

# INCREMENTAL INNOVATION:

ADAPTING TO PATIENT NEEDS



**IFPMA**



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## List of abbreviations

ACE	angiotensin converting enzyme
API	active pharmaceutical ingredient
DNDi	Drugs for Neglected Diseases initiative
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IFN	interferon
PEG	polyethylene glycol
R&D	research and development
RBV	ribavirin
TRIPS	(Agreement on) Trade Related Aspects of Intellectual Property Rights
WIPO	World Intellectual Property Organization
WTO	World Trade Organization



# Introduction

Innovation is well known to be the keystone of the research-based pharmaceutical industry.<sup>1</sup> Patients benefit from the importance of innovation when they are treated with cutting-edge medicines. While industry analysts often evaluate innovation by examining research and development (R&D) pipelines for promising products, pharmaceutical innovation is much broader than a handful of promising products. Innovation includes the application of knowledge created throughout the R&D process, including research failures – research that never produces a marketed product. Pharmaceutical innovation may thus be described as a spectrum of various research activities, all directed at a common goal of increasing therapeutic efficacy and safety.<sup>2</sup>

Innovation can be classified into three categories: revolutionary, radical, and incremental (Figure 1).<sup>3</sup> Revolutionary innovation is marked by conceptual advances, such as new scientific theories or principles, which form the basis for subsequent research.<sup>4</sup> A new biological or metabolic pathway, for example, can be considered revolutionary. Putting these conceptual advances into practice can produce radical products that set the standard for utilizing an underlying principle. A “first-in-class” medicine (the first medicine of its type) is normally considered a radical product.<sup>5</sup> Incremental innovation can best be described as the process of exploring and improving radical products. Using a first-in-class medicine as a benchmark for quality, safety, and efficacy, subsequent improvements adapt to patients’ needs. In fact, incremental innovation is sometimes referred to as adaptive innovation.

Incremental innovation advances medicines by expanding therapeutic classes, increasing the number of available dosing options, discovering new physiological interactions of known medicines, and improving other properties of existing medicines. Incremental innovation can include reformulating a medicine to encourage children’s compliance with treatment regimens or increasing a medicine’s shelf-life and heat-stability to ensure that the medicine is effective in diverse environments. In this manner, incremental innovation only affects medicines already approved by regulatory bodies because modifications to compounds in an R&D pipeline are naturally subject to numerous rounds of experimentation. This type of incremental innovation only affects medicines already approved by regulatory bodies.

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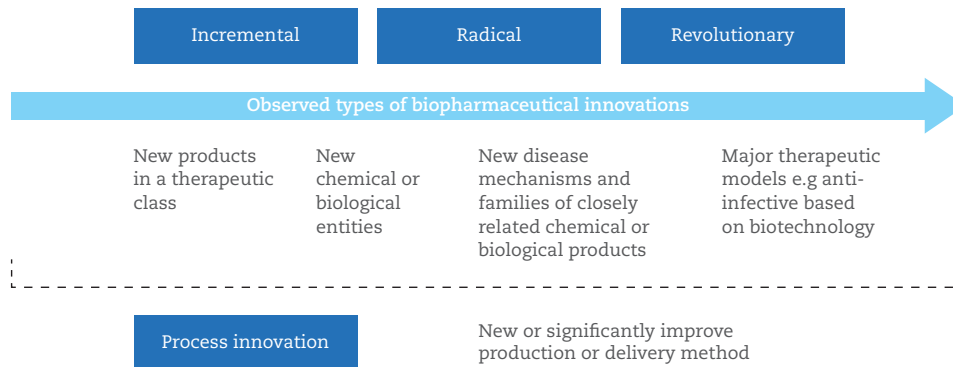
1 IFPMA (2012) *The new frontiers of biopharmaceutical innovation*. Geneva: International Federation of Pharmaceutical Manufacturers and Associations.

2 Charles River Associates (2012) *Policies that encourage innovation in middle-income countries*. Boston, MA: Charles River Associates.

3 *Ibid.*

4 *Ibid.*

5 *Ibid.*

**Figure 1:** Categories of pharmaceutical innovation

Some commentators claim that incremental improvements to existing medicines are trivial and provide minimal medical advancement.<sup>6</sup> They take the view that obtaining intellectual property rights, namely patents, for medicines based on incremental improvements is merely a strategy to delay generic market entry, preventing other firms from entering the market at lower prices. According to these critics, this strategy, often referred to as “evergreening,” is employed by the research-based pharmaceutical industry to prolong the market exclusivity of blockbuster drugs.<sup>7</sup>

This line of criticism loses sight of the fact that patents associated with a medicine based on incremental innovation do not affect the patent term for the existing medicine. In other words, patents relating to a subsequent improvement of an existing medicine will not prolong the patent term of that existing medicine because the two patents are independent of one another.<sup>8</sup> Once the patent exclusivity period of the existing medicine expires, any firm, regardless of the patenting activity related to a subsequent improvement, may begin to produce and market that medicine so long as appropriate regulatory requirements are met. Thereafter, only patient needs will determine whether there is a demand for the subsequent improved medicine.

