SIAR POSITION PAPER

Timely access to therapies for severe diseases with unmet medical need: a proposal for the European Countries

1. Introduction

In many European Countries patients have to wait a long period of time before the medicines, approved by the European Commission on the basis of the EMA/CHMP positive opinion, are really available in a democratic way.

Many efforts have been done to improve the situation and in some particular cases national legislation, like the French ATU and the Italian 648 Law, have addressed this issue although with a certain degree of variability among treatments. However for many severe diseases and in many Member States the situation is far from being satisfactory.

The European legislation has provided many tools to favor the early availability of therapies, when a severe disease is concerned and there is an unmet medical need.

In fact the Orphan Medicinal Product status (according to Regulation 141/2000), the conditional approval (according to Regulation 507/2006) and the accelerated procedure (according to Regulation 726/2004) have been conceived to favor the early availability of therapy for severe diseases with an unmet medical need. The recent "Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)" expresses the same objective.

However in many cases these admirable intentions are frustrated by the time requested by the national procedures for the reimbursement, which are mandatory for a real democratic availability of the therapy to the patients.

One interesting exception is the German Act on Reform of the Market for Medical Products (AMNOG). According to this law, right after the European Marketing Authorization, a medicine can be reimbursed at a price defined by the owner of the MA. At the same time a procedure for the negotiation starts. At the end of the negotiation the price will be modified accordingly.

However this German procedure cannot be proposed for all the European Countries, because most of them have not the resources to bear the connected economic impact or have different political agenda with lower willingness to invest on pharmaceuticals / healthcare

2. Patient need

The priority for patients with a severe disease, life threatening or strongly debilitating, is the availability of the best therapy as soon as the positive benefit / risk ratio has been established. This is particularly true if the new therapy addresses an unmet medical need or has demonstrated a significant clinical benefit compared with the available treatments.

3. Rational for a new proposal for the real timely availability for *"priority treatments"*

Presently the evaluation of the severity of the disease and the unmet medical need, at European level, is already done in the following cases:

- For Orphan Medicinal Products by COMP, according to Regulation 141/2000
- For the extension of indication by CHMP (on the basis of a request by the applicant) (Article 14(11) of the Regulation 726/2004)
- For the Conditional MA by CHMP, according to Regulation 507/2006
- For the Accelerated procedure by SAWG/CHMP, according to Regulation 726/2004

In the future also the "PRIME" procedure will include this evaluation according to the *"Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)"*

In conclusion in these cases the centralized procedure for the marketing authorization includes an assessment, made by CHMP or COMP, regarding the severity of the disease and the unmet medical need or the significant benefit.

It is worth reminding that, in case of Orphan Medicinal Products, Regulation 847/2000 article 3 clarifies that "significant benefit" means a "***clinically relevant advan-***

***tage or a major contribution to patient care"*.**

4. New Proposal : additional administrative "Special Timely Procedure" for the reimbursement of therapies for severe diseases having an unmet medical need or a significant benefit in comparison with the existing therapies.

For therapies for severe diseases and an unmet medical need or a "significant benefit" as evaluated recently* by CHMP or by COMP, Member States, on a voluntary basis, trigger an administrative mechanism of immediate reimbursement and so of immediate availability for all the patients in need. Because also the compatibility with the economic resources has to be respected, a special national procedure has to be studied in the details, taking into account sustainability.

With the aim of making this administrative national procedures sustainable, the following limitations are suggested:

a) The national administrative ***"special timely procedure"*** will be used just for therapies for **severe diseases**, which means life threatening or chronically debilitating conditions, according to a recent* CHMP or COMP evaluation. The definition of "severe diseases" is already defined in the European Regulation for OMPs (Regulation 141/2000, article 3).

b) The national administrative ***"special timely procedure"*** will be used just for therapies recently* recognized by the CHMP or by COMP to address an **unmet medical need or to have a significant benefit** in comparison with the current therapies for the same condition (as in the European Regulation 847/2000, article 3).

c) The national administrative ***"special timely procedure"*** will be restricted to the following cases:
   a. Orphan Medicinal Products according to Regulation 141/2000
   b. Extension of indication with significant benefit according to Article 14(11) of Regulation 726/2004
   c. Conditional MA according to Regulation 507/2006
   d. MA approved through the accelerated procedure according to Regulation 726/2004

d) The national administrative ***"special timely procedure"*** will be used just for Marketing Authorization or extension of indication following a positive opinion by CHMP by consensus.

e) The national administrative ***"special timely procedure"*** allows the **immediate reimbursement** by the NHS: no additional assessment by the NHS is necessary

f) The **initial price** is decided by the sponsor, and it is equal to the lowest price for the same medicine available in the European Union. This price could be immediately aligned in case other lower prices would be agreed, at the end of the usual procedure for price and reimbursement, in Countries sharing this special national timely procedure

g) Possible **100% payback** by the sponsor, when the usual National procedure of negotiation will be finished, equal to the difference between the used free price and the price established at the end of the procedure.

h) A national "**Register**" for the new treatment, if requested by the National Authority, could be placed effective from the initial drug availability

i) A **maximum turnover** (ceiling), in the first 12 months could be fixed: for example 0.5% of the total national expenditure for medicines reimbursed by the NHS. In case the expected expenditure is higher, the sponsor has two alternatives:
   a. Renounce this national timely procedure
   b. Supply the medicine as free of charge after the fixed ceiling during the first 12 months.

j) **Failure** of the usual P&R negotiation: a failure of the usual national negotiation is quite unlikely in case of therapies for unmet need or with additional clinical benefit for severe diseases. In any case, if a failure occurs, the applicant will be obliged to payback a certain percentage of the turnover (for example 20%) and the medicine will be classified in class C (this outcome is valid for Italy: for other Countries a specific clause has to be studied, Country by Country, depending on the National legislation).

k) This administrative ***"special timely procedure"*** does not substitute but is in addition to the usual national procedure for P&R negotiation. It has the objective of reducing the time between the European Marketing Authorization and the real availability in the Country for therapies with an additional significant benefit and for severe diseases.

l) This administrative ***"special timely procedure"*** does not substitute but is in addition and could be synergetic to the procedure under evaluation by EMA and EUnetHTA for a "first European HTA at the time of the MA". It has the limited objective to reduce at a minimum the gap in time between the MA and the real availability of the medicine in many Member States.

