

GSK Public policy positions

Incremental Innovation

The Issue

Research literature tends to distinguish between categories of innovation and, in particular, between “breakthrough” and “incremental” innovation. Although sometimes blurred, this distinction can be most readily applied in the pharmaceutical sector where the development of a “first-in-class” medicine, with a new mechanism of action, may be regarded as ‘breakthrough’ innovation. ‘Incremental’ innovation meanwhile can be used to describe both new medicines in an existing class (which have a similar mechanism of action as the first-in-class, but differ in features such as metabolism, adverse effects, dosing schedules and delivery systems) and improvements relating to existing medicines (for example, slow release formulations, new combinations, or new uses/indications).

Launches of new medicines in existing classes, or developments of existing medicines, have led to a perception that the industry is focusing its effort on so-called “me-too” medicines or trivial improvements that provide little or no added advantage over existing therapies, and therefore do not deserve recognition and reward. This is misguided. Crucially, it fails to appreciate the value of such innovations to patients. It also shows a lack of understanding of scientific progress and ignores the fact that most pharmaceutical R&D, like R&D in other sectors, is incremental.

This paper summarises the value of incremental innovation in the healthcare sector for society, makes the case for adequately supporting and rewarding it and argues that if the products of incremental innovation were precluded from the marketplace by restrictive policies, pharmaceutical innovation would be undermined to the detriment of public health.

GSK’s Position

- Incremental innovation provides great value for patients, for healthcare professionals and for healthcare systems.
 - For patients, it offers a range of therapeutic options. The first medicine to market is often not the best possible option for all patients. New medicines in an existing drug class will not be identical. They may differ in their therapeutic profile, metabolism, adverse effects, dosing schedules, delivery systems, improved formulation, pharmacokinetic properties and other features. As such, later medicines may be clinically superior generally or for particular classes of patients.
 - For healthcare professionals, its offers the flexibility to treat the individual needs of diverse patients with more precision while improving patient compliance by, for example, eliminating or reducing adverse drug reactions and side effects.
 - For healthcare systems, it drives increased price competition among manufacturers, thereby generating cost savings. For example, since the introduction of sofosbuvir in 2013, the entry of five new competitors has led to a 30% decrease in the average price of innovative Hepatitis C treatments in France. And since the entry of the first DPP-4 inhibitor for the treatment of diabetes in 2008, 7 innovative competitors have entered the Bulgarian market with DPP-4 based monotherapy or combination therapy products, resulting in a 41% reduction in average treatment price.

Evidence suggests that this kind of competition is rapidly increasing. For example, a 2004 DiMasi and Paquette study found that the period of market exclusivity enjoyed by the first market entrant in a therapeutic class fell from 8.2 years in the 1970s to just 1.8 years in the period from 1995 to 1998, a decrease of 78%.

- Incremental innovation that adds value should be recognised in government pricing policies. A new or improved medicine should be measured and rewarded on the basis of its value in actual therapy instead of a simplistic classification of “breakthrough” versus “me-too”. The concept of value should encompass a range of different criteria reflecting different perspectives on what can be of value - clinical benefits, patient benefits and societal and public health benefits.
- Cost-containment policies that undervalue incremental innovation will discourage research that benefits patients. A failure to price a medicine based on its therapeutic value by dismissing it as “only incremental” may dash the hopes of particular sub-groups of patients with unmet medical needs, reduce competition and significantly decrease the chances for successful and cost-effective disease management on a population level.
- Incremental innovation can support global health initiatives by driving adaptation of medicines for conditions found in developing countries. For example, it can provide for an increase in the shelf-life or heat-stability of a given medicine to ensure effectiveness in diverse environments, or adjust the drug’s delivery mechanism to allow for easier administration by untrained, non-medical personnel.
- It has been suggested that patent protection should not be given to inventions comprising new uses of known compounds, different dosage forms or means of administration. However, incremental innovation resulting in improved products or new uses, while not always as costly as the development of a new chemical entity, (ie. a ‘breakthrough’ invention) is still lengthy, risky and expensive and thus requires incentives.
- The criteria for patentability are clear. Patents must be available for any invention, whether product or process, in any field of technology, provided it is new, involves an inventive step and is capable of industrial application. If an invention meets these criteria, it is entitled to patent protection. If it does not, it is not patentable.
- The value of incremental innovation in the healthcare sector to patients and wider society is such that where an innovation fails to meet technical patenting requirements, alternative incentives should be explored. Options include extending the range of product modifications to which regulatory data protection applies. Similarly, where patents are available but do not give practical protection (as can be the case with ‘second medical use’ patents), other means of delivering reward for the innovation may be needed if therapeutically valuable innovation is not to be inhibited. Options might include changes within prescribing and/or dispensing regimes that support use of a specific medicine for its specific indication.
- The rarity and unpredictability of breakthrough innovation means that incremental progress is inherent to the sustainability of the pharmaceutical industry and helps to safeguard its role in addressing unmet medical need. This is no different from any other industry; no mature industry can survive from income derived from breakthrough innovation alone.

