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OSSERVATORIOFARMACIORFANI
JOINT VENTURE BY CREA Sanità & OSSERVATORIOMALATTIERARE

ABSTRACT PROCEEDING

FIRST PUBLIC MEETING
OSSERVATORIO FARMACI ORFANI
OSSFOR
(OBSERVATORY FOR ORPHAN DRUGS)

ROME - 16.11.16

The sector of Rare Diseases and Orphan Drugs, after years of inattention, is now at the center of a wave of interest, both from the public and private sectors. This has led to an abundance of analysis and studies, an excessive number of meetings and discussion occasions that are not always supported by true technical expertise. In addition, when data and information were quality-relevant, they rarely were able to change the management of the sector because they did not follow concrete initiatives and proposals. The Rare Disease sector is therefore paying the price of this disorganization with slow evolution and a non-optimal programming of the sector. The consequences are felt by the NHS, patients and companies. Therefore there is the need for an initiative that provides reliable data and information and on this basis favors inter-institutional dialogue aimed at defining policies that are really useful for effective governance in the sector.

Osservatorio Farmaci Orfani OSSFOR (Observatory for Orphans Drugs)

KEY POLICY MESSAGES OF OSSERVATORIO FARMACI ORFANI OSSFOR

1. In-depth knowledge of epidemiology and the needs of rare patients must become a priority of health policies in order to anticipate needs and to govern the system.

2. The efficiency and effectiveness of orphan drugs and other related technologies must be rigorously demonstrated, but patients should have rapid access to therapies to limit the health and human costs of late treatment.

3. Orphan drugs should be evaluated from a pharmaco-economic point of view, like any other drug, but with dedicated methodologies suited to their peculiarities, ensuring an adequate return of investment and sustainability of the system over time.

4. The use of orphan drugs should be optimized to maximize their health return by coordinating therapy within a comprehensive management process, taking into account all the social and health needs of the patient.

5. Regional policies must ensure that healthcare companies can support the economic impact of rare diseases, regardless of the different prevalence at local and regional level.

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OSSERVATORIO FARMACI ORFANI (OBSERVATORY FOR ORPHAN DRUGS) OSSFOR

OSSFOR is the first center of studies and think tank dedicated to the development of innovative policies for the governance and sustainability of the treatment sector for rare diseases. It was born in 2016 by a joint initiative of the research center C.R.E.A. Sanità (Consortium for Research in Economics Applied to Healthcare) and the OMAR Observatory for Rare Disease, a journal, with the aim of filling the gap in knowledge and information in the sector, as well as promoting open and direct confrontation between institutions and key stakeholders.

The vision of OSSFOR is a rare disease management system perfectly integrated into the National Health System and regional ones through dedicated pathways. A system in which the use of therapies can be optimized in order to maximize the return on health by offsetting the important investments needed to support it. A system in which orphan drugs are properly evaluated but which provides for patients to have quick access to therapies thus limiting the health and social costs of late therapy.

OSSFOR's mission is to foster synergy between the institutional, political, academic and business worlds through an open discussion to identify the strategies to be implemented. The basis of this discussion is the economic analysis of the impact of rare diseases and the evaluation of orphan drugs and the information the Observatory is committed to generating with continuity. In particular, OSSFOR intends:

1. Aggregate and systematize existing information on Rare Diseases and Orphan Drugs
2. Conduct own research activities in order to systematically generate analyzes, studies, insights, information, and data, useful to stimulate the technical-political discussion
3. Represent a real think-tank or a place of active discussion among all industry stakeholders
4. Systematically propose organizational solutions and legislative or normative initiatives for the optimal management of the orphan drugs and rare diseases sector

The research will therefore be ample with the aim of providing an organic picture of the industry. The research work will eleborate an annual report with a first section that will be replicated year after year by providing continuity in the provision of data and information, and a second section that will address themes that will be subject to specific annual focus.

The OBSERVATORY operating model will explicitly be inspired by the experience of the most important Anglo-Saxon THINK TANK.

At the beginning of each year, a specific theme to be addressed will be selected on which the Observatory will carry out research activity and will publish a focus within the annual report and, in the process, several positioning documents. The results of this activity will be debated with the institutions by alternating between open and closed roundtables to advance national, regional and national policy.

