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Research Article

Incremental Innovation and its Value in Health Care System

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Abstract

Incremental Innovation is a peculiar characteristic and a substantial feature of science and pharmaceutical progress. It links several commodity sectors in which assumes particular shades, weights and perspectives. As a group of science driven healthcare professionals in the fields of Italian patient access and regulatory affairs, we managed to unsystematically review and compare Incremental Innovation definitions, challenges, outcomes and examples in major care scenarios. The objective of this review article is to contribute to an enhanced value perception of non-disruptive drugs and technologies, in a field where little improvements in drug's effectiveness, safety and compliance often determined enormous results for patients and welfare state in general. We summarized the reasons why a first-in-class drug rarely remains the optimum choice to treat a disease and evaluated how me-too drugs performed in demanding therapeutic areas such as cardiovascular, nervous system, respiratory and oncology. SIARV believes in in the importance of providing the maximum range of therapeutic options to achieve better outcomes. Payers and Health Authorities' attention on break-through medicine is widely accepted and justified but we are confident to report an increased need and value of improved existing products parallel to a renewed drug's related services. We also discussed how the appraisal of a medicinal product, if based on its "simply-incremental therapeutic value'', can easily deceive patients hopes, reduce competition and significantly decrease the range of valid pharmacological approaches. In our experience, Italian Regulatory Agency, AIFA, heavily focuses in keeping a stable balance between investments and budget re-allocations, exploits biosimilar drugs and uses tailored strategies to reimburse the value of R&D products. In this frame, it is important that professional roles involved in health technology assessment and value based healthcare activities worldwide, will preserve their regard for Incremental Innovation as the recognition of a rightful, patient and citizens oriented commitment.

Keywords: Value of Innovation; Incremental Innovation; Pharmaceutical Progress; Appraisal; Healthcare Outcomes

Abbreviations

NHS: National Healthcare System; COPD: Chronic Obstructive Pulmonary Disease; CNS: Central Nervous System; EMA: European Medicine Agency; EXPH: Expert Panel on effective ways of investing in Health; ISTAT: Italian Institute of Statistics; WHO: World Health Organisation

Introduction

A medicinal product is a technology in constant evolution that is able to satisfy the health needs of the population in a safe and well-established manner. Although modern medicine is constantly waiting for revolutionary therapies, conventional clinical practice and chronicity management in today's healthcare setting are based on

established and continuous therapies evolution. The improvement of certain pharmacological aspects of treatments, such as adherence, combination of different active substances, and integration with ad- hoc medical devices, have led to noteworthy health results in those therapeutic areas still lacking ultimate therapies. However, both budget constraints and the continuous increasing of pharmaceutical spending and health demand ask for a specific definition of the "incremental innovation value" concept, whose foundations lie on small improvements, - i.e. ease of use, effectiveness, and safety – which are link to positive impact both for patients and the systems. Medical products with incremental innovation value include a large variety of modified or combined off-patent products. They provide new pharmaceutical forms, routes of administration, dosages, therapeutic indications, digital solutions, and projects that improve the care experience of patients. When evaluated individually, the incremental value of a new drug could be perceived as marginal resulting in a complex appraisal for regulatory bodies.

In order to measure the impact of these drugs is essential to include them in a broader scenario - i.e. contemplating different therapeutic alternatives - and use a methodology that contemplates different therapeutic alternatives, the entire diagnostic-therapeutic care pathway, the cost-effectiveness ratio, the quality of life, and patients' preferences and priorities in the allocation of resources (payer). In such a complex frame, to establish the incremental value of a new drug, it could be mandatory to use a methodology that contains objective and reproducible assessment criteria. All these aspects lead to significant benefits for the patients (equity of care access), for the National Healthcare Service (economic and financial sustainability), for healthcare professionals (tailored therapies), and for the Industry (R&D investments). In recent years, pharmaceutical companies, together with national bodies and regions, made significant investments defining methodologies to analyse patient pathways in order to capture patient perspectives and outcomes.

In this scenario, this paper focuses on those therapeutic areas, where the public expenditure is significantly high and linked to this topic. Among these therapeutic areas, we select – and limit our study to – the ones where the incremental innovation played and is playing a key role.

Healthcare incremental innovation in numbers

Nowadays, healthcare organizations face critical challenges, in terms of increasing population needs, rising costs, and scarcity of invested resources [1]. The progresses on scientific knowledge, as well as a rise in expertise in the clinical research, determined a technological progress in the context of medicine, medical device, electro-medical equipment, diagnostic-therapeutic procedure, and modern technology, both combined and genomic.