This brochure illustrates the role of incremental innovation within the pharmaceutical industry by highlighting how incremental improvements to medicines affect healthcare systems and patients. Incremental innovation is marked by improvements in therapeutic quality, safety, and efficacy over existing medicines. In practice, such improvements inherently expand the number of treatment and dosing options available, thereby allowing healthcare providers to better treat diverse patient groups.

6 Correa CM (2011) Pharmaceutical innovation, incremental patenting and compulsory licensing. Research paper 41. Geneva: South Centre.

7 Ibid.

8 For example, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) of the World Trade Organization (WTO) outlines that “the term of [patent] protection...shall not end before the expiration of twenty years...from the filing date.” A subsequent improvement, thus, does not affect the patent term of the original invention.





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ESSIGESTER  
ESSER

Methylether

AETHANOL

Methanol

HEPTAN

100 Einweghandschuhe  
Gants à usage unique  
Wooly-Lite  
Polyma Plus Extra  
M  
weilacare

PARAFILM  
LABORATORY FILM  
For Use in Your Dispense  
Simply Press Through  
Puncture in Center Mark  
PUNCH HERE  
FIBLY



# What is incremental innovation

Incremental innovation is the process of expanding therapeutic classes, increasing the number of available dosing options, discovering new physiological interactions of known medicines, and improving other properties of existing medicines. This process is often dependent on the experiences of healthcare providers and patients' needs. Incremental innovation can include expanding existing therapeutic classes by improving complex molecular structures, reformulating medicines to improve patient administration, or exploring new uses for existing medicines. For example, one way to improve a medicine's therapeutic efficacy profile is to ensure that patients comply with dosing requirements. Thus a once-a-day formulation of a medicine often eases patients' compliance to dosing regimens.

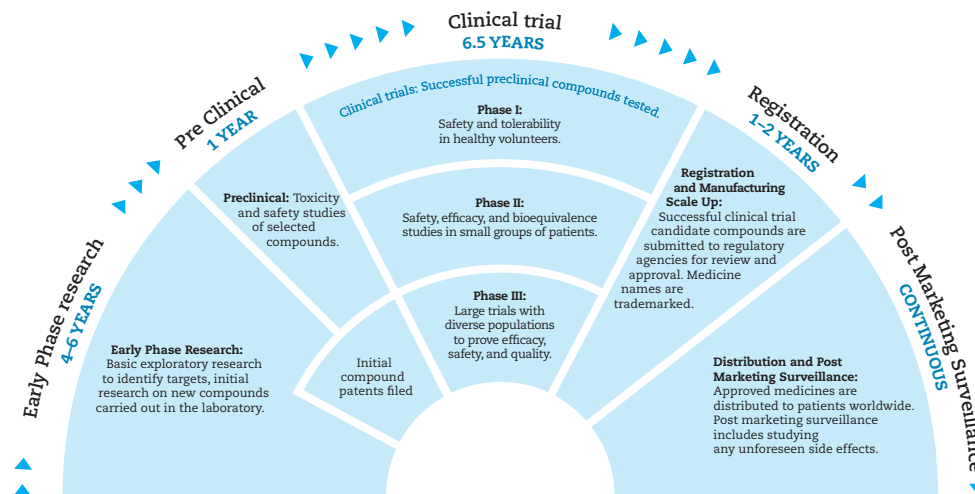
Regardless of the improvement to an existing medicine, incremental innovation may involve many of the same R&D and clinical trial inputs as first-in-class medicines. As the following sections will illustrate, incrementally improved medicines are the product of complex research and development efforts.

## Expanding therapeutic classes

Incremental innovation expands the number of medicines in therapeutic classes and enables researchers to better understand physiological pathways. Identifying and understanding human physiological pathways – biological, metabolic, and disease mechanisms – are arguably the hallmarks of modern pharmaceutical innovation. By exploring these pathways, researchers can compare molecular changes during various stages of disease progression, with the goal of identifying promising medicinal interventions. Once a new pathway is discovered, medicines exploiting it are generally categorized into a "class." The first medicine belonging to a class is normally considered the benchmark for safety, efficacy, and quality.



**Figure 2:** The innovation cycle<sup>9</sup>



Like the contemporary collaborative pharmaceutical innovation model,<sup>10</sup> early-phase research dedicated to exploring human physiological pathways is becoming a joint endeavor between private, public, and academic stakeholders through various “precompetitive” collaborations.<sup>11</sup> Such collaborations can reduce the cost of R&D because identifying a physiological pathway provides the rudimentary knowledge needed to develop a medicine. Once a promising pathway is identified, respective partners can independently “race” to be the first to develop a first-in-class medicine. However, physiological pathways can be exploited in various ways and a first-in-class medicine represents only one of many options (Table 1 and Figure 3).