Closed-door meetings with only institutional decision-makers will have the objective of facilitating an open discussion free from the weight of communication on issues that will be questioned. Roundtables will progressively expand to all industry stakeholders to foster an operational debate around the issues dealt with during "closed-door" meetings and disseminate the results of research conducted during the year.

The ultimate objective of the annual activity of the Observatory is to reach the proposition of organizational solutions and legislative or normative initiatives aimed at optimizing management of the orphan drugs and rare diseases sector.

The Observatory for Ophan Drugs is funded through an annual and unconditional contribution from the largest number of companies involved in the research and development of orphan drugs. The extreme "parcelling" of the lenders is the utmost guarantee of independence and impartiality with respect to the lenders themselves and the institutions.

Reports, analyzes, preparatory documents, organizational and regulatory proposals and any other documents ellaborated and produced by the Observatory will be made public through the publication on www.osservatoriofarmaciorfani.it

ABSTRACT "ECONOMIC ANALYSIS OF THE IMPACT OF RARE DISEASES AND CRITERIA FOR EVALUATION OF ORFANIC DRUGS"

Rare Disease is an important test for health services: both in terms of ethical aspects that imply being able to cope with the needs of a fragile and numerically small population, as well as for the challenge to the organization of assistance, called to respond in a strongly individualized manner.

At the institutional levels all of this is known, starting with the Council of Europe which issued the J Recommendation of 8 June 2009, urging Member States to elaborate and adopt, within their health and social systems, national plans and strategies for rare diseases.
In Italy, the National Rare Disease Plan has been approved only on 16 October, 2014 at the State-Regional Conference , although already since 2001, to allow national and regional planning of measures to protect people suffering from rare diseases and to carry out their surveillance with the approval of the Decree of the Minister of Health 279 the National Network of Rare Diseases was established for the prevention, surveillance, diagnosis and therapy of rare diseases.

The objective of the Plan is to develop an integrated, global and medium-term strategy for rare diseases, centered on the needs of the person and family and defined with the involvement of all stakeholders, taking into account the experiences already gained.
The foregoing, however, does not suppose to have come to the end of the path that, by contrast, has just begun.

Ultimately, it appears obvious that rare disease is a priority public health issue that needs to be tackled by taking decisions based on scientific evidence both on the epidemiological and the clinical side in a "evidence based healthcare" approach.

The starting point can only be the definition of rare disease: as is known a disease "gains the rare qualification" and enters the perimeter of analysis if it has a prevalence of no more than 5 cases per 10,000 inhabitants.

Obviously it is a starting point that opens up other research questions: e.g. how many rare diseases are there actually and how do they distribute by prevalence of their pathologies? How much do they cost? etc ...

These questions are, however, extremely complex and difficult to give a clear and unambiguous answer.

With the above objectives, C.R.E.A. Sanità has devoted both to organizational and cost analyzes within the rare diseases sector.

Through regional and corporate collection of data, it was possible to find that there is no information infrastructure capable of rendering the phenomenon of rare diseases globally intelligible and therefore governable. (Second Report on the Organizational and Management Models of Rare Disease Support Networks, C.R.E.A. Sanità, Federasanità, ANCI, Recordati).

For example, there is a considerable difficulty for healthcare companies to quantify the burden of rare disease assistance: as a proof of this, there is a lack of ability at local level to quantify the number of patients in local healthcare or however, the pertinent cases in of the Centers of reference.
Likewise, more or less missing, is a preferential process for upgrading and granting exemptions for rare diseases, delaying the actual taking charge of the same.

We can observe how the planned and implemented information infrastructure at the regional and local level is in fact more clinical than organizational: although the clinical aspect is a "necessary condition" for every reasoning, without a clear project of taking charge of social-health burden, the mandate of the European recommendation can not be said to be completely met.

Even as regards to the economic and financial aspects, one can observe how the information on the impact of rare disease patients on healthcare budgets is deficient: many local health agencies complain about the difficulty of having detail information, except for some pathologies. In other words, although local health agencies identify the issues related to the costs and funding of rare diseases as extremely important, they do not have the ability to govern the problem, however, lacking knowledge of the specific costs incurred.