Health "innovation" differs from other contexts in the following main aspects:

- "Nature of the goods"; these fall in the context of care service, and, therefore affect the evaluation of the "innovation goodness". As such, social and ethical aspects, as well as technical-economic factors, should also be taken into account;
- Heterogeneity of the stakeholders involved in the innovation process (e.g. industries, institutions, doctors, patients, politicians, payers, advocacy), which often play contrasting roles;
- Centrality of the patients and the main health professionals (physicians) in the identification of the potential innovation paths, with knowledge sharing in all the steps of the innovation process [2].

Figure 1 shows amounts, type, and affected therapeutic areas of the innovations introduced in Europe in the last decade. The highest number of healthcare innovations are in the oncologic area (35%), followed by chronic diseases, i.e., diabetes (21%) and diseases of the respiratory system (18%). As far as the types of innovation encountered in the different therapeutic areas, there is a clear prevalence of the fixed combinations in chronic disease's context (e.g. diabetes, COPD, HIV). Such an innovation is able to foster treatment adherence. On the other hand, the follow-on type is the most used one in both the oncology (88%) and multiple sclerosis (75%) areas. This is due to a diverse response of patients to different drugs of the same therapeutic class [3].

Figure 1: Number and type of therapeutic innovations by disease area [3].

Incremental vs. disruptive innovation

We now shift the attention from single patients to a more general scenario that takes into consideration the needs of all the stakeholders involved in the decision-making system. In this context, a recent publication by the Expert Panel on effective ways of investing in Health (EXPH) of the European Commission has defined some subcategories of incremental innovation. As reported in table 1, the incremental innovation can be "discontinuous" (also known as "transformative", "revolutionary", or "radical"), or "continuous" (also known as "evolutionary") [4]. The EXPH has also defined the disruptive innovation in the health sector as "a type of innovation which creates new networking opportunities and new organizations on the basis of a new set of values, involving new actors, and which also leads to health improvements and achievement of new precious goals, such as equity and efficiency". Anyway, the disruptive potential of an innovative technology should be framed in the underlying care context. For example, in Europe, where universalistic care models prevail, a disruptive innovation can correspond to either a technology or a drug, which enables a generalized access to therapeutic responses that have previously been accessible only for patients with serious therapeutic needs or patients who do not encounter high access barriers.

The traditional distinction between incremental innovation and disruptive innovation appears, in some cases, schematic and reductive. In fact, it should be considered that disruptive innovation is part of scientific and care contexts which allow to satisfy concrete and mandatory therapeutic needs, even if in an ameliorative way only. While disruptive innovation is able to radically modify old-fashioned systems, on the other hand, incremental innovation is the result of a deep understanding of the therapeutic needs, care preferences, and feedback about care experience of patients. According to the most renowned experts on the evolution of the health systems, the healthcare innovation process is mainly incremental, and is driven by a real information exchange between producers and users. For instance, incremental innovation can be encountered whenever there is an improvement in tolerability, ease of use, effectiveness, adherence improvement and safety of drugs (i.e. modified or combined off-patent products, new pharmaceutical forms, new routes of administration, dosages, new indications, digital solutions). Unlike disruptive innovation, incremental innovation creates continuity in therapies, cares, and reference market, while also improving and advancing an already consolidated system [4].

Incremental	Innovation not impacting on existing market	
	Evolutionary (continuous or dynamic)	Innovations that improves products in an existing market
	Revolutionary (discontinuous or radical)	Unexpected innovations unable to influence existing markets
Disruptive	Innovations that create or expands new or existing markets applying different sets of values, in the end resulting in overcoming existing markets	
	Main characteristics: Better health or clinical outcome Create a new professional culture Serve new groups and/or new products/services Create new players Change old schemes	

Table 1: Incremental vs disruptive innovation – EXPH – Consideration for health and health care in Europe.

The innovation management in the pharmaceutical sector is very complex. For this reason, an objective and shared methodol-

ogy is needed, which allows for evaluating the entire diagnostic-therapeutic care path of a patient, while also favoring NHS economic sustainability. Patients have become more and more central in the evaluation process: identifying patients' therapy preferences constitutes another facet of the evaluation process, which is not implemented yet.

In the "Assessing person-centered therapeutic innovations" white paper [3], an example of value framework is proposed (Figure 2), which lies on two fundamental aspects:

- "Outcome", which is based on the clinic, economic and efficiency measures that are often considered in the evaluation of payers;
- "Experience", which considers the patient journey to achieve the target clinical outcome, in a direct or indirect way, through the experience of the patient herself, or her family or doctors, and the provider support.