**Table 1:** Examples of therapeutic classes and medicines in those classes<sup>12</sup>

DISEASE AREA	EXISTING MECHANISMS	NEW MECHANISMS
Diabetes	GLP-1 (albiglutide, dulaglutide, lixisenatide) DPP IV (anagliptin, gemigliptin, teneligliptin, trelagliptin)	SGLT inhibitor (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, tofogliflozin)
Hepatitis C	NS3/4A proteinase inhibitor (asunaprevir, BI 201335, simeprevir)	N5SA inhibitor (daclatasvir)
Melanoma	BRAF kinase inhibitor (dabrafenib)	Oncolytic HSV vector (talimogene laherparepvec)
Ovarian cancer	Folate-targeted drug conjugate (vintafolide)	Kinase inhibitor (nintedanib)
Prostate cancer	Antidrogen (enzalutamine/MDV3100)	Kinase inhibitor (cabozantinib) Radiotherapeutic (radium-223 chloride)

9 IFPMA, The new frontiers of biopharmaceutical innovation, op. cit.

10 Ibid.

11 Ibid.

12 Adapted from IMS Institute for Healthcare Informatics (2012) The global use of medicines: Outlook through 2016. Parsippany, NJ: IMS.

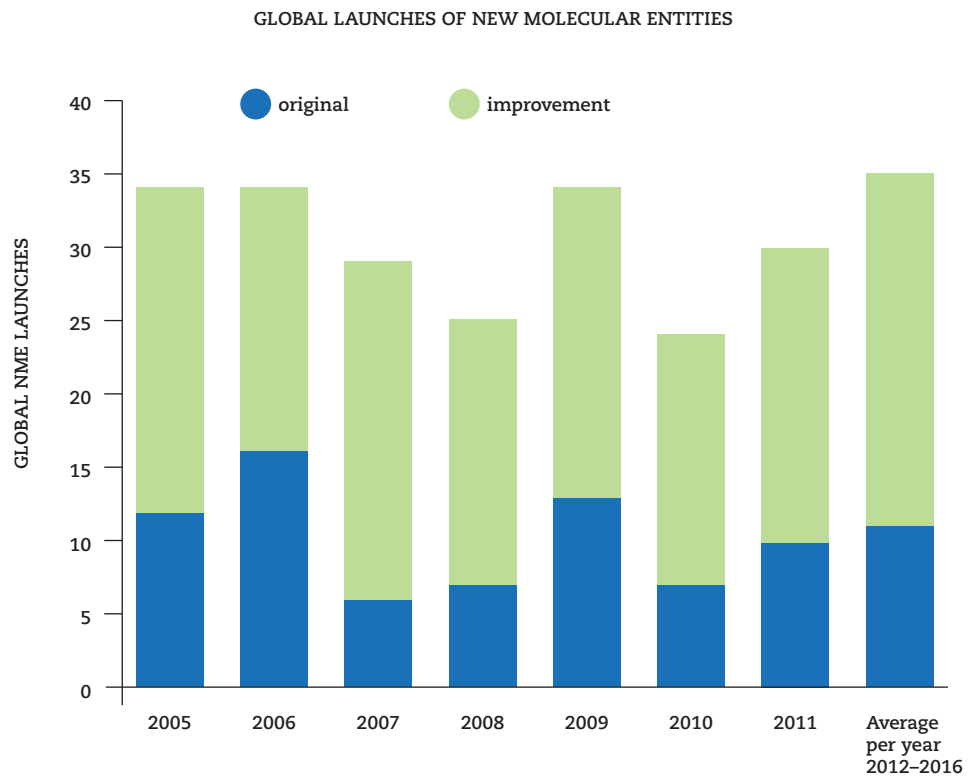
Incremental innovation helps researchers to better understand physiological pathways and to develop medicines with increased specificity. In some circumstances, although a first-in-class medicine has debuted, researchers do not fully understand other possible therapeutic interactions. Research that leads to a subsequent addition to a class may shed light on the underlying mechanism of how the medicine works. For example, captopril was the first medicine to inhibit an enzyme, *angiotensin converting enzyme* or “ACE,” that was found to be linked to congestive heart failure. It was later discovered that captopril was accompanied by unpleasant side effects such as itching and headaches. Subsequent R&D to address the limitations of captopril not only eliminated unwanted effects, but also yielded a completely new understanding of the enzyme involved.<sup>13</sup>

Often, improvements to first-in-class medicines adapt to the experiences and needs of patients and healthcare providers by increasing the number of therapeutic options (see Table 1 for an overview of various medicines in development). After a medicine is approved for sale, companies collect information about their products to ensure safety and quality; this process is usually considered as the last phase of the innovation cycle – “post-marketing surveillance” (Figure 2). Companies work closely with healthcare providers during this phase to determine how different patient groups tolerate medicines.