An important consequence of this is that the issue of financial risk transfer is not addressed either regionally or locally, implying potential resource shortages to meet the needs expressed by the population with rare diseases.

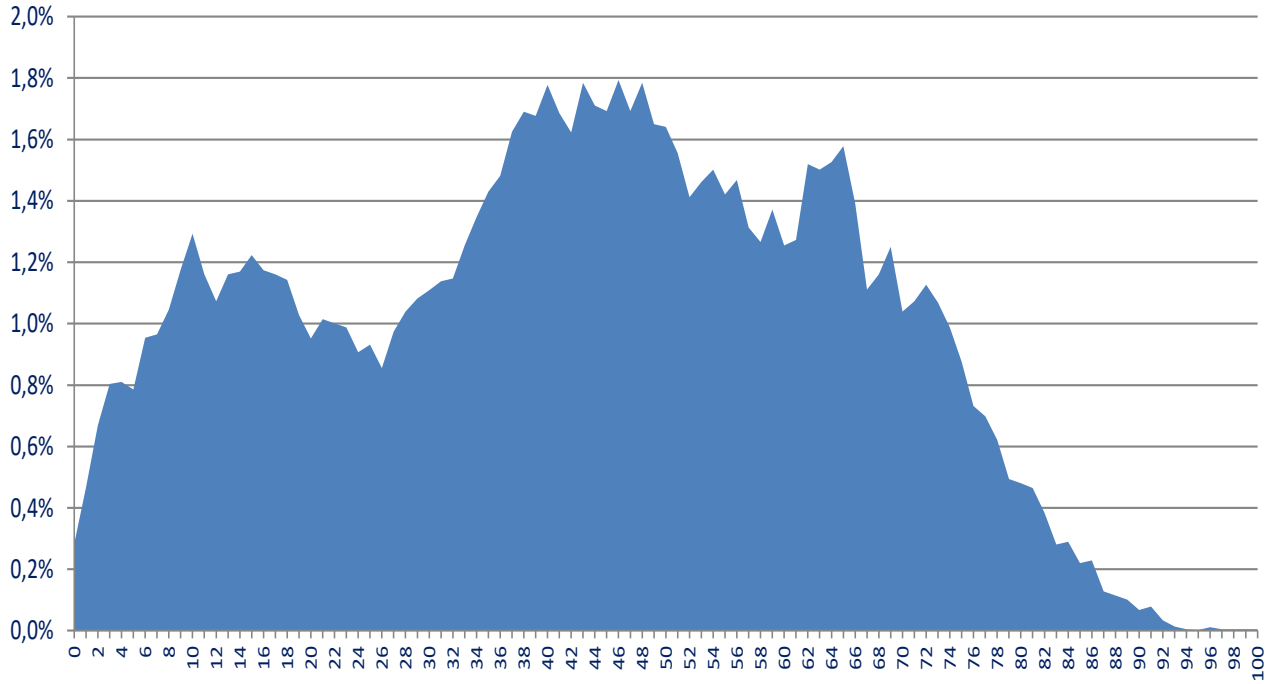
C.R.E.A Sanità then carried out an analysis of the administrative databases of the Lombardy Region, with various objectives including the research, at least in part, of the above mentioned shortcomings.

In practical terms, the first objective was to estimate the consistency of rare disease patients with exemption and their characterization.

An analysis of consumption profiles and the absorption of resources of rare disease patients followed. From these analyzes, a prevalence of rare disease ranged from 0.46%: 0.53% for females and 0.39% for males.

It seems to be important to note that this is underestimated because it does not include rare disease patients who have no exemption code as well as those that are not exempt (e.g. because they have a "stronger" exemption than that for income, or have decided to not ask for it).
By extrapolating data from the Lombardy Region to the Italian population, with the implicit limits of not considering any regional specificity, it can be assumed that rare diseases in Italy are about 271,000.
The age distribution of rare disease patients shows a peak in adolescent age (10-19) where 11.6% of rare diseases are concentrated and a further peak in 40-49 years where 17.2% of MRs are concentrated.