19 January 2016

*In this proposal "recent" and "recently" mean no more than 6 months before the Marketing Authorization

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Notes on the German procedure for price regulation of medicines

Introduction
Since 2011, when AMNOG (the Act on Reform of the Market for Medical Products) came into force, in Germany a new procedure has been settled for the definition of the price of innovative/patented pharmaceuticals.
This Act aims to guarantee an appropriate refund rate for the innovations (pharmaceuticals which produce a valuable benefit for the patients), to ensure a timely availability to German patients of medical products through a well-defined reimbursement mechanism and , finally, to safeguard jobs (Bundestags Drucksache 17/2413, S.1.). A reduction of the increase in expenditure for new pharmaceuticals is also expected.
According to this Law, right after the European Marketing Authorization, a medical product can be reimbursed at a price defined by the pharmaceutical company owner of the patent.
At the same time, the pharmaceutical company has to subject its medical product to the IQWiG (Institute of Quality and Efficiency in Health Care), which is in charge of the evaluation of the additional benefit of new product after being launched on the market (see below). On the basis of their assessment – which is released within 3 months – the G-BA (Federal Joint Commission, composed by physicians', hospitals' and health insurance funds' head associations) has 3 further months to complete the appraisal, defining which services in medical care has to be reimbursed by the SHI. Patients are not part of the G-BA but they are allowed to attend meetings and to say their opinion.
Before the beginning of the assessment, the pharmaceutical company could ask for an advice to the G-BA.
After these two steps, if the benefit assessment is positive, the price negotiation with GKV-SV (Federal Association of the Statutory Health Insurance Funds) will begin, lasting 6 months. If pharmaceutical company and GKV-SV reach an agreement, the procedure will finish and the medical product will be definitely reimbursed at the agreed price. So, the entire procedure will last 1 year. Most agreements have a time horizon after which new negotiations are possible.
In case there is no agreement after the negotiation, the Act provides further 3 additional months of "arbitration". At the end of this period, the Arbitration Board defines the final price and reimbursement amount for the medical product. If the pharmaceutical company doesn't agree with the Arbitration Board, it can withdraw the medical product from the German market while it is not possible to appeal in order to change reimbursement details. In this case, the entire procedure will last 15 months.
Therefore, the AMONG process introduced in theory the concept of decision making based on "Value-based pricing", since the reimbursement for a medical product is lead by the medical need: if the pharmaceutical demonstrates a benefit of a meaningful magnitude and it is the only way to obtain this added value, the negotiation should end with the recognition of a "premium price" for the medical product. Otherwise, the "right price" will be defined by the Arbitration Board. However the sick funds have a strong power and often the comparison is with generic medicines. As a consequence, in many cases, the value is transformed into money without the assurance of a sound economic basis.

ATV: Additional Therapeutic Value
As written before, to start the assessment of a new medical product, the pharmaceutical company has to submit a dossier to demonstrate the additional therapeutic value (ATV) of the product compared to the appropriate comparator.

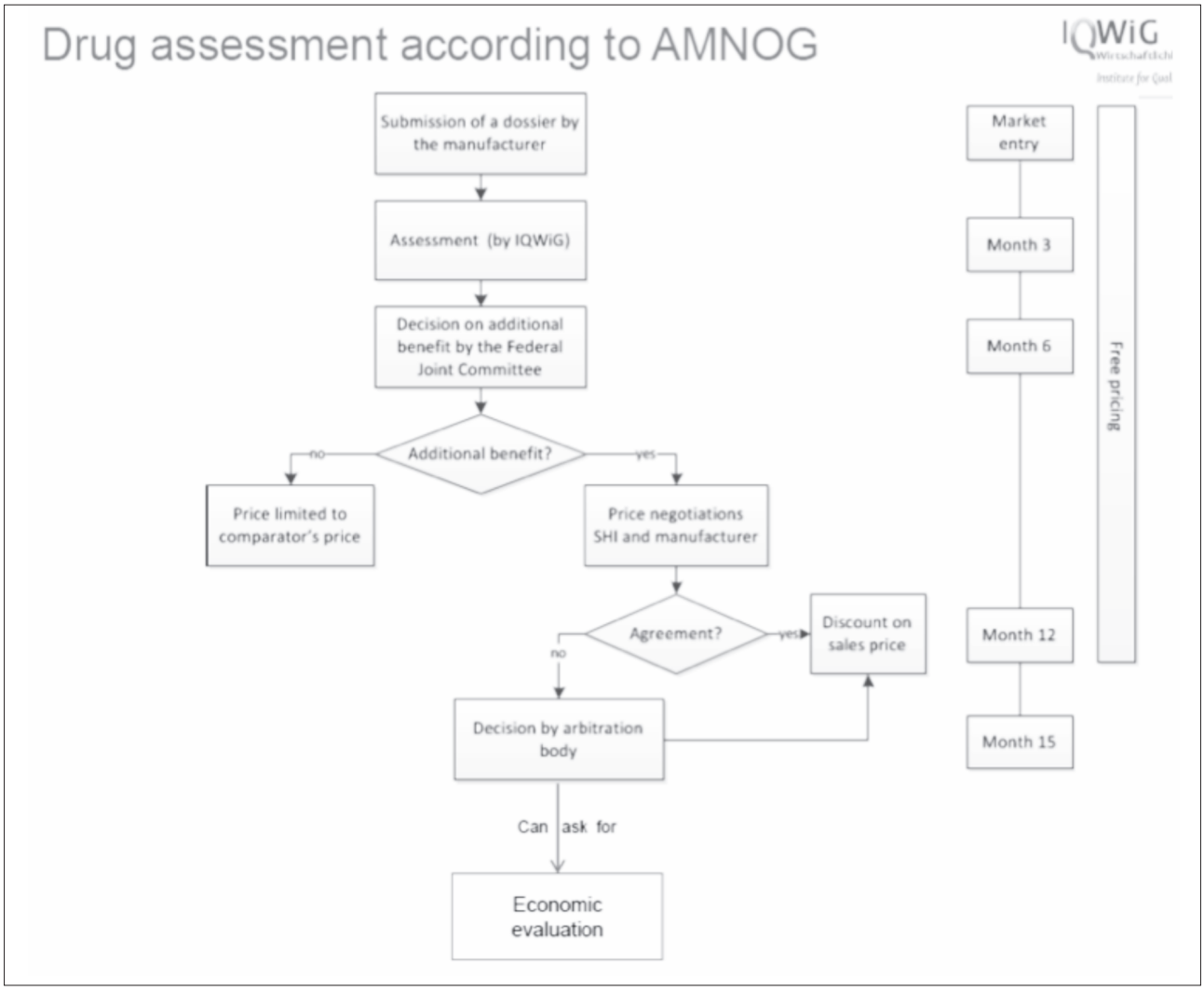
The dossier is made up of 5 modules (of which modules 1-4 are published), as follow:
Module 1
- Administrative information
- Summary