In addition, once a particular physiological pathway is identified, researchers can use computer-based methods to explore possible modifications to existing medicines to increase efficacy, safety, and quality. This process usually involves “mapping” how a medicine interacts with a certain pathway and further optimizing that interaction. Because some patients respond differently to medicines in a therapeutic class, expanding a class gives healthcare providers the ability to treat a more diverse range of patients.

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13 Patchett AA, Harris E, Tristram EW et al. (1980) A new class of angiotensin-converting enzyme inhibitors. *Nature* 288 (5788): 280–3. doi:10.1038/288280a0.

**Figure 3:** Relative number of first-in-class and incremental products<sup>14</sup>

## Improving dosing options

The therapeutic component of any medicine is called the active pharmaceutical ingredient (API) and is the basic molecular structure that interacts with a physiological pathway to induce a medicinal effect. However, due to intermediate metabolic processes in the human body, APIs are often broken down into other, ineffective compounds. In addition, medicinal efficacy profiles largely depend on patients' compliance to treatment regimens. The efficacy of a medicine can be greatly influenced by the way it is delivered for patient use. Researchers can counteract API degradation by formulating new delivery mechanisms or ease treatment regimens by formulating other dosing options.

<sup>14</sup> Adapted from IMS Institute for Healthcare Informatics (2012) *The global use of medicines: Outlook through 2016*, op. cit.

Dosing options are especially important for complex API structures, such as biotherapeutic medicines and medicines requiring strict regimens. Biotherapeutics often require complex and frequent dosing regimens because the APIs can be absorbed and metabolized quite rapidly. Complicated dosing regimens have been shown to decrease patient compliance and thus therapeutic efficacy.

For example, interferon alfa (IFN $\alpha$ ) is a biotherapeutic treatment for patients with chronic hepatitis C virus infections. The frequent dosing requirements and rapid absorption rate of older IFN $\alpha$  led to fewer than half (38–43%) of patients responding positively to treatment. Researchers subsequently modified the formulation of IFN $\alpha$  to slow the absorption rate, using a process called “pegylation” (see Annex). The new formulation raised response rates to about 54–56% because dosing regimens were drastically simplified, thereby easing patient compliance.<sup>15</sup>

#### **PARTNERING TO DEVELOP NEW FORMULATIONS FOR MALARIA**

Sanofi and the Drugs for Neglected Diseases initiative (DNDi) partnered to develop a new and easily administered combination of two anti-malaria medicines, artesunate and amodiaquine. The project, “ASAQ” (Adapted, Simple, Accessible, Quality), drew on Sanofi’s knowledge and know-how and DNDi’s regional outreach to create a new malaria formulation that reduced dosing regimens for adults from eight tablets a day to only two.

More than 150 million ASAQ treatments have been distributed in over 33 countries. The overall cost of treatment is about USD 1 for adults and USD 0.50 for children.

More information at <http://www.dndi.org/asaq.html>

In order to ease administration of medicines to patients, researchers may develop easier-to-use or longer-lasting dosing options. This requires rethinking the mechanism of administering medicines. Transdermal delivery, delayed-onset, and extended-release formulations have all contributed to patient compliance with treatment regimens. Sometimes, the method of administering a medicine is crucial for optimal efficacy. For example, etonogestrel implants are contraceptives that are implanted into a patient and have a therapeutic effect for a fixed period. This eliminates the need for patients to follow strict regimens, but also requires physicians to insert the implant with precision. In the past, proper insertion was dependent on the skill of the physician, but today an improved applicator ensures the correct insertion angle and pressure.

<sup>15</sup> For more information, see, *infra* Annex 1.

### EASING STRICT TREATMENT REGIMENS FOR TYPE 2 DIABETES

While new classes of medicine have provided additional options for treating type 2 diabetes, this progressive disease often requires treatment with multiple drugs. Combining two medicines into a single dosage form simplifies medicine administration and increases treatment compliance. However, medicine release profiles, chemical compatibility, and dosing requirements can complicate the design of effective combinations.

One such challenge was to combine two treatments for type 2 diabetes, metformin and saxagliptin, while preserving the safety and efficacy profiles of both medicines. Metformin releases slowly, over about 10 hours, while the DPP4 inhibitor saxagliptin needs to be released as quickly as possible, within a few minutes.

The combined formulation encloses saxagliptin in a thin layer of a highly water-soluble polymeric carrier, which surrounds the slow-release metformin tablet. Intermediate layers minimize migration of ingredients from one part of the dosage form to the other, which would lead to reduced shelf life if not controlled. Patients are now offered a single dosage form containing the two medicines, with their very different doses, delivery and stability characteristics, managed in a simple once-a-day drug therapy regimen.