FIGURE 1: DISTRIBUTION FOR RARE DISEASE



By classifying patients in 4 prevalence groups, the first group based on the European ultra-rare pathology definition and the subsequent 3 in arbitrarily selected classes what emerges is the "fractionation" of pathologies and cases exponentially increases with the prevalence decrease: in the class with a prevalence of major pathology we find over 40% of patients with only 8 rare conditions (exemption codes); at the other extreme, that of patients with ultra-rare diseases, little more than 16% of subjects are concentrated, but divides into 228 different rare conditions.

It is evident that organizational complexity in terms of assistance is strongly correlated with diseases with lower prevalence. The prevalence of ultra-rare diseases, specifically, is 0.08%.

TABLE 1: RARE DISEASE DISTRIBUTION FOR PREVALANCE CATEGORY

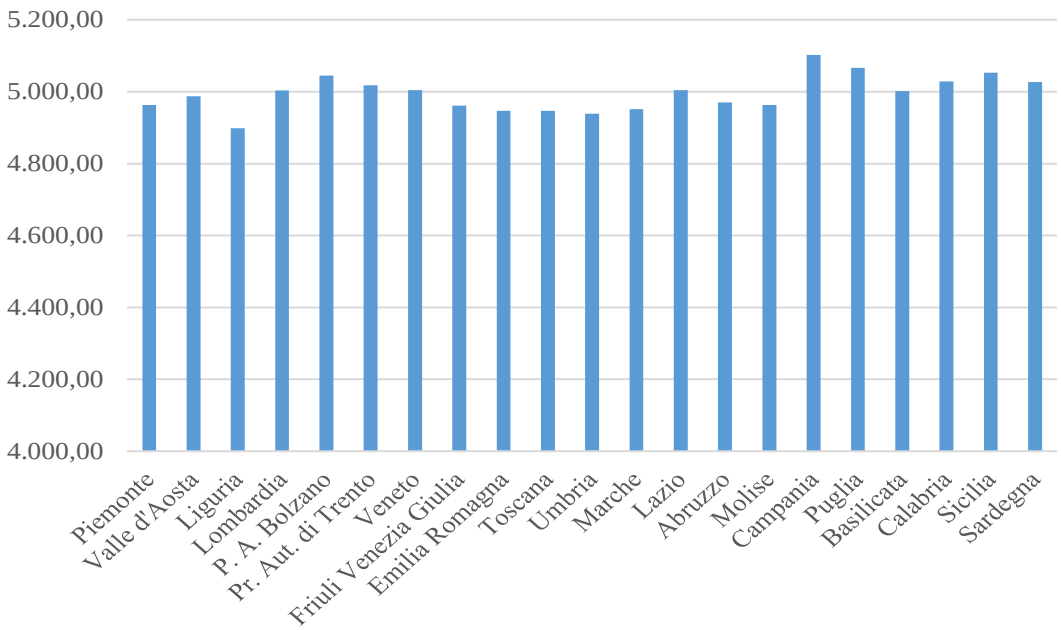
Fascia di prevalenza	Distribuzione % dei casi
1-Minore di 0,002%	16,52
2-Tra 0,002% e 0,005%	21,43
3-Tra 0,005% e 0,01%	20,50
4-Maggiore di 0,01%	41,55
Totale	100,00

Always by extracting data obtained from Lombardy Region databases and taking into account that the economic estimates that will be described do not represent the actual costs incurred (for some items, such as medicines and services from accredited structures, the actually incurred expenditure is available fom the Region, but for others, such as admissions to public facilities, the theoretical tariffs have been used), it is estimated that a rare disease costs to NHS on average € 5,006.26 per year, or € 1.36 billion, at national level, or 1.2% of health spending.

It should be noted that the impact of a rare disease patient on NHS is in fact in line with that of a patient suffering from tumor or neurological disease, and significantly lower than the average of a patient with a transplant or with renal failure or, HIV; the impact that NHS supports for a rare disease patient instead is higher than the average cost of a patient with gastrointestinal diseases, diabetes or respiratory diseases, metabolic endocrine, cardiovascular and ultimately autoimmune (€ 2,177.9). In other words, a rare disease on average absorbs less of resources for a patient than a chronic disease: the average expenditure for a rare disease patient exceeds the average shared costs of € 3,168 (average between consumers and non-consumers), as well as that sustained for patients with at least one chronic disease (€ 3,552.8), closer to that of patients with at least two chronic diseases (€ 4,500.2).