Module 2
- General information on the drug
- Description of approved indication

Module 3
- Description of appropriate comparator
- Number of patients with relevant additional benefit
- Costs for the SHI
- Requirements for quality-assured application

Module 4
- Systematic review of the benefit and additional benefit (description of methods and results)
- Description of patient groups with a relevant additional benefit

Figura 1



Module 5
- Full texts of references
- Data on the documentation of information retrieval
- Study reports for all manufacturer-sponsored trials
- Approval documents
- Evaluation report of the regulatory authority
- Checklist for the review of formal completeness

One of the issue that arises from the former list is the **choice of the appropriate comparator**. In this way, two examples presented at the "Payer's Forum Europe 2014" [1] are emblematic.

The first one was the case of lixisenatide for diabetes, for which were available various clinical trials with different comparators. Here, G-BA chose only Sulfonylurea as the appropriate comparators – being strict in the choice – where the label obtained is quite broad – lixisenatide is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycemic control in patients not adequately controlled on oral antidiabetics and/or basal insulin.

The case of teriflunomid in multiple sclerosis is also very interesting. Because teriflunomide has demonstrated "no superiority" in a head to head study with interferon beta (according to a G-BA advice requested some time before by Sanofi) the lowest price in the class (Extavia) has been taken as reference price. This is in compliance with the 3rd amendment to the law (paragraph 130b SGB V (3)). So if you have not demonstrated an additional benefit towards one therapy for the same disease , the lowest price of the class becomes the "reference" on the basis of the assumption that no superiority has been demonstrated between the different options.

Once the appropriate comparator is chosen and the ATV is evaluated, there are two possible results:

Scenario 1: additional benefit is proven

If the ATV is recognized, it will be classified as follow:
- Major additional

- Significant
- Minor
- Additional but unquantifiable

Given this classification, the pharmaceutical company enters in the negotiation process with GKV-SV. It is not clear how the magnitude of ATV influences the final price of the medical product. In any case the report of Cassel and Ulrich (**2**) underlines that the methodology uses a "bottom-up" approach, without taking into account the costs sustained for research and development. No mention also regarding the "Return of Investment" (ROI) which should be relevant in particular when an innovative therapy for a severe disease is concerned.

Scenario 2: additional benefit is not proven

If no additional benefit is recognized (or if it is hypothesized that the new product is associated to less benefit than comparator), the lowest price of the pharmacological class is taken as reference price for the new product, according to the 3rd amendment to the law (paragraph 130b SGB V (3)). So if the new pharmaceutical has not demonstrated an additional benefit versus one single therapy chosen as "appropriate comparator" for the same disease, the lowest price of the class becomes the "reference" on the basis of the assumption that no superiority has been demonstrated between these options. Again, the result is strictly related to the choice of the right comparator, but also to the definition of the most valuable endpoints needed to recognize the ATV, that could be not only clinical, but also related to the quality of life or the therapeutic setting. For example, a new product could reduce the hospitalization (and consequently the costs), increasing patients' quality of life, even it is not superior to the comparator in terms of overall survival gain.

Results of AMNOG processes (2011-2014)

Between 2011 and 2014, it was reached an agreement for reimbursement for 60 pharmacological products through a negotiation or an arbitration process (**2**).

In the same period, G-BA performed 103 early benefit assessments, of which for 47 (45,6%) were not recognized any additional value. The remaining 56 (54,4%) showed an additional benefit, but in 8 of these the benefit was considered "unquantifiable" while in the others it was categorized as "minor" or "significant". No one was considered a "major ATV".

It is interesting to highlight that in more than 70% of therapies for which AVT was recognized, the reference price for the subsequent negotiation was the price of some generic medical product, chosen as appropriate comparator. Of course this price is low to marginal. This scenario contributes to create a strong pressure on the prices which, according to the mentioned report [**2**], brings the reimbursed price of nearly 90% of medical products in Germany under the average of other Countries.

Our analysis about Orphan Medicinal Products (OMPs) and anticancers

As SIAR Working Group on pharmaceutical access in Europe, we have evaluated the "market access history" of medical products approved between July 2012 and December 2014 with the aim of defining the time lapse from the Market Authorization (MA) by the European Commission and the real availability – in terms of reimbursement by NHS – in 7 European Countries: Belgium, France, Germany, Italy, Netherlands, Spain and UK.

We have limited our research on two different categories of pharmaceuticals, which are considered the "cost-drivers" in pharmaceuticals expenses: oncologic drugs (recognized by ATC L) and orphan medicinal products.