More information at <http://www.kombiglyzexr.com>

## Increasing uses of existing medicines

In addition to expanding therapeutic classes and improving efficacy, safety, and quality profiles, existing medicines and compounds may be useful for addressing conditions beyond their initial indicated uses. Healthcare providers treating patients for one set of conditions may observe therapeutic benefits for seemingly unrelated conditions. However, the exact nature of these observed therapeutic effects may not be fully understood at this stage because clinical trials have not been conducted, or regulatory approval granted, for these indications. New-indication research frequently involves designing clinical trials to test whether the medicine is safe and effective for an additional use. Optimal dosing and formulation regimens will often be different for these other indications.

In some circumstances, a medicinal compound that did not receive regulatory approval for one particular use may prove effective for a different indication. Pharmaceutical R&D failures – compounds that never become marketed products – can provide useful insights for future research. In fact, the failure rates for small-molecule and biotherapeutic products are about 86% and 96% respectively.<sup>16</sup> As classes of medicines utilize new physiological pathways, so future R&D can be expected to uncover new uses for existing compounds.

<sup>16</sup> IFPMA, *The new frontiers of biopharmaceutical innovation* at 14, *op. cit.*



### **ADAPTING AN ANTI-FUNGAL MEDICINE TO TREAT CHAGAS DISEASE**

Eisai and DNDi partnered to further explore the effects of the antifungal medicine ravuconazole against the pathogen that causes Chagas disease. Once administered to patients, ravuconazole naturally metabolizes into other compounds. When such compounds exhibit therapeutic effects they are known as “prodrugs.” During the course of ravuconazole metabolism, researchers have identified a potentially useful prodrug for treating Chagas disease, “E1224.”

Under the terms of the partnership, DNDi is executing clinical trials to determine the safety and efficacy of prodrug E1224. Eisai is supplying the medicine for the clinical trial and providing scientific expertise. Initial data are promising, and E1224 may soon become an effective treatment against Chagas disease.

More information at <http://partnerships.ifpma.org/partnership/dndi-chagas-r-d-collaboration>

# Incremental innovation and intellectual property rights

Because pharmaceutical innovation is the sum of various, and often discrete, activities, incremental innovation can be misconstrued as “trivial.” Despite its important role in expanding therapeutic classes and dosing options, critics claim that incremental innovation may be a strategy to artificially extend exclusivity rights on medicines. According to this view, patenting activity relating to incremental improvements preempts generic versions of first-in-class medicines. However, existing intellectual property systems and regulatory procedures prevent exactly this situation. In fact, the patent term of an improved medicine is wholly independent of the term of the first-in-class medicine. The following section illustrates how intellectual property and regulatory procedures affect families of medicinal products.

## Pharmaceutical innovation and intellectual property

The goal of sound intellectual property regimes is twofold: to promote innovation through securing exclusive rights for a limited time, and to disseminate knowledge to the public through incentives for inventors to disclose their inventions. Intellectual property protection is especially important for the research-based pharmaceutical industry because the R&D process is time-consuming and costly. There is also no guarantee that a particular research stream will become a marketed medicine. In addition, patients’ needs are sometimes better understood only after a first-in-class medicine is introduced. Subsequent experience may prompt researchers to improve upon the originally available medicine, and patenting activity may be revived.

Domestic patent laws and international agreements have set thresholds for determining the level of innovation required to receive patent exclusivity. Most domestic patent laws and regulations are modeled after the *Agreement on Trade Related Aspects of Intellectual Property Rights* (TRIPS) of the World Trade Organization (WTO). Under this agreement, patents are available for “any... products or processes...in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application.”<sup>17</sup> Moreover, TRIPS requires the term of a patent to “not end before the expiration of twenty years” from filing an application.<sup>18</sup>

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<sup>17</sup> TRIPS, Part II, § 5, A. 27, Cl. 1.

<sup>18</sup> TRIPS, Part II, § 5, A. 33.

Although TRIPS does not expressly address incremental innovation, domestic patent laws of some WTO member states do so. For example, the United States considers “any new and useful process, machine, manufacture, or composition of matter, or any new and useful *improvement* thereof”<sup>19</sup> as patent eligible subject matter. Similarly, the European Union Working Group on Pharmaceuticals and Public Health acknowledged that innovation includes “many different options, going from the development of a completely new medicine...to modifications of known pharmaceutical formulations.”<sup>20</sup> To this end, intellectual property rights relating to an improved invention are distinct and separate from the earlier original invention.

