PHARMACEUTICAL INNOVATION AND SOLVENCY OF THE WELFARE STATE

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The pharmaceutical industry (PI) and the national health system (NHS) have a common interest to promote therapeutic innovation, but conflicting interests in terms of the price and spending on medicines. However, both need each other and finding a balance is in their best interest. This article will go over some of the burning issues concerning the pharmaceutical policy, such as social value, complexity, lifecycle, pace, costs and profitability of R&D+I (research, development and innovation) and the innovation-sustainability dichotomy of the NHS. It will also study the case in Spain and draw up some conclusions.

1. Social value and complexity of pharmaceutical R&D+I

The pharmaceutical industry (PI) is based on science, research and the innovation of products. OECD countries spend 14% of their added value on R&D, just behind the aeronautical and space industries (18%), and electronics and optics (17%), and much more than the average for the entire industry (6%) (OECD, 2017). The subsequent social value is an influx of new medicines that improve our health, allowing us to treat, heal or alleviate illnesses or symptoms. The large industrial economist, Scherer, estimates that "they have provided substantial benefits in terms of prolonging the human life and reducing the burden of diseases" (Scherer 2010) and, in terms of the economy of the development and the economic history, Nobel Deaton states that "they have saved millions of lives [...] and allowed millions of people [...] to continue working, having an income and loving each other..." (Deaton 2015, p. 159). One only has to point out the spectacular recent events in the treatment of hepatitis C, oncology, rare diseases and other spheres.

However, new treatments frequently carry high costs, with five or six-digit figures in euros per patient. Tisagenlecleucel (Kymriah®), the first of the CAR-T therapies, was included in the portfolio of the Spanish NHS in 2018 with a price of €320,000 (although this is a "catalogue" price subject to special risk-sharing agreements). This was a cause for concern, for the sustainability of the NHS and the displacement effect of other possibly more cost-effective treatments. Orphan drugs are another example. They have proven that motivation in R&D works but there are doubts as to whether the implicit order of priorities over other options, according to effectiveness, cost and the populations affected, is the right one.

These concerns lead us to question the allocative efficiency of R&D+I processes and medicines[1]. Is all the research necessary for social welfare being carried out, including in developing countries? Is the industrial R&D model efficient? Does the health value of medicines compensate for their price? To respond to these questions, the innovation must be defined and measured.

1 A more extensive examination of these questions can be seen in Lobo (2019a) and Lobo (2019b), articles that we will touch on here.

2. Innovation in the life cycle of a medicine

Innovation is defined and measured in different ways that are often contradictory. In terms of administrative decisions, an explicit and operational definition would be appropriate. Given that we are dealing with healthcare medicines and technologies, it seems reasonable to focus on the added therapeutic value; that is, on whether it has incremental effects on health and well-being, with regard to the best existing technology. This implies that not all newly marketed medicine is necessarily innovative.

The public decisions that mark the life of a medicine and have an influence on its contribution to health are: the patent, the marketing authorisation, the pricing and the financing or acquisition.

2.1. Patent

The aim of patents is to promote private investment in innovation, allowing the innovative product an exclusive marketing timeframe (monopoly). To obtain this, the requirements are: a) novelty, b) inventive activity and c) industrial application. However, in the case of medicines, the patent is requested and granted a long time before the clinical trials which determine its efficiency and safety. Thus, the patent does not guarantee contribution to health, but simply a molecular structure or a production process that is different to those that already exist. Despite the homogenising international legislation (WIPO or TRIPS of the WTO), the specific definition of innovation is decided by each country and, in practice, there are notable differences.

2.2. Marketing authorisation

In all countries, the marketing of a medicine requires prior administrative authorisation, conditioned to demonstrate efficiency and safety through clinical trials. If the clinical trials compared the new medicine with the best existing alternative, in theory, this would guarantee its innovative character. However, the legislations don't have that much scope and allow for comparison with a placebo, or a demonstration of its non-inferiority to an already available medicine. Thus, the authorised medicine may not imply a therapeutical advantage over the existing ones, although it may add other values, such as a reduction in costs.

2.3. Pricing and financing

If we want to maximise overall health and well-being to determine whether a product is innovative, as well as its therapeutic effectiveness, we must consider the costs and other effects on resources. If the cost makes a treatment unaffordable, the therapeutic innovation is not effective and the product cannot be considered a true innovation but, at the very least, a potential innovation.