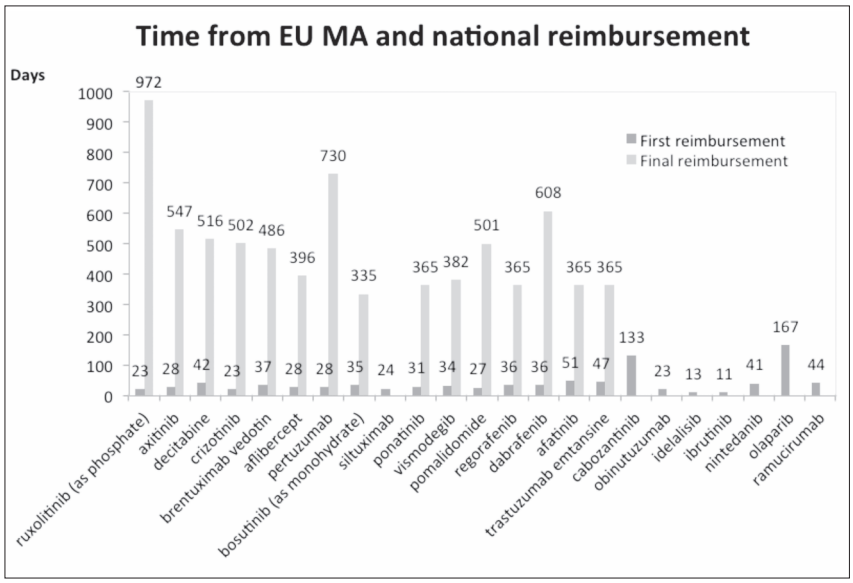
From June 2012 to December 2014, 42 pharmaceuticals overall were approved by European Commission. Of these, 13 were only anticancer, 12 were both anticancer and OMPs and 17 were only OMPs.

Oncologic drugs

For the overall 25 anticancer pharmaceuticals, in 2 cases (lipegfilgrastim and trametinib) no national reimbursement was granted, not even in the first step of the process (update June 2015).

Regarding the others 23 medical products, the average time lapse

Figura 2



from MA and the first national reimbursement under AMONG procedure was 42 days, with a minimum of 11 days for ibrutinib (both anticancer and OMP – for the indication in mantle cell lymphoma and chronic lymphatic leukemia) and a maximum of 167 days for olaparib (both anticancer and OMPs – for the maintenance treatment of ovarian, fallopian tube or primary peritoneal cancer).
Analyzing, in June 2015, the time lapse from the MA to the final national reimbursement, 8 of 23 have still the process "ongoing", but all of them are still within the maximum time of 15 months for the reimbursement procedures.
Among the others, the average time lapse is 496 days, longer than the 15 months declared by AMNOG as the maximum duration of negotiation process (including "arbitration"), with a minimum of 335 days and a maximum of 972 days (more than 30 months).

Orphan Medicinal Products
For orphan medicinal products, the ATV is considered proven and the assessment by G-BA cannot give the grade "no additional benefit" or "negative additional benefit" if the budget impact on SHI is less than 50 million Euro per year. In any case, the refund rate has to be negotiated between GKV-SV and pharmaceutical company.
Regarding OMPs, we have only qualitative information related to 20 drugs (8 only ODs and 12 both ODs and anticancer). Only in one case (bedaquiline fumarate) there was no reimbursement, for an issue regarding the pack size, while for the others the additional benefit of COMP was taken into account. In any case the delays between the European MA and the national reimbursement seem to be quite si-milar to the timings of oncologic drugs.

Conclusions
In principle the AMONG process represents an advantage for the real timely availability (reimbursement) of new Medicines in Germany. However some criticisms can be raised about the actual outcomes of the new system. In fact the implementation of the Law seems to affect the real availability of the new medicines in Germany for most of the patients. This effect depends on the "prescription recommendations" from health insurance associations and on the fear, in some cases, that the "additional benefit" are not valid for some subpopulations. For this reason some Experts advocate a restructuring of the Law (3).
In any case the idea to reimburse the medicines immediately after the MA, could represent a valid tool also for other European Countries, perhaps devoting this mechanism just to medicines for severe diseases.
Finally we have to recognize that the German paradigm for the immediate reimbursement, ***per se***, could not be feasible in other less wealthy European Countries.

17 December 2015

References
1. Presentation by W.D. Paar and M. Heck during the "Payers' Forum Europe 2014" in Berlin – 1-2 October 2014
2. Report by D. Cassel and V. Ulrich commissioned by the German Pharmaceutical Association (BPI) – May 2015
3. IMPLICONPlus – Analyses of health care policies by D. Cassel and V. Ulrich – October 2015