Figure 2: Value framework [3].

A further relevant definition in the field of incremental innovation is concerned with the identification of drugs leading to a real improvement with respect to previous treatments used before their marketing. Based on the number of years they reached the market after the First in Class drug (x), they are classified into:

- Fast- followers (0-5 years);
- Differentiators (5-15 years);
- Late–comers (15+ years).

Figure 3: Overview of the innovation pathway in pharmacology.

Figure 3 reports an overview of the pharmacological innovation, and introduces the notion of "overtaking innovation", which is a key concept to analyze the market dynamics of those drugs corresponding to an incremental innovation. The concept of "overtaking innovation" in the pharmacological field refers to the market success that has been achieved by an incremental innovation (likely, a First-follower or a drug that represent an Early Incremental Innovation). This success is typically due to advantages in terms of tolerability and manageability, and guarantees the shares of all the competitors for years. A noteworthy paper, published by the "Drug Discovery Today" journal, states that this phenomenon has repeated several times during the years, also in very different therapeutic areas, maintaining a pattern of common characteristics [4].

The first example of overtaking innovation dates back to 1913, before the penicillin discovery. The therapeutic area at hand is infectious diseases, specifically syphilis. For this pathology, in 1910, salvarsan was marketed all over the world. This drug was very successful, despite its high toxicity. In 1913, salvarsan was replaced

by neosalvarsan, which contained a smaller amount of arsenic, and was more soluble and easier to administer by the clinicians. In 2 years, neosalvarsan achieved the 90% of the market share. The percentage remained unchanged after the marketing of silversalvarsan, 8 years later, which was recognized as more effective, but less manageable for clinicians. The same happened after the introduction of myosalvarsan and the more effective solusalvarsan as well, respectively 13 and 18 years later.

A similar trend was observed in more recent pharmacological areas, even though with different timing and modalities. As an example, in the area of proton pump inhibitor, omeprazole – a drastic innovation of the 1980s – was outclassed by the early follower pantoprazole. The latter had kept dominating the market, despite the introduction of better medicines (e.g. rabeprazole), which were penalized by the fact of being late-comers [5] The most likely hypothesis by the journal authors, supported by data collected from three other pharmacological areas (sulfonamides, beta-blockers, and glucocorticoids) is that the advantages in tolerability and manageability of an early comer or very early fast follower may result in the likelihood of greater success more than pharmacokinetics and pharmacodynamics late improvements.

Unmet medical need: a possible Innovation-driver

The progressive aging of the population, the increase of life expectancy, together with a higher attention on the quality of life by the health systems, led to the development of different medical approaches. More in detail, these approaches are concerned with specific target patients (e.g. gender medicine), or fragile subjects (e.g. pediatric or geriatric), or neglected therapeutic areas such as, rare diseases [6].

In this context, the concept of unmet medical needs has become fundamental to identify the real value of a new drug. European legislation defines an unmet medical need as "a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected" [Art. 4 paragraph 2 - Commission Regulation (EC) No. 507/2006].

In the context of technology innovation, the identification of an unmet medical need becomes particularly important, essentially because:

- It is often an innovation driver;
- It can detect problems related to an established drug technology or treatment, or it can highlight a completely new requirement
- An unmet need can be experienced by a single individual, or a group, or by the entire population, in order to determine its impact on a social-health level [7].

Figure 4: Elements of unmet medical need found in definitions and possible ways to measure them based on the review [6].

Incremental innovation and chronicity

Italy ranks as one of the oldest countries in the world with 23.2% of over 65s on the total population and a negative ratio between new births and deaths [8].

According to ISTAT forecasts, in 2032 27.6% of the total population will be represented by over 65s with a consequent high increase of chronic diseases burden. As evidenced by the 2012-2013 data of PASSI d'Argento, 33% of the sample studied reports at least one chronic disease, 19% two, 8% three, 4% four and 1% five or more [9].

The most frequent pathologies are cardiovascular diseases - CVD (32.8%), chronic respiratory diseases (24.5%), diabetes (20.3%), tumors (12.7%), renal failure (10.1%), stroke (9.9%) and chronic liver disease (6.1%). 13% of the population has 3 or more chronic diseases among those mentioned.

In the aforementioned scenario, innovation in both sanitary and pharmaceutical field is fundamental and shows its magnitude as an unstoppable process. Innovation, also intended as result of small improvements, is well known and accepted by all stakeholders as a substantial characteristic/trend of modern healthcare systems, capable of improving patient experience and outcomes from the roots.