The regional-level estimate shown in Figure 2 has been made to according to varying distribution by population age.
It is noteworthy that rare disease and chronic disease outcomes are similar, showing a U-trend: higher in adolescent age, tend to stabilize in adulthood when the disease is presumably under control, and then reinvigorated after the age of 65, age in which the pathology is accompanied by other problems related to aging.

FIGURE 2: AVERAGE EXPENDITURE FOR RARE DISEASE PER REGION



Obviously, the ultimate goal of rare disease policy is not just to provide patient care, but to "defeat" them, finding more effective therapeutic solutions.

From this point of view, research plays a key role and, in this regard, a fundamental sector is certainly the pharmaceutical and the related regulations for orphan drugs.

With respect to the latter, it should be said that in Italy they are significantly incentivized: in addition to the benefits recognized by international regulation other include specific aspects such as the exemption from payback and the "fast track" for the assessment of reimbursement.

But the benefits recognized for orphan drugs are likely to remain on paper as a result of the economic crisis, generally restricting access to the reimbursement of innovative drugs, especially if at high cost, impacts drugs irrespective of whether they are orphaned or not.

On the price of orphan drugs, however, a proper in-depth study is necessary: if it seems reasonable that their value is recognized on the basis of the incremental efficacy produced, and therefore that their cost-effectiveness is tested, one can not forget that, by definition, they are characterized by small markets, and this strongly affects the return on investment.
In other words, it is evident that the pathology is rarer, the market potential is less, and a return from investment (despite any public research grants that are recognized), demands that the price is adequate: that may imply A cost-effective relationship that is not comparable to that of large-scale drugs.
The cost-effectiveness of orphan drugs, in the health and especially pharmaceutical policy debate, is frequently discussed.

Not least, a recent Picavet (2015) study shows that approved and reimbursed medicines at European level cost QALY about € 40,000, a value that is certainly comparable to that of non-orphan drugs. At the same time, the study cites how the range in drugs considered is just over € 6,000 for QALY to nearly € 1,000,000, with a difference of more than 150 times. Such a strong variability may seem unjustifiable, but a deeper insight suggests that it is potentially explained by the epidemiological factor. In other words, the prevalence range of rare diseases may have discards with a difference order of 10,000, which can obviously explain why medicines for very few patients have, with equal benefits, far greater costs than those who have rare but not extremely rare diseases.

A study by Messori et al. (2010) tried to estimate the "premium price" recognized by AIFA to orphan drugs, depending on the number of eligible patients.

The analytical report is estimated in the study:

$$CAXP = 10{,}000 + e\text{-}0{,}004NP$$

where:
CAXP = Annual cost per patient
NP = Number of patients

To exemplify, according to the study, in Italy, AIFA would on average consider approving the reimbursement of orphan drugs, recognizing an annual cost per patient of around € 10,000, with a prevalence of> 0.5 per 10,000 inhabitants, or more than 3,000 eligible. But according to the estimated model, for a drug intended only for five patients, AIFA would be willing to accept an annual cost of about € 2,000,000.

Although figures of this magnitude can "frighten", it can in fact be shown that epidemiological differences can explain cost-effectiveness differences, and even that the first molecule would be more profitable for the producer, despite a much lower price.

To justify the first assumption, it should be noted that simplifying and equating the efficacy of the two hypothetical molecules (we hypothesize a benefit of 0.5 QALY annually), in the first case it would cost QALY for €20,000, and in the second of well €4,000.000; despite this, revenues would be € 30 million annually in the first case and less than € 10 million in the second. Already in the first case it is doubtful that the molecule can be profitable (i.e. to guarantee return from the investment), but certainly not in the second case.

The "regularity" of the above shows, therefore, that the regulatory agency has actually evaluated orphan drugs, avoiding aprioristic choices. The report also shows how, in such cases as those of orphan drugs, the evaluation largely prevails on distributive (and hence ethical) motivations on the simple cost-effectiveness of technologies.

In other words, the specificity of rare diseases, and hence the epidemiological aspect, explains the strong differences in cost-effectiveness, and indeed requires that the latter criterion be subordinated to the appearance of the achievement of invoices capable of ensuring an adequate return of all investment; without such attention / awareness, the risk becomes to disincentive research, especially for the most rare conditions, or to not give access to therapeutic opportunities for patients.