Data exclusivity, a form of intellectual property relating to regulatory filings, can be another important mechanism to facilitate improvements of medicines relating to narrow therapeutic areas. Clinical trial data and supporting materials submitted to regulatory authorities as a basis for regulatory approval are a form of intellectual property. Moreover, clinical trials are the costliest phase of R&D and access to this data can be a competitive advantage. They can be protected by giving innovating companies exclusive rights to those data for a defined period, thereby helping those companies recoup a certain amount of investment needed to research and develop improved medicines. Governments, through various policies, can encourage R&D efforts directed at improving medicines for certain diseases, conditions, or unmet healthcare needs.

## The innovation cycle and patenting

The innovation process goes hand in hand with the process of patenting. The earliest R&D stages often take place in universities and research hospitals in partnership with private enterprise. For example, technology and innovation offices of universities can ensure that the patenting process has a central role in these early stages. These early patents form the foundation of further technological innovation. The patent system continues to be an integral part of the process in which therapeutic approaches are developed in the form of new chemical and biological compounds and then modified in creative ways to ensure that delivery mechanisms make them available as medicines to patients.

Medicines are constantly improved. As more information becomes available about disease and patient behavior, this can be used to modify products to ensure that the specific needs of patients are met even more effectively. Such information becomes available early during clinical trials through patient and physician input and continues after a product is approved as part of “post-marketing surveillance” programs. Based on this information, researchers can explore how to meet patients’ needs by investigating new ways to interact with an underlying physiological pathway, reformulating an existing medicine, or proving the efficacy of known medicines for a new indication.

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19 35 U.S.C. § 101(emphasis added). In addition, improvement innovations in the United States must satisfy the legal principles of novelty, obviousness, and utility in order to receive a patent. See, 35 U.S.C. §§ 101–03.

20 Working Group on Pharmaceuticals and Public Health (2000) Pharmaceuticals and public health in the EU: Proposals to the High Level Committee on Health for policies and actions in the framework of the Treaty of Amsterdam [online]. [http://www.ec.europa.eu/health/ph\\_overview/Documents/ke02\\_en.pdf](http://www.ec.europa.eu/health/ph_overview/Documents/ke02_en.pdf).

Patient and physician experiences are especially useful for developing improved medicines. Depending on a number of factors, such as a patient's genetic disposition or geographical location, medicines may be developed to better meet patient needs. Research may be coordinated with local academic and healthcare institutes, and countries might host subsequent clinical trials for improved medicines that address local needs. Successful improvements, in turn, can expand the number of treatment options available to patients and physicians.

Inventors may seek patent rights for improved medicines. Such patents only cover the specific improvements and cannot affect the exclusivity rights to the original medicine. Likewise, the exclusivity period of a first-in-class medicine cannot be extended through such patents. Once that exclusivity period expires, generic manufacturers will be free to market copies of the innovator's medicine. In some countries, health authorities facilitate generic market entry by requiring innovator companies to list patents and expiration dates related to a particular medicine. In this manner, generic manufacturers are made aware of the different patents relating to existing medicines.

# Conclusion

Incremental innovation advances medicines by expanding therapeutic classes, increasing the number of available dosing options, discovering new physiological interactions of known medicines, and improving other properties of existing medicines. Once a new medicine is introduced, critical insights from healthcare providers during the “post-marketing surveillance” phase help researchers to identify unmet patient needs. Incremental innovation ranges from formulation alterations to designing complex molecular structures. However complex an improvement may be, the overall goal of incremental innovation remains the same: to increase the number of treatment options available to patients.



# Annex

## Case Study: Better treatment of hepatitis C through incremental innovation

### CONTEXT

Between 130 million and 170 million people worldwide are chronically infected with the hepatitis C virus (HCV). If treated ineffectively (or left untreated), HCV can lead to the progression of chronic liver disease, cirrhosis, liver failure, hepatocellular carcinoma and, ultimately, death. In Europe, HCV infection is the leading indication for liver transplant and is thought to account for approximately one-third of deaths attributed to cirrhosis and liver cancer. Conventional interferon alfa (IFN $\alpha$ ), including the Roche product Roferon-A<sup>®</sup> and Merck and Co's (MSD) Intron-A<sup>®</sup>, was the treatment of choice in the early 1990s; when used together with ribavirin (RBV), IFN $\alpha$  achieved cure rates of 38–43% of the treated HCV-infected patient population. Clearly, many patients were still in need of effective treatment options. Advances in HCV treatment were made possible by modifying the molecule's pharmacokinetics and mode of action. Today, there are two modified IFNs approved for commercial use: MSD's PegIntron<sup>®</sup> and Roche's PEGASYS<sup>®</sup>. When used in combination with ribavirin, these drugs can achieve overall cure rates of 54–56%.

