July 17 is the 182<sup>nd</sup> anniversary of Sir *Frederick (Augustus) Abel's* birth. He, with Sir James Dewar, invented cordite 120 years ago in 1889. The 20<sup>th</sup> is the 40<sup>th</sup> anniversary of Neil Armstrong's first walk on the moon.

*Rosalind Franklin*, who contributed to the discovery of the structure of DNA, was born on July 25, 1920. This day also marks the 50<sup>th</sup> anniversary of the first hovercraft crossing of the English Channel between Calais and Dover by SR.N1. *Raoul Pierre Pictet*, a pioneer of cryogenics, died 80 years ago on July 27; *John Dalton* preceded him some 85 years earlier (1844). *Francis Crick* died 5 years ago on July 28 and *Dorothy Hodgkin* 15 years ago on the 29<sup>th</sup>.

Sir *George Thomas Beilby*, the Scottish industrialist who developed the process for manufacturing potassium cyanide (widely used to extract gold from low-grade ore) died on August 1, 1924. It is also the day 235 years ago (1774) that Joseph Priestley identified a gas which he called *dephlogisticated air* – oxygen.

*Feodor Lynen*, the 1964 Nobel Laureate (with Bloch) in Physiology or Medicine for his research concerning the mechanism and regulation of the cholesterol and fatty acid metabolism, died on August 8, 1979, while Sir *Edward Frankland*, famed for his proposals on the chemical bond and valence, died 110 years ago on Aug. 9. The first use of the radio distress call *SOS* was made by the liner *S.S. Arapahoe* on Aug. 11, 1909.

Sir *Ernst Boris Chain*, the German-born British biochemist who shared the 1945 Nobel Prize for Physiology or Medicine (with Fleming and Florey) for work on penicillin, died 30 years ago on August 12. This day also mark the 13<sup>th</sup> anniversary of NZ becoming the second country to establish a national DNA databank when the enabling Act took effect. August 14 marks the 15<sup>th</sup> anniversary of the death of *Linus Pauling*

*Sune K. Bergstrom*, the Swedish biochemist who shared the 1982 Nobel Prize (with Samuelsson and Vane) for Physiology or Medi-

cine for the isolation, identification, and analysis of prostaglandins and related biologically active substances, died 5 years ago on Aug. 15. *Robert Bunsen* died on Aug 16, 1899. August 18 is the 15<sup>th</sup> anniversary of *Richard Syngé's* death. He was a British biochemist who shared the 1952 Chemistry Nobel Prize (with Martin) for the development of partition chromatography, notably paper chromatography.

*Franz C. Schmelkes* discovered azochloramid (*N1,N2*-dichloro-1,2-diazenedicarboximidamide), which is used to sterilize wounds and burns. He was born 110 years ago on Aug 19, while *Jöns Jacob Berzelius* was born 210 years ago on Aug 20, 1799.

Aug. 27 marks the 150<sup>th</sup> anniversary of the drilling of the first oil well by Colonel *Edwin L. Drake* (in the US near Titusville, Pennsylvania) and 20 years later Aug. 27, 1879, was born *Carl Bosch* (of Haber-Bosch fame). Aug. 30 is the 125<sup>th</sup> anniversary of the birth of *Theodor H.E. Svedberg*, the Swedish chemist who won the 1926 Nobel Prize for Chemistry for his work on colloids. Sir *Ernest Rutherford* was born on August 30, 1871.

The first use of chemotherapy was 100 years ago on Aug 31 by Nobelist *Paul Ehrlich*. Some time before, he had given his assistant, Sahachiro Hata, two organic arsenic compounds to test as a treatment for syphilis caused by *Treponema pallidum*. Hata became the first to discover how to infect rabbits to produce syphilis. After many careful experiments, success was gained with *Preparation 606* (the 606<sup>th</sup> chemical devised by Ehrlich's team). On 31 Aug 1909, Ehrlich watched Hata inject 606 into a rabbit with syphilitic ulcers that were cured within a month. Thus, syphilis was the first disease caused by a microorganism to be cured with a specific drug.

*Paul Vieille*, who invented smokless powder (Poudre B,) was born on Sep. 1, 1854. Austrian *Fritz Preg* pioneered organic microanalysis and received the 1923 Nobel Prize for it; he was born on 3 Sep. 1869. Australian-born British chemist Sir *John Cornforth*, who shared the 1975 Nobel Prize for Chemistry (with Prelog) for his work on the stereochemistry of enzyme-catalyzed reactions, is 92 on Sept 6. *August Kekulé* was born on Sept. 7<sup>th</sup> 1829, 180 years ago. Sept. 10<sup>th</sup> marks the 10<sup>th</sup> anniversary of the death of *Waldo Semon* who invented plasticized PVC in 1926, and 25 years to the day when DNA fingerprinting was discovered (Leicester, England) by *Alec Jeffreys*.

*Thomas Graham* (of Graham's Law fame) died on Sept 14, 1869, the day 50 years ago that the first space probe, Soviet *Luna 2*, struck the moon. The use cocaine as a local anaesthetic to immobilize a patient's eye for surgery was by *Carl Koller* 125 years ago on Sept. 16. His success initiated the modern era of local anesthesia, with cocaine also quickly adopted for nose and throat surgery and for dentistry; Lavoisier observed the generation of O<sub>2</sub> on heating HgO the same day in 1874.