Price & Reimbursement System in France

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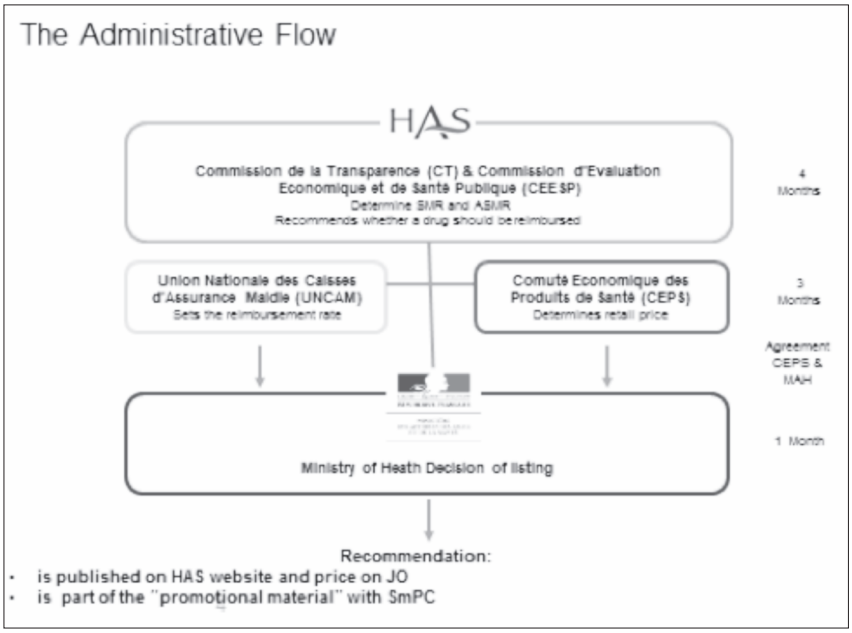
Background
In France, general conditions of reimbursement are established by law and implemented principally at national level by Governmental Bodies. In May 2012 establishment of the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) has been one of the key reforms of the NHS in France.
When marketing authorization licence is granted either by the EMA or at local level by the ANSM: the company has to apply for reimbursement on positive lists to obtain funding by the mandatory health insurance (assurance maladie obligatoire). Pharmaceutical Company submits a request to the Commission de la Transparence at Haute Autorité de Santé (HAS). The recommendation of this commission is then forwarded to Comité Économique des Produits de Santé (CEPS) to determine the price and to l'Union Nationale des Caisses d'Assurance Maladie (UNCAM) to decide the rate of reimbursement. The final decision belongs to Ministry of Health and is published in Journal Officiel (Fig. 1).
There are two lists: one for reimbursable drugs dispensed by retail pharmacies (Liste des Spécialités remboursables aux Assurés Sociaux) – "Liste Ville" and one for hospital drugs (Liste des Spécialités agréées aux collectivités). A pharmaceutical product can be listed on the two lists. – "Liste Collectivités". Since 2004, hospital drugs can be listed on two additional lists: hospital drugs delivered to out-patients ("liste Retrocession") and hospital only costly drugs that are charged to health insurance in addition to hospital stay fees based on Diagnosis Related Groups tariffs ("liste T2A").

HAS (Haute Autorité de Santé): French National Authority for Health was set up by government in August 2004 to bring together under a single roof a number of activities to improve the quality of patient care and to guarantee equity within the healthcare system: assessment of drugs, medical devices, and publication of guidelines to accreditation of healthcare organizations and certification of doctors. HAS is an independent public body with financial autonomy. It is mandated by law to carry out specific missions on whom it reports to Government and Parliament. HAS is Led by a board (Le Collège) of 8 appointed members & evaluates a drug to determine its SMR and ASMR by CT &

Figura 1



CEESP; recommends whether a drug should be reimbursed and transmits its advice to CEPS. HAS liaises closely with government health agencies, national health insurance funds, research organisms, unions of healthcare professionals, and patients' representatives.

Commission d'Evaluation des Médicaments (Tranparency Commission):
The purpose of the Commission is to provide scientific advice concerning the usefulness, interest and good use of drugs. It is composed by: 20 voting members (healthcare professional, doctors, pharmacists, methodologists) + 6 deputy members. 8 representatives of various Institutions (Ministry of Health, National Insurance Funds etc) meet twice a month; the evaluation department (25 persons) prepares each appraisal.
The opinion of the French Transparency Commission is used to assess the medical service provided by a new drug and the improvement of this medical service subsequent to its use for establishing the reimbursement rate applied by the social security organizations and the selling price set by the administration.

Commission d'Evaluation Economique et de Santé Publique (CEESP):
CEESP recommends whether a drug should be reimbursed and leads clinical and economic assessment for both Marketing Authorization and Renewal. It is restricted to product with a significant impact on Health Expenditure.

Health Ministry
The Health Ministry determines if a medicine will be registered on the refundable list, and the UNCAM decides of the reimbursement rate.

UNCAM (Union Nationale des Caisses d'Assurance Maladie)
The UNCAM is a public health care organizational system following reform law of 12 August 2004. Its first purpose is the coordination of the three mandatory sickness funds, links with complementary scheme and with health care professionals, to obtain a better health insurance management. Its second purpose is the intervention in negotiation of agreements with medical professionals in decision concerning prescription drug and health care reimbursement procedures with an **"actual benefit" assessment**:
CEPS *(Comité Economique des Produits de Santé)*
The Economic Committee on Health Care Products fixes the medicine price after negotiation with the MAH: CEPS manages national drug budget, determines retail price at which a drug will be reimbursed in a drug list, sets sales/volume agreement and any special conditions and decides on penalties for manufacturers exceeding price/volume. The Decision Making Process to provide health solution to French population stands in an almost universal coverage (99% of the population) by Statutory Health Insurance (*Assurance-maladie*), a branch of the social security system *(Sécurité Sociale)*. Pharmaceuticals are enlisted in two steps:
Step 1 is the *technical assessment* by la *Haute Autorité de Santé* (HAS) which hosts CT & CEESP:

- Eligibility to reimbursement and reimbursement rate (SMR); the product's medical benefit or therapeutic value or *Service Médical Rendu* is based on five criteria:
  1. Efficacy and safety.
  2. Position of the medicine in the therapeutic strategy and the existence or absence of therapeutic alternatives.
  3. Severity of the disease.
  4. Type of treatment – Aim of the Drug: preventive, curative or symptomatic.
  5. Public Health Impact (burden of disease, health impact at community level, transposability of clinical trial results).
- There are 3 rates of reimbursement defined by UNCAM based on SMR: important (65%), moderate (30%) and weak (15%); the gap not covered by UNICAM has to be covered by voluntary insurance. Insufficient to justify a reimbursement (none): small effect and AEs; efficacy in a population different of the MA population; not so severe disease symptoms; fixed dose combination drugs without demonstration of its interest. Anyway medicines with insufficient level are recommended not to be registered on the reimbursable list. The final decision is taken by the Health Minister (Fig 2).
- Full indications or restricted to situations and subpopulation, assessment of clinical added value or *Amélioration du Service Médical*

Figura 2

		Severity of the disease	
		High	Low
Medical Benefit (SMR)	Major or Important	65%	35%
	Moderate or Weak	35%	35%

The drugs recognized like irreplaceable are reimbursable at 100% (e.g. HIV drugs). Patients with chronic/severe diseases listed on a list (Liste des ALD) benefit a 100 % reimbursement rate for all their medications prescribed for the disease.