Background

Incremental Innovation and ‘me too’ medicines

Scepticism about the benefits of incremental innovation is particularly pronounced in the context of the pharmaceutical industry. Regulators in a growing number of countries are exhibiting increasing reluctance to fund so-called “me-too” drugs on the grounds that they offer no significant benefits to patients.

However, there is no guarantee that the first medicine to market will be the best. In fact, a first-in-class has rarely remained the optimum response to the treatment of a disease. Some new medicines will be revolutionary breakthroughs in disease therapy; however, others will deliver incremental benefits over existing treatments, in efficacy, improved tolerability or improved mode of administration. There is tremendous individual variation in patient response to, and tolerance of, any particular drug. ‘Me too’ medicines provide doctors with the flexibility to precisely treat the individual needs of diverse patients.

Examples of incremental innovation transforming treatment options within the same drug class include:

- Contraception: Use of the first generation of oral contraceptives in the early 1960s increased the risk for thromboembolic disorders. Subsequent research resulted in the development of new pills within the same drug class with lower doses of estrogen, which dramatically reduced the side effects.
- Hay fever/allergies: First generation antihistamines had anticholinergic effects (such as dry mouth) and also produced driving impairment similar to that produced by alcohol. New antihistamines, such as *Allegra*, retain the activity of earlier compounds but have improved tolerability, reduced side effects, and enhanced safety.

Incremental Innovation and improved versions of Established Products

Over time, great strides have been made in the area of drug delivery systems and dosage forms. These are critical. Beyond the significant therapeutic value of a given drug exists a precarious network of factors affecting the drug's therapeutic impact. It is well known that a drug's rate of absorption plays a significant role in determining its therapeutic value. Fast absorption can cause increased adverse effects and may necessitate more frequent dosing; by contrast, advanced delivery systems can provide molecules with staying power, prolonging their therapeutic effect.

Examples of advances in delivery systems and dosage forms include transdermal delivery, delayed-onset and extended release oral formulations. More specifically:

- Cardiovascular therapy: The adoption of controlled-release formulations of anti-hypertension drugs has resulted in greater efficacy, safety, and compliance.
- Bacterial infections: Modifications of the original version, penicillin G, allowed for greater oral effectiveness, longer half-life, and resistance to inactivation by staph bacteria.
- Type-1 diabetes: Insulin administered through an inhaler has been shown to have a more rapid onset of action than injected insulin.
- Epilepsy: Lamictal (an anticonvulsant) was originally marketed by GSK as oral tablets to be swallowed with a little water to treat epilepsy. Subsequent research led to the development of a chewable/dispersible tablet that simplified use and so enhanced compliance.

