



THE POWER OF COMBINATION DRUGS

COMBINING DIFFERENT DRUGS INTO A SINGLE PILL CAN HAVE ENORMOUS THERAPEUTIC BENEFITS BUT RESEARCH AND DEVELOPMENT IS DIFFICULT AND COSTLY, WRITE **PHILIP STEVENS** AND **JACK ELLIS**

Putting two medicines together to treat a single disease is a cornerstone of modern medicine. The treatment of tuberculosis was transformed in the 1950s when Sir John Crofton devised his 'Edinburgh Method', in which patients were simultaneously dosed with multiple drugs, each with different but complementary mechanisms of action. Taken together, this combination of medicines reduced the chances for drug-resistant strains of tuberculosis bacteria to develop.

In 1965, a team of researchers discovered that a similar approach could be employed to treat children with acute lymphoblastic leukaemia (ALL).

Several sets of random clinical trials showed their method of administering four different drugs in unison worked; after refining the regimens in further trials, ALL became a largely curable disease in children. The same strategy was later used to develop a combination treatment for Hodgkin's and non-Hodgkin's lymphomas.

More recently, the management of HIV infection – which has eluded a cure due to its ability to rapidly mutate – has been revolutionised by combination therapies that can suppress the virus.

■ THERAPEUTIC, COST AND ADHERENCE BENEFITS

Beyond these therapeutic benefits, combination treatments have brought other benefits to patients – particularly when packaged as a single pill or tablet for delivery, otherwise known as a ‘combination product’ or a ‘fixed-dose combination’.

Such products, consisting of two or more active pharmaceutical ingredients (APIs) can give significant benefits to patients.

Fewer pills mean treatment regimens are less complex; as such, patient adherence rates are better for combination products. This is particularly important in the context of treating infectious diseases, where anything less than complete adherence to the treatment programme could result in the disease developing drug-resistant strains. Combination drugs remove the need for patients to remember to take multiple pills every day. This is particularly important for the treatment of infectious diseases that can rapidly evolve and become resistant to treatment – such as malaria, HIV and tuberculosis.

This in turn delivers substantial cost savings to healthcare systems by averting avoidable hospitalisations.

Combination drugs also reduce the administrative costs associated with multiple, separate drugs – such as dispensing costs, insurance co-pays and separate packaging – as well as the number of prescriptions required for a patient.¹

“Combination drugs also reduce the administrative costs associated with multiple, separate drugs”

■ EXTENDING LIFE WITH CANCER

Combination drugs also hold promise for the treatment of non-communicable diseases such as cancer, diabetes and cardiovascular problems. One example is the combination of three ‘checkpoint inhibitor’ immunotherapies for simultaneous use. These checkpoint inhibitors block certain proteins on cells in the human body, thereby disabling cancer’s main defences and enabling the immune system to mount a more powerful attack on tumours.

These immunotherapies have been shown to significantly extend the lives of cancer patients who have been given poor prognoses for

¹ ‘Combination Drugs: Innovation in Pharmacotherapy’, Albert I. Wertheimer, PhD and Alan Morrison, PhD, 2002

survival; however, they are only effective for around a third of patients.

Pfizer is one of a handful of major companies at the forefront of checkpoint inhibitor development. Pfizer believes that combining these drugs will generate rapid improvements in sick patients and extend lives well beyond what is currently possible. “To go from months to years, there is only one path, and that is combination therapies,” says Mikael Dolsten, head of research and development at Pfizer.²

The US company is now in the process of running clinical trials in which it is administering three checkpoint inhibitors to patients at the same time, with early signs suggesting that two of the drugs speed up the body’s response to the third. The vision is to have a single combination drug that will demonstrate marked therapeutic benefits over each of its constituent parts.

■ COMBINATION DRUG R&D IS NOT SIMPLE

Combining existing drugs is a simple idea. But putting them together, determining exactly how they act on disease, their side effects and quantifying any potential risks to patients is not a simple process. It requires scientific insight, high-tech innovation and significant investment in research and clinical trials.

For one thing, the combination of different active ingredients could lead to unexpected results in patients, such as potentially harmful side-effects. Other risk factors include multiple drug-drug interactions in patients on additional courses of medication; loss of therapeutic flexibility, depending on the amount of each active ingredient needed to be effective; and physical design of the combination drug (e.g., a pill that proves too large or difficult for some patients to swallow).³

There are also a number of pharmaceutical and manufacturing challenges that have to be overcome, such as potential chemical incompatibility between the constituent active ingredients.