Rendu (ASMR) - is the result of a comparative assessment of the new product with existing ones: unless the product is first in its class, the evaluation is done in comparison with products of the same pharma-therapeutic class that are already enlisted.
There are five ASMR levels:
- Major innovation (ASMR I) effect on mortality in a severe disease; a significant therapeutic benefit.
- Important improvement (ASMR II) clinical effect in terms of efficacy and tolerance in reduction in side effect profile.
- Moderate improvement (ASMR III) clinical effect in terms of efficacy and tolerance in reduction in side effect profile, where equivalent pharmaceuticals exist.
- Minor improvement (ASMR IV) clinical effect in terms of efficacy and tolerance, but still granted recommendations to be listed.
- No improvement (ASMR V) when a no inferiority has been demonstrated, negative opinion, no inclusion in reimbursement list (Fig. 3).

• Target population eligible for treatment in the reimbursement scheme and quantitative estimate, uncertainty (any need for additional data collection) and recommendations (use in clinical practice).

In some cases, the Committee recommends reimbursement is restricted in contrast with MA for a selection of indications, groups of patients, or granted only when prescribed by a specialist physician or when the patient is complying with a test and requires the company commitment to perform studies for assessing real life effectiveness or drug utilization after admission to reimbursement. They repeat the HTA (every 5 years and anytime when significant information are available).

Step 2 is the enlisting on the lists with price fixing by the CEPS and reimbursement rate fixing by the UNCAM.
A MAH can set the price of the new drug but to be reimbursed by the national health insurance fund, reimbursement must be granted by *Commission de Transparence* considering the opinion of the Commission d'Evaluation des Médicaments, the reimbursement rate is fixed by a decision of the Union Nationale des Caisses d'Assurance Maladie (UNCAM) within rate limits defined by decree.

CEPS is composed by 10 voting members and an Executive Secretatiat – 10 persons preparing and following up decisions on: a) Pricing reimbursed medicine & Regulate Public Spending, b) Ensuring Social Security Finance & Equal Access to best medicines for all, c) Fair Pricing for Innovation. The CEPS meeting takes place once a week and pricing rules are set through both Law & Ministerial Instructions and agreement with Industries (on prices, expected sales volume, «real life» use of medicines.). A claw-back system is set on yearly basis.

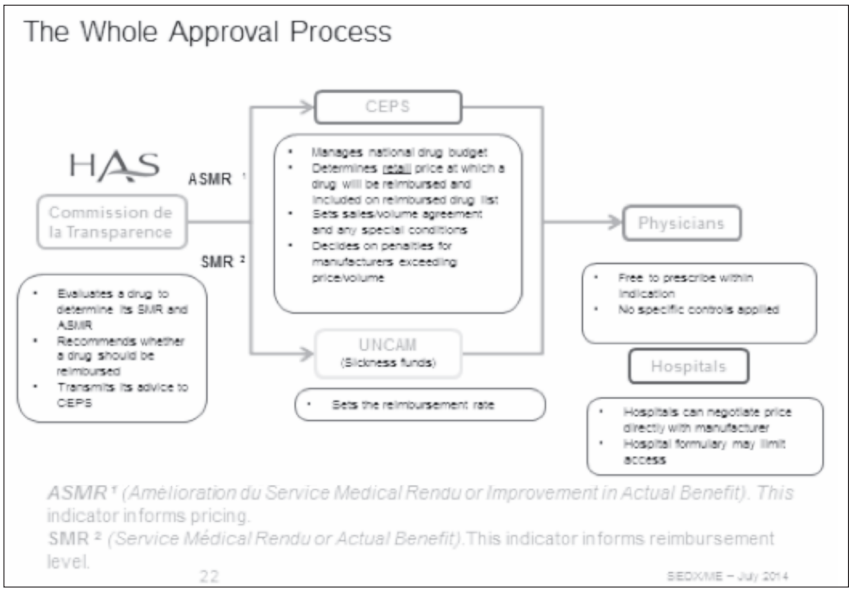
Figura 3 - Price fixing by the CEPS after economic evaluation, negotiation and its publication in the O.G.

➢ Price depends mainly on :
- ASMR level (advice from the CT)
- Price of comparators
- Price of product in other markets
- Sales forecast
- Size of expected population

➢ Price contract will set out :
- Average daily dose
- Sales/Volume agreement
- Promotional penalties
- Pay-back clauses (rebates/price cuts)
- Follow up studies (if required)

CT Evaluation		CEPS Price Process
ASMR	Description	
I	Major	Submission of a dossier and price negotiation Time of procedure depends on readiness of company and CEPS to agree
II	Important	
III	Moderate	
IV	Minor	Parity or discount
V	No improvement	Significant discount

Figura 4



In France as in other EU Countries such as Italy the decision of MEA adoption has been based on increasing cost of new medicines, the presence of a significant degree of uncertainty at time of making coverage decisions, but also a need of innovative solutions to make new drugs available to patients while ensuring the long term financial sustainability of healthcare systems.
Risk Sharing Agreement and Financial Price Volume Agreement are very common both on Therapeutic Class Level: Volume ceiling calculated based on annual projected growth per class. Historically the volume ceiling has never been reached; but as of Dec 2012 the growth rate for certain classes have been set as 0% and Performance: Data collection on outcomes.
Transparency Commission (TC) prefers hard clinical endpoints (eg overall survival is preferred) – is more likely with ASMR I – III drugs and may also ask for data on safety or compliance with TC guidelines. Moreover drugs with high budget impact tend to have a study requirement - outcome guarantee.
Differently from Italy, France has been reluctant to engage in many performance-based RSAs. This is mainly due to its ability to negotiate prices and IT infrastructure to collect data, especially at regional/county level

SIAR Analysis about Anticancer and Orphan Medicinal Products (OMPs)

As SIAR Working Group on pharmaceutical access in Europe, we have evaluated the "market access history" of medical products approved between July 2012 and December 2014 with the aim of defining the time lapse from the Market Access Authorization (MAA) by the European Commission and the real availability – in terms of reimbursement by NHS – in 7 European Countries: Belgium, France, Germany, Italy, Netherlands, Spain and UK.
For France the analysis has been conducted both on anticancer and orphan medicinal products as "cost-drivers" in pharmaceuticals expenses and which has been considered for "fast track".
From June 2012 to December 2014, 42 pharmaceuticals overall were approved by European Commission. Of these, 13 were only anticancer, 12 were both anticancer and OMPs and 17 were only OMPs.
Only 22 have obtain reimbursement, 7 have faced some "issues", 15 are still under evaluation.