Incremental innovation is particularly vivid in cardiovascular disease CVD area where constant improvements in molecules towed evolution of therapeutic approaches.

Figure 5: Evolution of major cardiovascular therapeutic classes between 1960 and 2000 [10].

Figure 6 shows the evolution of active substances inside β-blockers therapeutic class. This continuous advance underlies both pharmacodynamic and pharmacokinetic improvement, but also a significant outcome amelioration in terms of efficacy, safety and usability [10].

Figure 6: β-blockers class evolution. PE: patent expiry; L: launch [10].

Despite the amount of efficacious therapeutic options developed in order to manage cardiovascular diseases, these pathologies represents the first mortality cause in our country, being responsible of 35.8% of total deaths (32,5% in male and 38,8 in female patients) [11].

As reported in scientific literature, this phenomenon is clearly linked to a bad care pathways management but also to particularly complex therapeutic schemes with consequent risk of errors in posology timings or even worse, leading to therapy discontinuation. WHO indicates low adherence phenomenon as the major cause of hypertension and estimates up to 50% of patients not regularly following therapy.

From this point of view, 'polypills' or fixed dose combinations of already consolidated active substances can be considered as distinct Incremental Innovations. The simplification of the therapy in terms of daily doses but also of treatment burden consequently effects adherence.

"Fixed-dose drug combinations may have advantages over the single medicines given concomitantly, including increased adherence and reduced pill burden. The potential value of fixed-dose

combinations of currently listed essential medicines, with regulatory approval and demonstrated bioavailability for the management of chronic non-communicable diseases, is recognized" [12].

A further therapeutic area whose social burden is progressively reducing due to the uptake of incremental innovations is that of Multiple Sclerosis MS. We reported the main innovations which, alongside to the continuous development of diagnostic power, characterized the evolution of an area as peculiar as heavy for public spending. Keeping in mind MS disease heterogeneity but also the absence of definitive therapeutic solutions, we focused on Disease Modifying drugs as an evolving area capable of driving not only pharmaceutical solutions but also clinical outcomes criteria and pathology awareness.

The urgency to develop pharmacological treatments that would increasingly delay progression of the disease both in physical and cognitive terms traduced in the continuous improvement of drugs. Safety profile optimization, tolerability attention and patient needs consciousness drove pharmaceutical company to search for tailored solutions. Neuroprotection and motor activities preservation became major targets of multiple sclerosis therapeutic approaches.

If in 1950s the only therapeutic target of Multiple Sclerosis treatment was represented by inflammation. Afterwards, the understanding of the role of the immune system together with the development of the most advanced magnetic resonance techniques paved the way for the progressive swich from corticosteroids to interferons. Interferons beta-1b and beta-1a are still today used as first-line treatments in clinical practice. As shown in figure 7. Subsequent understanding of the role of citokines, T cells, cell maturation and movement regulatory pathwayes, enabled the development of specific target solutions such as receptor modulators sphingosine-1-fostafate (fingolimod), pyrimidine synthesis inhibitors (teriflunomide), selective antibodies mediated CD-52 and and CD20 inhibitors (alemtuzumab and ocrelizumab). Since 2010, oral OS formulations also hesited in a better pathology control reducing emotive burden of diasease and likewise the necessity of hospitals visits.

Wanting to give a further example that clarifies the concept of incremental innovation in a slightly different perspective, brolucizumab represents a significant evolution of anti-VEGF drugs for ophthalmic use. Brolucizumab is now the first approved single chain Fv antibody fragment (scFv) that, thanks to its small size, allows to inject a higher number of molecules of active principle in the same volume, distributing rapidly in wet AMD patient's retinal tissues. The superior anatomical outcome has been reached both in terms of resolving the retinal fluid and restoring the retinal morphology to a physiological state, more rapidly than preavious therapeutic alternatives and with a longer effect.

Figure 7: Timeline of major innovations in disease modifying drugs for multiple sclerosis [13].

Conclusion

Cumulative effect of incremental innovation over years is clear especially in poly-treated patients and areas where research is struggling to find and develop disruptive solutions. Scientific progress evolves togheter with patient needs and the amount of incremental solutions helps patients to gain not only time but more importantly a better quality of life.

The implementation of cost containment policies that underestimate the potential of incremental innovation risks to discourage this research for solutions of viable alternatives for patient care. The evaluation and remuneration of a medicinal products based on their "simply-incremental therapeutic value'' can deceive patients hopes, reduce competition and significantly decrease the range of valid pharmacological approaches.

Conflict of Interest

No grants or funding have been received for this study.

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