### CHALLENGES

IFN $\alpha$  is an essential component of the current treatment for chronic hepatitis C. However, its molecular structure presents some challenges for improving response rates:

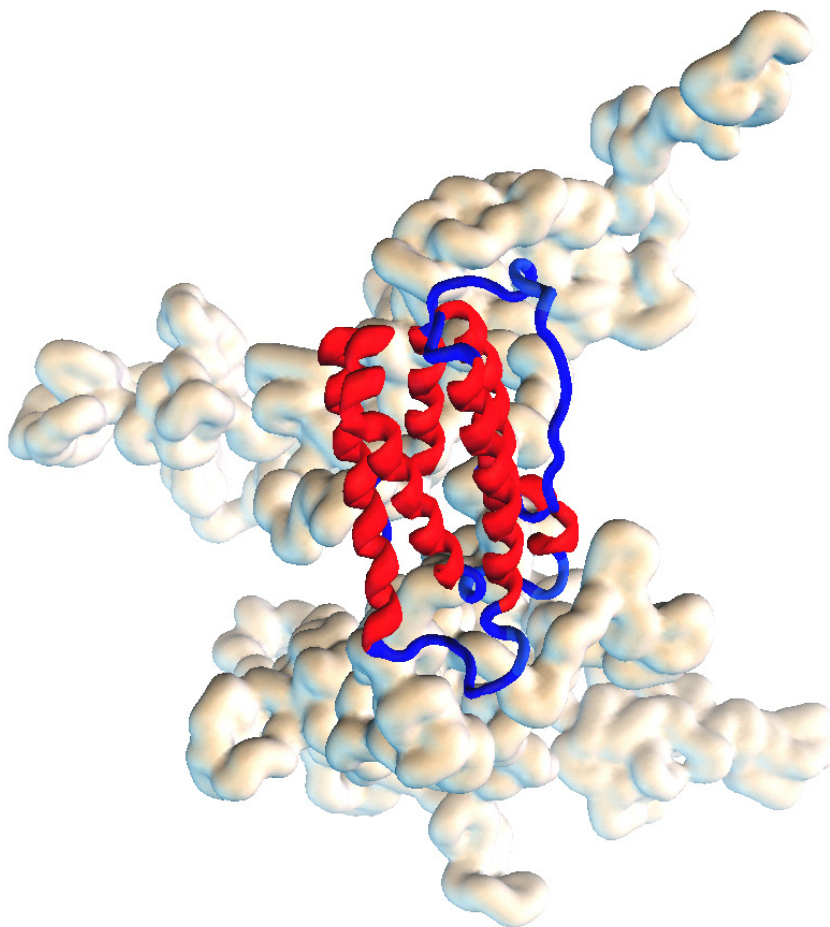
- **Poor delivery of conventional IFN $\alpha$ :** Following subcutaneous administration, IFN $\alpha$  is rapidly absorbed (with an absorption half-life of just 2.3 hours), metabolized and cleared via the kidney. As a result, a complex dosing schedule is required to maintain adequate serum concentrations of the drug and sufficient antiviral activity. In addition, IFN $\alpha$  is widely distributed throughout bodily fluids and tissues, preventing concentration of the drug at the desired target site of the liver.
- **High dosing frequency:** Due to the short duration of action, the recommended dosing frequency for conventional IFN $\alpha$  is 3–7 times weekly. Patients are more likely to miss or omit medications if they are prescribed on such a frequent and complex schedule. Poor adherence to a prescribed treatment makes a cure less likely.

- **Suboptimal efficacy:** As a result of the short absorption half-life of conventional IFN $\alpha$ , it is unable to keep the hepatitis C virus continuously suppressed. Sustained virological response rates as low as 38–43% for the older regimen combining IFN $\alpha$  with ribavirin meant that many patients remained uncured.