In Health Technology Assessment (HTA) it is common practice to measure the therapeutic contribution in terms of the incremental cost-effectiveness ratio, with respect to an appropriate comparator. Effectiveness is measured through a gain in QALYs (quality adjusted life years), a general health index that combines increased survival with a life quality indicator. The value of this index, in relation to an expressive set threshold of willingness to pay, gives us, in theory, a decision criterion, as we know how many additional euros we have to pay for each QALY gained and we can compare with other alternative interventions.

3. The pace of innovation

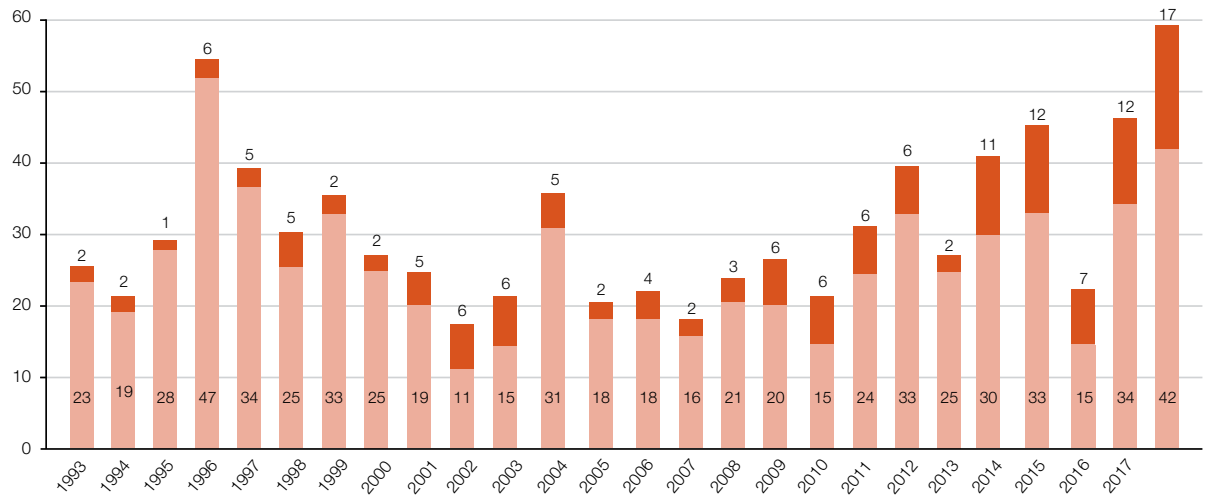
Does innovation oscillate over time or is it stable? One measure in response to this is the one in point 2.2: the newly marketed products approved by the health authority, for example, the American one (FDA) or the European one (EMA). Since 1950, the annual average of "new molecular entities (NMEs)" approved by the FDA rose to 15 in the 1970s and between 25-30 in the 1980s. There was a peak in 1996 followed by a steady decline until approximately 2005 (Kinch et al. 2014). This decline, together with the high increase in the alleged R&D costs brought about the thesis of the decrease in pharmaceutical R&D productivity (figure 1), which led to a demand for more protection and justified high prices.

Today, this thesis seems to be refuted by data that quantify a wave of innovation in biotechnological products and in spheres such as immunology and oncology. Between 2011 and 2018, the FDA approved 309 medicines, with a record of 59 in 2018 and an average of 38 per year, "the greatest sustained productivity in the modern era" (LaMattina 2019). However, it is still too early to state that there has been a Copernican turn.

However, the measure used (NME) is debatable. Not all NMEs constitute an innovation, given that one need only demonstrate a positive risk-benefit balance, but not one that is better than that of products that already exist[2]. Therefore, it doesn't take into account the varying quality. In 2018, the FDA qualified fourteen products as *breakthrough therapy*, 24% of the annual cohort (Mullard, 2019).

2 There are some differences between the US and European law on this topic, which we will not go into here.

Figure 1. New molecular entities and biological products approved by the FDA (1993-2018)



Source: Mullard, 2019.
Note: includes all NMEs and PBAs approved by the Center for Drug Evaluation and Research (CDER) of the FDA. Excludes strictly biological products approved by the Biologics Evaluation and Research (CBER) of the FDA, such as clotting factors and vaccines.