Incremental Innovation and new uses for Established Products

Incremental innovation can also result in new uses of existing products. Unexpected new indications may reveal themselves through market use or through deliberate post-marketing research in the existing class. Nearly one-quarter of the therapeutic indications described by the WHO Essential Drug List are treated by medicines originally indicated to treat some other disease or condition. Beta-blockers, for example, currently have more than 20 different uses.

The research required for new indications involves new clinical trials to test the safety and efficacy of the medicine for an additional use, since the optimal dosing and formulation regimes may differ across indications. Follow-on research is often less costly than developing new therapies; however, it is still risky and expensive and companies need incentives in order to undertake the additional expense and risk.

Examples of where incremental innovation has resulted in new, therapeutically valuable, uses of such products include:

- Rheumatoid arthritis: Rituximab was originally approved for the treatment of cancer, but was later found to treat rheumatoid arthritis.
- Colorectal cancer: Bevacizumab was initially approved to treat colorectal cancer and has since been shown to be effective against certain lung cancers, breast cancer, and possibly kidney cancer.
- Crohn's disease: Infliximab was initially approved for the treatment of rheumatoid arthritis, but was then found to treat Crohn's disease.
- Psoriasis: Etanercept was originally approved for the treatment of rheumatoid arthritis, but was then found to treat psoriasis.
- Strokes: Atorvastatin was originally approved as an effective cholesterol-reducing medicine, but has since been shown to prevent strokes.

HIV: A Case Study

The development of treatments for HIV demonstrates the significant impact and value of incremental innovation.

The U.S. Food and Drug Administration (FDA) approved the first antiviral drug zidovudine (ZDV; AZT) developed by Burroughs Wellcome (now GSK) in 1986. AZT is part of a class of drugs formally known as nucleoside analogue reverse transcriptase inhibitors. After 1991, several other nucleoside analogues were added to the anti-HIV arsenal, as was a new class of anti-HIV drugs called the non-nucleoside analogue reverse transcriptase inhibitors which work in similar ways to the nucleoside analogues but which are more quickly activated once inside the bloodstream. Next to be developed was the class of antiviral drugs known as protease inhibitors, which were distinctly different from the reverse transcriptase inhibitors in that they do not seek to prevent infection of a host cell, but rather to prevent an already infected cell from producing more copies of HIV. And more recently, we have seen the development of integrase inhibitors which block the insertion of viral DNA into the DNA of the host CD4 cell, thus preventing the HIV from replicating.

By 2013, there were 6 classes of drugs for HIV treatment and over 25 products had been approved. Each drug in each class has different safety and efficacy profiles and the existence of such a range helps doctors to prescribe the best possible treatment for each, individual patient. The first drug in each class could be regarded as a form of breakthrough innovation. Each class has more than one member; the second and subsequent drug in each class might be regarded as a "me too" product of incremental innovation.

Despite this expansion of drug options, the standard antiviral therapy for HIV-infected individuals between 1986 and 1995 for the most part remained "monotherapy" or treatment with a single drug. These drugs however were proving only partly efficacious, because HIV could quickly develop resistance to any one medication. The expansion of the number of distinct classes of antiviral medications, however, made a shift from monotherapy to combination therapy possible, in which drugs from two or more classes are used simultaneously. This switch to combination therapy (also referred to, in the case of triple therapies, as highly active antiretroviral therapy or 'HAART') has had dramatic effects because, in essence, combination therapy suffocates mutated forms of HIV before they have a chance to flourish. By using more than one drug at a time, combination therapy is able to "pin down" HIV from more than one angle, so that even if one drug fails, another can continue to suppress viral replication.

Since the introduction of the first combination therapy in 1995, about 15 combinations have been approved for HIV treatment. Again, the first of these might be characterised as a breakthrough innovation and the others as incremental innovations.

The history of HIV treatment, evolving from no therapy to monotherapy to combination therapy, is a history of breakthrough and incremental innovation. By giving doctors numerous treatment options and countering resistance to the virus, it has meant that instead of being a death sentence, for millions of people HIV is now a manageable part of their lives.

May 2019