#### SOLUTION

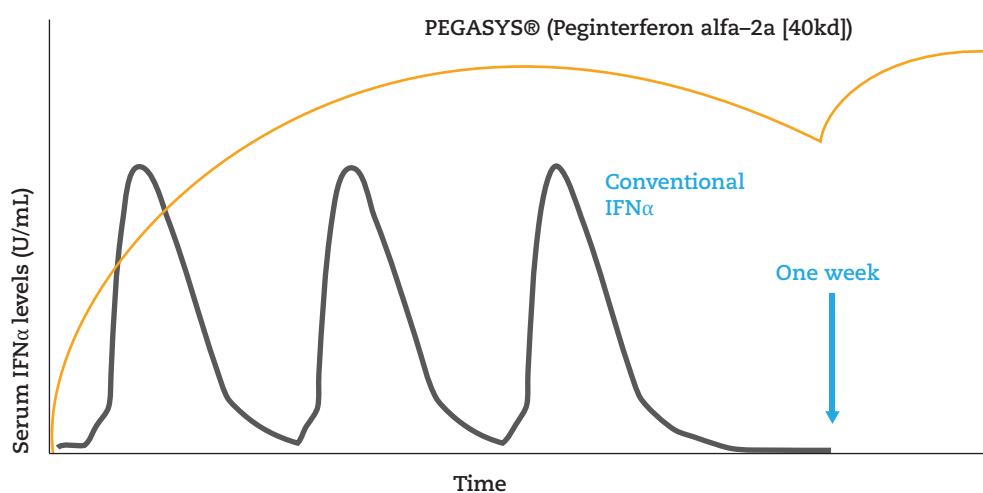
In order to optimize drug delivery and the pharmacological profile of conventional IFN $\alpha$ , the molecule was modified by attaching a polyethylene glycol (PEG) chain, a process called “pegylation.” Pegylation of therapeutic molecules (in particular antiviral agents) has proved to be an effective way to improve their delivery, maintain constant drug concentrations, and ultimately increase their efficacy. Furthermore, the size, geometry, and attachment site of the PEG chain all play a crucial role in determining the pharmacokinetic properties of the modified protein. In 2001, two different PegIFNs were brought to market: PegIntron<sup>®</sup> (MSD), which consists of IFN $\alpha$  linked to linear PEG chains, and PEGASYS<sup>®</sup> (Roche), which is the IFN $\alpha$  protein attached to a branched PEG chain (Figure A.1). Both products show enhanced, though differing, therapeutic characteristics compared to their conventional IFN $\alpha$  predecessors.

**Figure A.1:** High-resolution image of PEGASYS<sup>®</sup>

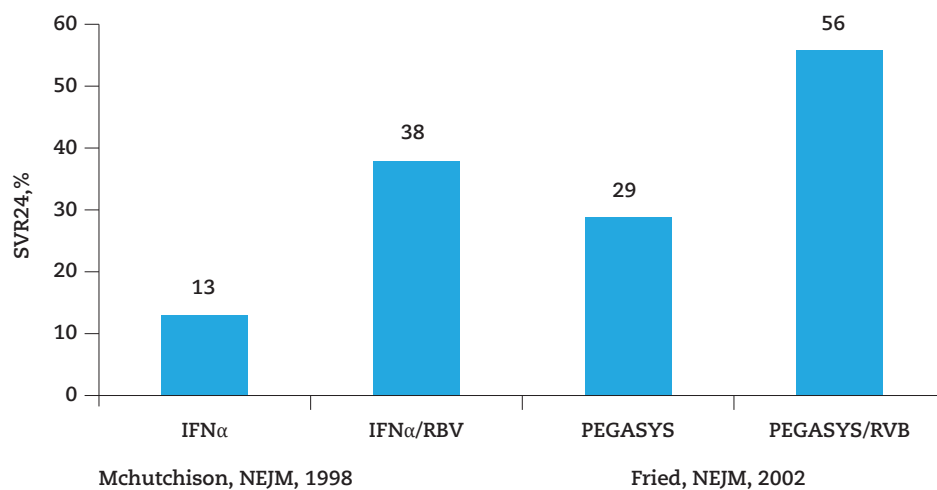


Improved delivery: Compared with conventional IFN $\alpha$ , PEGASYS $^{\circledR}$  is absorbed at a sustained rate and, because of its large molecule size, has a much slower rate of renal clearance. Consequently, constant drug serum concentrations are maintained for longer (Figure A.2), permitting simpler dosing regimens and greater antiviral potency. In addition, PEGASYS $^{\circledR}$  displays a restricted biodistribution with the highest concentrations occurring in the liver, the drug site of action.

**Figure A.2:** Comparison of average plasma concentrations of PEGASYS $^{\circledR}$  and IFN $\alpha$  over time



- **Less complex dosing regimen:** PEGASYS $^{\circledR}$  is a long-acting formulation of IFN that can be injected less often. It is administered once a week as compared with the 3–7 times a week dosing regimen of the conventional IFN $\alpha$ . It is far easier for patients to adhere to this simpler, once-a-week dosing schedule, which translates into greater cure rates.
- **Improved efficacy rates:** Branched pegylation of the IFN $\alpha$  molecule allows the drug to stay in the body longer, resulting in a greater suppression of the hepatitis C virus. Overall, cure rates achieved with PEGASYS $^{\circledR}$ /RBV treatment are significantly superior to those achieved with conventional IFN $\alpha$ /RBV (56% versus 38%)(Figure A.3).

**Figure A.3:** Sustained virological responses (SVR) by treatment regimen

The innovation of attaching the large branched PEG chain to the IFN $\alpha$  protein has provided solutions to pharmacokinetic issues associated with low cure rates for HCV, and has ultimately demonstrated proven success in HCV therapeutics. PEGASYS<sup>®</sup> has led to substantial clinical improvements across a broad range of patient populations, giving even difficult-to-treat patients, such as those with cirrhosis and patients co-infected with the human immunodeficiency virus (HIV), a good chance of a cure.





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