Precisely, in the US and in Europe, there are currently discussions underway regarding the preferential authorisation procedures used in the last decade that try to speed up the availability of new medicines for patients with evaluations and assessments that transfer some of the trials and final decisions on their clinical application to real practice. For some, the controls are less rigorous and favour the marketing of products that are not very innovative. Wieseler et al. (2019) estimate that 75% of medicines introduced into Germany between 2011 and 2017 do not contribute significant therapeutic benefit and that the international R&D+I processes and legislations should be reformed. Is this 25% that has contributed large or considerable benefits a lot or a little? The glass can be considered half empty or half full. On the other hand, innovation that does not focus on products should be taken into account, such as that based on new uses of existing ones (new clinical uses), which would increase their productivity.

4. Profitability of R&D+I

One big question is whether the R&D of medicines provides "adequate" profitability or if it is excessive and society is paying exaggerated business profits. In the sphere of business, the profitability of the PI really stands out. Measured by the after-tax rate of return as a percentage of the capital, it is consistently higher than in other industries. In the period from 1968-2006 it featured 27 times in first or second place in the list of 22-50 sectors ordered by *Fortune* (Scherer 2010, pg. 562). However, the persistence of higher profits may indicate a monopoly problem and has generated many criticisms.

The fact that there have been higher gains has been justified with two arguments. First, that investments in pharmaceutical R&D are considered high risk. This is a crucial question as a higher risk demands more return on capital with the consequent rise in R&D costs and prices. How is the risk measured? It has been noted that the success rate of clinical trials (probability of a product that is beginning to be studied in humans being authorised for marketing) is from 7% to 12% according to the most recent studies, and this has dropped over time. In addition to this, the risk of failure persists in later stages. However, some argue that the investor associates risk with profit stability, more than the technical characteristics of the innovative process. Because the profits of the PI remain stable over time at a high level, the risk would be less acute.

Secondly, it is alleged that the accounting rate of profit has limitations as it doesn't represent the internal business return rate. However, using other more refined variables, Scherer (2010)

concluded that the gross margin of the PI in 1987 was the sixth highest and double that of the industry as a whole, and the Office of Technology Assessment (OTA) of the United States Congress, now defunct, using a risk-adjusted "cash flow recovery rate" (close to the company's internal rate of return), found that the profitability in the PI between 1976 and 1987 was two or three percentage points higher than that of similar industries, which would be enough to encourage a substantial flow of new investment into pharmaceutical innovation. The OECD, in its recent and significant study on innovation and access to medicines (2018), provided calculations with recent data (2002-2016) on the difference between rate of return and cost of capital, which would already take into account the various risk profiles, which reveal that it has been more profitable than other innovative industries (aerospace and defence, information technologies, other health technologies...).

We can also analyse profitability from the point of view of R&D products or projects. To do this, we need to define and be aware of the costs, something which is incredibly important, as they affect the pace of innovation, condition the type of innovative companies and have a decisive influence on the prices of the medicines, which are usually justified by the level of costs mentioned.

But large question marks hover over these justifications. The first is the lack of reliable and transparent data. The studies that are best known and most used by the industry, those of DiMasi, Grabowski and Hansen (the latest from 2016) and that of Mestre-Ferrándiz et al. (2012), cannot be duplicated, as they are based on confidential surveys of pharmaceutical companies[3]. As stated by the Office of Technology Assessment (OTA, 1993) of the United States Congress, which no longer exists, companies "could overestimate costs, without the slightest chance of being discovered", although their information corroborated data from the first studies in this series.

New questions arise from other methodological characteristics of these studies and their serious limitations, which are summarised in table 1. It is extremely important to highlight that they attribute an opportunity cost to the capital invested to reflect the expected return on what investors relinquish when they invest in R&D, instead of an equally risky portfolio of financial assets. The results depend critically on hypotheses surrounding the magnitude of this cost — which is about 50% of the total estimated cost — and other key parameters.

It is not surprising, therefore, that there is much discussion about the real extent of medicines' R&D costs and the acceptability of the studies cited. On this topic see, among others, the reviews of Light and Warburton (2011), as well as the response of DiMasi et al. (2016).