The delays between the European MA and the national reimbursement is so different also within the two categories; the "average time" to obtain local reimbursement is of 188 days for anticancer and 196 days for OMPs; the national reimbursement process for these drugs lasts 14 months overall.

Conclusions

Medicines must be a real benefit for the patient to be reimbursed and priced French Authorities are

Figura 5

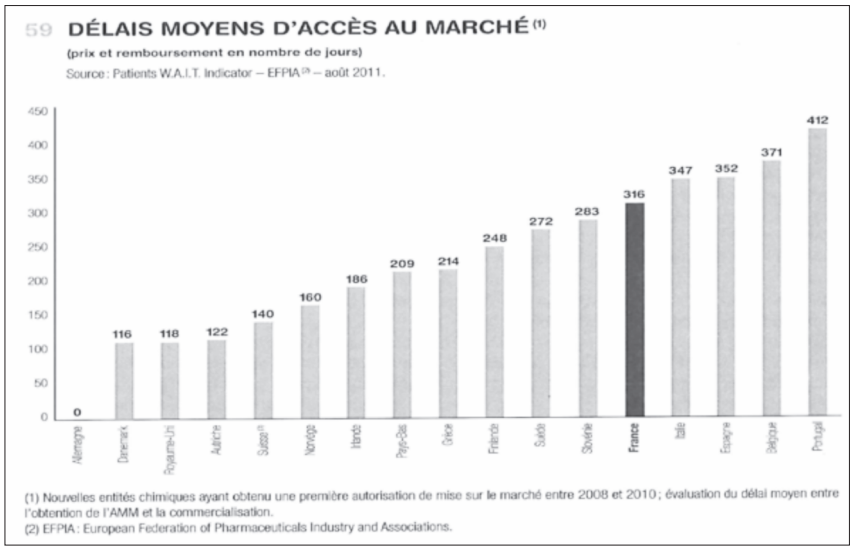
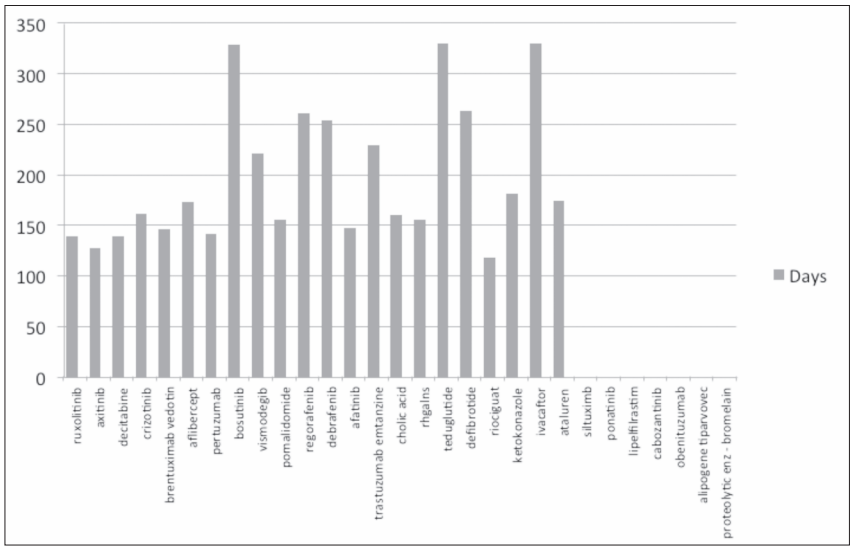


Figura 6



pushing to seek relative effectiveness with active comparators and additional data collection are requested post marketing. There is a real need for early dialogue between developers, HTA assessors and Regulators.
Need for bridging activities and cooperation between HTA Bodies in Europe EUnetHTA: Assessment (guidelines, template) & Data collection to reduce redundancy and facilitate European Collaboration.
Need for cooperation with EMA and ENCePP (European Network of centers of Pharmacoepidemiology and Pharmacovigilance), how to coordinate request for post-launch data collection.
This need has going to be raised throughout EU and its Countries and is going to be a reality in Italy in the next future.

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Using Registry Data to Inform Decisions about New Cancer Drugs: example from the RWE registries in The Netherlands