Drugs cannot therefore just be spliced together and launched on the market. Potential combination drugs must undergo a rigorous process of multi-stage clinical trials in volunteers. The US Food & Drug Administration has its own requirements and a distinct regulatory pathway for the regulatory approval of combination drugs, which requires proof of the synergistic effect of the two drugs.

As with other classes of medicines, the path from lab to patient is complex and time-consuming, but this effort can be well worth it to

“The combination of different active ingredients could lead to unexpected results in patients, such as potentially harmful side-effects”

² ‘Pfizer to trial triple-combination cancer treatment’, Financial Times, May 2016 (<https://www.ft.com/content/c1c2f508-15ee-11e6-b197-a4af20d5575e>)

³ ‘Unique Risks, Benefits, and Challenges of Developing Drug-Drug Combination Products in a Pharmaceutical Industrial Setting’, Nazaneen Pourkavous, 2012

deliver significant benefits to patients.

Take the well-known migraine treatment Treximet, a combination of migraine medicine sumatriptan and non-steroidal anti-inflammatory drug naproxen. A significant number of sumatriptan users complained of ‘rebound headaches’ where their migraine initially disappeared, but returned after a few hours – and often more painfully than previously.

While some doctors advised patients to address the problem by upping their sumatriptan intake, one physician – Dr John Plachetka – identified the ‘rebound headaches’ with a residual inflammation persisting after treatment with sumatriptan.⁴ He came up with the idea of addressing this issue with the simultaneous administration of an anti-inflammatory.

Extensive clinical trials sponsored and carried out by the makers of Treximet, POZEN, Inc. and its licensee GlaxoSmithKline, showed that Dr Plachetka’s combination could provide migraine sufferers with significantly more relief than each of its two components administered separately.⁵

Individually, both sumatriptan and naproxen are widely available in inexpensive, generic forms. GlaxoSmithKline’s marketing of Treximat as a new product, with a higher price tag to match, was met with criticism from some quarters – in spite of the level of investment required to develop and test the combination product for efficacy and safety, and its clear benefits to migraine sufferers.

Several generic manufacturers sought to enter the market with their own versions of Treximet, and challenged POZEN’s patents on the product on the basis that it was ‘obvious’ and therefore did not clear the bar for patentability.

In the end, POZEN’s patents were upheld⁶ by the US courts, including unanimous backing from a panel at the US Federal Circuit, which rejected the challengers’ contention that they were invalid because they covered obvious subject matter; in fact, there was nothing in the prior art – evidence predating an invention that might indicate that it is already known – that suggested combining these two drugs.⁷ The combination of two separate drugs to make Treximet constituted real innovation.

But what of claims that patents on combination products constitute a ‘backdoor’ to lengthening the period of market exclusivity conferred by a patent?

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4 ‘A Response to Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective’, Christopher M Holman, 2016

5 <http://www.treximet.com/Areas/Patient/Contents/pdf/prescribing-information.pdf>

6 <http://www.businesswire.com/news/home/20110808005396/en/Pozen-Patents-Upheld-Treximet-Patent-Litigation>

7 *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1160-65 (Fed. Cir. 2012).

The reality is that patents awarded to combination drugs represent a new patent for a new product. That new patent does nothing to extend the patent term of the individual drugs that form the combination. Generic drugmakers are therefore not blocked from manufacturing and marketing the separate component medicines, so long as those component medicines are off-patent.

■ COMBINATION DRUG PATENTABILITY

Moreover, obtaining a patent on a combination drug is far from being a ‘rubber-stamp’ process for the companies or research organisations that develop them. When determining what is and what is not patentable, major patent offices reject the simple juxtaposition of two known products, unless it can be demonstrated that the combination demonstrates a new non-obvious working relationship.⁸

Further, the European Patent Office requires that technical data be submitted along with a patent application that shows the combination product’s non-obviousness⁹ – and getting that data obviously requires time-consuming and expensive work in the clinic.

Jedd Wolchok is a medical oncologist at Memorial Sloan Kettering Cancer Center in New York City, and at the vanguard of new research into combining immunotherapies with other unrelated drugs to treat cancer. He recalls the hard work that went into developing the first drug combinations that were used with such success against ALL.

“It wasn’t just about pounding drugs together,” he told Nature magazine. “It was about understanding the mechanism and figuring out what should be given when.”¹⁰

Incentivising and nurturing this kind of vital research will be central to meeting current and future healthcare challenges. It is key therefore that patent law reflects this reality.

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⁸ https://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_viiia_2.htm

⁹ <http://www.iptonline.com/articles/public/DYoung&CoLLP.pdf>

¹⁰ <http://www.nature.com/news/cocktails-for-cancer-with-a-measure-of-immunotherapy-1.19745>