Subsequently, we must handle these average cost estimations for developing a new product with care. The last calculation by DiMasi et al. (2016), with secret data, refers to 2013 and reaches 1,476 million of monetary expenditure, capitalising 2,706 million dollars. However, Prasad and Mailankody (2017), with public and reproducible data, albeit limited, on ten companies and ten cancer medicines, authorised by the FDA between 2006 and 2015, reach a much lower average per product of 793.6 million dollars.

With all of these cost insecurities as baggage, we may ask ourselves about the average profitability per successful product that ends up being marketed, to find out whether the return on investments in R&D is larger or smaller than the rate required to encourage investors. If returns greater than the amount needed to justify costs and risk persist, we would be facing unnecessary power over prices.

Table 1. Limitations of the cost studies

Small samples
Lack of data transparency
Little data from the pre-clinical phases
They critically depend on hypotheses surrounding fundamental parameters: • ratio between pre-clinical costs and total costs • success rate • time-lapse between the initiation and authorisation of the medicine • discount rate
Higher discount rate for public projects
Average variability of costs according to product types
The calculations are before tax

3 There is an interesting review of the studies on costs in R&D, but it ended in 2009 (Morgan et al. 2011). Mestre-Ferrándiz et al. (2012) also review eleven studies in detail.

There are not many analyses that provide an answer to this complex question. The OTA, in its 1993 study, concluded that profitability was positive, as the after-tax returns obtained from each product represented approximately 4.3% of the annual profit of each medicine along the duration of its life cycle. In contrast, a few years later, DiMasi and Grabowski concluded that the profitability of the PI was aligned with other industries and would only be slightly greater than its capital costs. On their part, Prasad and Mailankody (2017) deduced a much higher profitability. A simple comparison: the total costs including capital was 9.1 billion (7%) opposed to a total income of 67 billion in four years, for the ten medicines.

All of these estimates are affected by the limitations of the studies on the aforementioned costs. If the industry provided data or administrations gathered transparent and comprehensive statistics, we could carry out new analyses and come to more solid, valid and credible reproducible conclusions.

In any case, we are faced with three pending questions. The first, in the field of industrial economy, as highlighted by Scherer (2010): how does one explain the combination of high research spending on sales, high gross margins and rates of return on investment that are only slightly higher than the average of all industries? If the expected benefits are regular, why invest in costly and risky projects? The response would be an income achievement model (excess profits) that would explain the dynamic of R&D activities: when faced with profit opportunities, companies compete by increasing their investment in R&D, until the growth of costs dissipates the majority or all of the profit (Scherer 2010). In the process, substantial innovations would be achieved.

The second and third questions involve political economy. If the research costs are high and increasing, and the investments have to be remunerated by fully offsetting the opportunity cost of the capital, the prices that consumers, health insurance companies or public health systems will have to pay must be high enough to cover them. However, it must always be guaranteed that they have some type of relation with the aforementioned costs, in a sector in which very distinct patients and products give companies wide discretion when fixing prices (in unregulated market conditions). To avoid there being deviations from the average and supra-normal profit, they are subsequently based on public interventions currently as widespread as regulations on public funding and prices, and the evaluation of efficiency, which aims to ensure that public resources spent on medicines are justified both by the health benefits they generate and by their cost.

The third question is that, even if the benefits of the PI were justified, in terms of efficiency, there is still the issue of distribution, equity, in relation to people or countries without resources. Price discrimination on an international scale — depending on income levels — can help to distribute research costs between countries. It is also inevitable to seek solutions other than the unregulated market — universal public health insurance (as in Europe) or specific subsidies (as in the US) — to facilitate access to medicines for all who need them.

5. Innovation and sustainability: the Spanish case

In the second half of last century, the Spanish PI had limited innovative capacity. In these conditions, it was logical to prioritise access to medicines with low prices and a relatively low cost, compared to industrial innovation and development. Pharmaceutical expense reduction policies combined price regulation and patents from fairly unprotected processes. Thus, Spanish companies were able to copy the medicines developed by the foreign research industry, as developing a new process for manufacturing a known molecule is less complex and costly than developing a whole new medicine. However, at one point, the pharmaceutical bill accounted for half of public spending on health. Entry into the EU and approval of TRIPS radically changed the situation, forcing a stricter and more favourable product patent regime for research companies, which came into force in 1992.