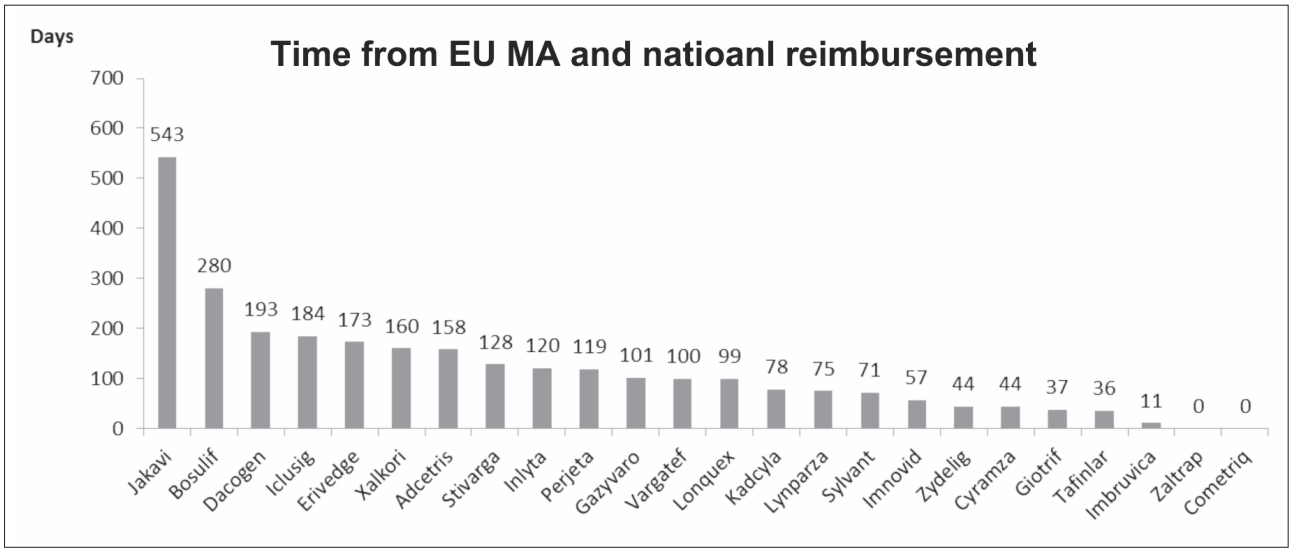
Abstract
Decision makers increasingly request evidence on the real world effectiveness (and cost-effectiveness) of new treatments (ie.: recent Legge 06/08/2015, n. 125 in Italy).
This paper presents drugs access analysis in the Netherlands with a focus on the role of utilization of real world data from the Dutch Population based Registries in performing economic evaluation in The Netherlands and reports positive impacts in terms of fast access for innovative drugs.
Real world data provide useful insights into the utilization, costs and effects of a treatment in real world settings. Decision makers should realize that real world evidence provides extremely valuable and relevant policy information, but needs to be assessed differently compared to evidence derived from a randomized clinical trial.

Pharmaceuticals governance in the Dutch system
Medicines have different reimbursement and financing systems according to the in-patient or out-patient sector.
In the out-patient sector, the Health Minister decides on medecines reimbursability; specifically, new medicines are assessed by the National Health Care Institute (ZiN), which advises the Minister if they should be reimbursed.
Reimbursed drgus are listed in the pharmaceutical reimbursement system (GVS) formulary.
In the out-patient sector, health insurance companies finance medicines used by their patients, at a reimbursement rate of 100%.
Ducth citizens have a policy excess of € 375/year (meaning that the first €375 of heath care expenditures, including pharmaceuticals, have to be paid by patients).
Therapeutically interchangeable medicines (clustered on Annex 1A) require co-payments if their price is above a predermined cluster limit.
In the in-patient sector (hospitals), all new medicines are automatically reimbursed if they comply with "established medical science and medical practice". This means that new hospital drugs approved by EMA are always reimbursed.
This open access does not usually require an assessment by Zin or a Minister decision and there are virtually no maximum reimbursement prices.
However, the government and ZiN in last few years are trying to extend the influence on reimbursement of hospital drugs, arguing that, although compliance with science is assessed by EMA, compliance with medical practice can only be determined by local authorities.
Recently, ZiN started to review in-patient medicines claiming added benefits and having an annual budget impact exceeding 2,5 Million euros. If the assessment is negative, the Minister can potentially exclude the drug from reimbursement.
In terms of financing, hospitals charge one price for all treatment activities performed for each patient. The total fixed amount, called DBC or DOT, also includes all medicines.

Real World Data availability and Access to innovative drugs
In the Netherlands, outcomes research requirement were implemented in 2006 for new expensive drugs to ensure timely access to promising drugs. Once a drug is included in this policy, hospitals have the obligation to collect data on appropriate use and real-world cost-effectiveness. Real-world data are often collected within a patient registry and are utilize to assess effectiveness and cost-effectiveness in real practice.

Orphan Medicine Products and Anticancers: time to access analysis
We have evaluated the "market access history" of medical products approved between July 2012 and December 2014 with the aim of defining the time lapse from the Market Authorization (MA) by the European Commission and the real availability in The Netherlands.
We have limited our research on two different categories of pharmaceuticals, which are considered the "cost-drivers" in pharmaceuticals expenses: oncologic drugs (recognized by ATC L) and orphan medicinal products.
From June 2012 to December 2014, 42 pharmaceuticals overall were approved by European Commission. Of these, 13 were only anticancer, 12

Figura 2



were both anticancer and OMPs and 17 were only OMPs.

Oncologic drugs
The majority of the 25 anticancer pharmaceuticals (including OMP) analyzed have already received the national reimbursement. Only trametinib has no national reimbursement yet in The Netherlands.
The average time lapse from MA and the national reimbursement procedure was 117 days, for aflibercept and cabozantinib the national reimbursement occurred in the same day of the EU approval. Ruxolitinib has the longer procedure with the maximum of 543 days.
Based on this analysis, only 11 of the 25 anticancers products had a longer procedure compared to the average of 117 days.

Orphan Medicinal Products
For the 17 only OMP the output is quite different. Only 6 of the 17 product obtained the final reimbursability. The process for the OMP took, on average, 173 days, with a minimum of 0 days (afamelanotide) and a maximum of 431 days (riociguat).

Conclusions - The Value of Real World Evaluations for Decision makers
It is crucial to clarify that the outcomes of economic evaluation based on registry data should be assessed differently from analysis based on RCT data as registry data are significantly different from RCT data.
The availability of data from registry data reduce the uncertainty of the outcomes from the clinical trials.
It's fundamental for the patients to have fast access for innovative drugs to allow earlier treatments and earlier collection of RW data, especially when limited evidence from RCT are available. In particular, in the context of the OMP this is even more applicable due to small population enrolled in clinical trials.
The Netherlands could be a useful reference for Italian systems in view of:

- allowing early access to hospital and orphan drugs at EMA approval
- approaching National renegotiation on the basis of RW data collected through AIFA registries.

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