To make the Italian market still attractive, which, as it is said, is to ensure patient access to innovation, it seems important to report what is an empirical relationship, to build a pricing algorithm that can make benchmarking for the decisions of regulatory authorities, considering inovation (cost-effectiveness), market size (and thus return on investment) and sustainability (although we are aware that the latter, in the case of orphan drugs, is hardly an imminent issue given the number of eligible patients).

The full version of the search is available on:
http://www.osservatoriofarmaciorfani.it/wp-content/uploads/2016/11/OSSFOR_RICERCA_Polistena-Spandonaro.pdf

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I PUBLIC MEETING OF OSSERVATORIO FARMACI ORFANI OSSFOR

The report "Economic Analysis of the Impact of Rare Diseases and Evaluation Criteria for Orphan Drugs", produced by CREA Sanità, was presented at the 1st Meeting of Ombervatorio Farmaci Orfani on 16 November 2016 in Rome, Italy at "Giovanni Spadolini" Library of the Senate of the Republic of Italy. The meeting was attended by representatives of the political, institutional and business sectors who welcomed the initiative and were available to actively become involved in the development of innovative policies that could stimulate development of orphan drugs, taking into account the challenges of sustainability.

During the meeting:

- Sen. Laura Bianconi, Hygiene and Health Commission, Senate of the Republic of Italy
- Francesco Macchia, Observatory for Orphan Drugs
- Federico Spandonaro, President of C.R.E.A. Sanità
- Ilaria Ciancaleoni Bartoli, Director of Observatory for Rare Disease
- Barbara Polistena – C.R.E.A. Sanità, Observatory for Orphan Drugs
- Paola Testori Coggi - CPR President, AIFA
- Armando Magrelli - Italian Delegate to COMP, EMA
- Monica Mazzucato - Permanent Interregional Rare Disease Technical Roundtable - Regional Conference of Health Ministers
- Tiberio Corona - Responsible for Pharmaceutical Policy Tuscany Region
- Giovanni Monchiero, Social Affairs Committee Chamber of Deputies
- Pierluigi Russo, AIFA Economic Evaluation Office
- Laura Crippa - Vice President of Biotechnology Group Farmindustria
- Ugo Capolino Perlingieri - Coordinator Working Group of Rare Diseases and Orphan Drugs Assobiotec
- Mario Melazzini, Director of AIFA

The reports are published in full on the YouTube Channel of Osservatorio Farmaci Orfani
https://www.youtube.com/watch?v=Nrm3BVApa4c

The report "Economic Analysis of the Impact of Rare Diseases and Evaluation Criteria for Orphan Drugs" and the I Public Meeting of Osservatorio Farmaci Orfani OSSFOR were made with the non-conditional contribution of: Amgen, Biogen, Biomarin, Celgene, Chiesi, Orphan Europe , Senofi Genzyme, Shire, Vertex.

PROMOTERS OF OSSERVATORIO FARMACI ORFANI OSSFOR (OBSERVATORY FOR ORPHAN DRUGS)

Consorzio per la Ricerca Economica Applicata in Sanità

C.R.E.A. Sanità (Consortium for Economic Research Applied in Healthcare) is a non-profit Consortium, promoted by the University of Rome Tor Vergata and the FIMMG (Italian Medical Association of General Medicine). The Consortium was born in July 2013, gathering the 20 years experience and skills of a multidisciplinary team of coordinated researchers, at the University of Tor Vergata, by Professor Federico Spandonaro, currently President of the Consortium. Team that over the years has become a point of excellence for economic and organizational research in the healthcare field.

C.R.E.A. Sanità

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The OMAR Observatory for Rare Disease is the only journal in Italy and Europe focused solely on the issue of rare diseases and orphan drugs and with full free access. Born in 2010, for over seven years it has exceeded the average of 9,000 daily accesses and built close relationships of information exchange and collaboration with the world of patient associations, institutions, medical practitioners and researchers active in the industry and with pharmaceutical companies engaged in orphan drugs. he portal has obtained the Hon Code certification for medical information reliability.

Observatory for Rare Disease - O.Ma.R.

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