Product patent put upward pressure on the prices of new medicines which, coupled with the progressive universalisation of the NHS and progress in innovation, generated tensions that made it hard to control pharmaceutical spending, which exploded when the economic crisis of 2008 affected the sector. From 2010-2012, heavy cuts were imposed which were not accompanied, however, by the necessary structural reforms. Since then, there has been constant concern for the financial sustainability of the NHS and for determining the level of innovation in medicines, in order to be able to set priorities when pricing them and admit them in public funding.

In any case, the financial stability of the NHS —some prefer to talk of solvency— is a concept that is vague and extremely subjective, as it depends on expectations and political choices. Without trying to put a lid on the issue, in this article we view sustainability as something related with the capacity of the NHS

to provide the services to which the population is entitled without incurring unwanted indebtedness, which could jeopardise its continuity.

In some cases, a real therapeutic innovation may reduce the costs of the treatment that it replaces but, in general, it tends to increase them, especially if the new treatment is more efficient or safer, or simply more convenient to administer, as the titular company is more likely to achieve higher prices than the competing products.

One instrument for monitoring sustainability are the budgetary impact studies of new high-cost medicines. Various types of risk-sharing agreements have also been put into place. Initially, they were limited to price-volume agreements but, recently, some contracts have been agreed with prices depending on the health outcomes obtained in real clinical practice. However, the systematic application of efficiency assessment is far from a reality.

At the macroeconomic scale, there is an agreement between the NHS and Farmaindustria to limit the increase in pharmaceutical spending to GDP growth. While this agreement puts a limit on spending on medicines, and can be seen to be a guarantee of sustainability, some critics argue that it is a privilege for the sector, as it "shields", in fact, the current level of this spending, which would be considered excessive.

6. Determining the degree of innovation

Since 1977, the General Council of Official Colleges of Pharmacists, in its publication *Panorama Actual del Medicamento (Current Medicine Overview)*, has been including evaluations of new drugs, albeit without regulatory implications on the prices or public funding.

The current legislation (reviewed text of the Law on guarantees and rational use of medicines and healthcare products approved by the Royal Legislative Decree 1/2015, of the 24th of July) includes, as criteria for the inclusion of medicines in the National Health System, the "therapeutic and social value of the medicine taking into account its cost-effectiveness" and the "medicine's level of innovation" (article 92.1, *c* i *f*). It also establishes that the "Inter-Ministerial Commission on Medicine Prices must take cost-effectiveness and budgetary impact analyses into consideration". It is subsequently clear that the evaluation of the level of innovation is required by law, directly and as an implicit element in cost-effectiveness analyses.

The main development in this sense are the Therapeutic Positioning Reports (TPRs), based on an agreement with the Permanent Pharmacy Commission of the Interterritorial Council of the NHS and Law 10/2013 (third additional provision). The basic content is a pharmacological and clinical evaluation of the comparative efficacy of the medicine, compared to the best therapies that are already available and, therefore, of its level of innovation or added therapeutic value.

The European pharmacological and clinical evaluation system for medicines traditionally focussed on the risk-benefit balance, without entering into comparisons that determine their added value. Subsequently, the marketing authorisation does not imply a recommendation for clinical use, as it may not provide advantages over those already available. This is changing and the European Medicines Agency (EMA) and the national authorities are taking steps towards comparative assessment.

Equally, the autonomous communities, responsible for management, decide the effective incorporation of medicines in healthcare practice and establish priorities and usage recommendations, something which requires a comparative assessment between the existing therapeutic options. The aim of TPRs is, precisely, to evaluate the incremental therapeutic benefit in a standardised manner which is shared by all administrations in the NHS.

Naturally, this is relevant for economic assessment and that of effectiveness, because if one of the arms on its scales represents costs, the other represents efficiency or effectiveness, and also for public funding and pricing decisions. Having a good pharmacological-clinical comparative evaluation allows progress to be made in all three directions and, if cost consideration is included, leads to a comprehensive "therapeutic positioning", which is a guide for funding, prices, prescription and use. However, the State Administration still has a long way to go in terms of regulating and establishing operational, objective, systematic, rigorous and transparent guidelines and procedures to evaluate efficiency and, therefore, only then can comprehensive therapeutic positioning be considered. Although the relationship between TPRs and economic evaluation still seems confusing in texts and in the practice of Administration, it appears that progress is being made in this direction.

On their part, the Inter-Ministerial Commission on Medicine Prices (CIMP), in a context of insufficient regulation and trans-

parency, seems to classify price requests into three levels of innovation, with the price differentials with respect to the comparator observed in Table 2.

The government of Pedro Sánchez, since June 2018, to date, has shown the capacity to manage pharmaceutical innovation and to introduce explicit and transparent criteria for evaluation, pricing and greater funding. Two of the star measures have been:

- The creation, in 2019 — eight years after being provided for by Law — of the Advisory Committee for the Funding of Pharmaceutical Provision of the NHS, which has already embarked upon its task (Ministry of Health 2019a).

- The launch of Valtermed, a patient-scale clinical micro-data information system to establish the therapeutic value of medicines (Ministry of Health 2019b).

7. Main conclusions and recommendations

- The flow of new medicines provided by the PI is of important social value, given that they undoubtedly have a positive impact on medical practice and the health of the population.

- The high cost of the new medicines is a concern for the sustainability of the NHS and its opportunity cost in terms of alternative treatments that are possibly more efficient. Orphan drugs could be considered an example of this conflict.

- The thesis of the decline in the productivity of pharmaceutical R&D, which was used to demand more protection and justify high prices, now seems to be refuted by a wave of innovation.

- In Europe and the USA, the flexibility of marketing authorisations is a concern. Reaching agreements on the definition, measurement and priorities of innovation in medicines is urgent.

- The greater profitability of the PI at enterprise level has been justified by the high risk of R&D+I and with quantifications at product level. But these are disputed by the lack of reliable data on R&D costs. Some studies conclude that it would match that of other industries and would only be slightly higher than their capital costs. However, other studies calculate a much greater profitability.

- High profitability, a symptom of market power, and the opacity of costs justify, among other reasons, the state regulation of public funding, prices and the assessment of efficiency.

- New, high-priced medicines pose equity problems. Universal health coverage is the way to put them on track in each country. Countries with fewer resources should benefit from lower prices.

- To ensure the financial sustainability of the public health systems, the governments should steer the definition, quantification and forecasting of innovation, as well as reviewing the current incentive scheme for R&D+I, which is nowadays too focussed on backing patents. In this line, non-monopolistic alternative ways of promoting bio-medical innovation should be explored.

Table 2. Innovation criteria used by the CIMP to determine the price of new medicines

Classification of the level of therapeutic innovation	Description of the therapeutic contribution	Expected improvements	Pricing scale compared to the comparator
Innovations of significant therapeutic interest	New active components that improve the aforementioned benefit/risk ratio, and increase the therapeutic arsenal	Demonstrable improvements in the efficiency of the medicine	0-15%
Medicines qualified as new with peculiarities	Those that are marketed for the first time. They do not always correspond to new molecular entities, although many of them are classified as such	Improvements in safety or in the management of some adverse effects	0-10%
Medicines of significant therapeutic interest	Those with active components that allow the risk/benefit ratio to be improved in relative terms compared to the alternatives that already exist	Improvements in compliance, in the target of patients to be treated or in the way that the medicine is administered	0-5%
Medicines of similar therapeutic utility	Innovations without significant interest. In general, they are funded because they contribute to the sustainability of the NHS	-	-

- In Spain, attempts are being made to juggle access to high-cost medicines with sustainability through price intervention, budgetary impact studies and various types of risk-sharing contracts. An agreement between the NHS and Farmaindustria limits the increase in pharmaceutical spending to GDP growth.

- With Therapeutic Positioning Reports (TPRs) and the new Valtermed tool, progress is being made in comparative assessment that tends to prioritise medicines that add therapeutic benefit.

- In times where there is a wave of innovation and new opportunities, such as those offered by mass data processing, the State must steer the definition and quantification of the NHS' needs and objectives, as well as guiding and promoting public and private investment into R&D+I.

- Anticipating the appearance of innovations and their cost through focusses such as *horizon scanning*, which is already being developed in Spain.

- The State Administration still has a long way to go in terms of regulating and establishing operational, objective, systematic, rigorous and transparent guidelines and procedures in terms of price intervention and the assessment of efficiency. ■

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