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Enrico Bosone
Paolo Scurati

Editoriale

Ci sono dei temi ricorrenti nel mondo della Sanità, anche se le definizioni ed il modo di affrontarli cambiano a seconda della cultura dell'epoca. Oggi sono oggetto di articoli e workshops la "Comparative effectiveness Research" e l'HTA, che si intersecano con l'attività delle Agenzie Regolatorie che rilasciano le AIC sulla base della efficacia, sicurezza e qualità, senza entrare nel merito economico. Ma la questione del confronto, non solo col placebo ma, dove possibile, con terapie alternative, tenendo conto anche degli aspetti economici, è quasi vecchia come il mondo...Così anche la definizione dei livelli "essenziali" di assistenza, dove l'essenzialità non può essere una variabile indipendente dal tempo in cui viene definita e dalle disponibilità economiche.

Basta ricordare il "Nuovo Prontuario" del 1992-93 quando molte necessità mediche furono definite "minori", a torto o a ragione, e portarono all'esclusione dalla rimborsabilità di molte classi di farmaci che, fino a quel momento, erano state valutate come meritevoli del rimborso da parte del SSN.

Oggi, in presenza di una profonda crisi mondiale ma sopratutto Europea, è ovvio che le ridotte disponibilità economiche spingano verso un ulteriore riesame della situazione. Ci auguriamo che il riesame tenga conto della Storia e cioè di quanto è stato fatto in passato, in modo da non ripetere quelli che si sono rivelati errori ed invece perseverare nelle attività che hanno dato buoni frutti.

A livello Europeo, nel campo farmaceutico, i Regolamenti che hanno istituito EMA e la procedura centralizzata, che hanno incentivato i farmaci orfani, che hanno incentivato i programmi di sviluppo in pediatria, che hanno istituito il Comitato per le terapie avanzate (terapia genica , cellulare e di tessuti ingegnerizzati) hanno rappresentato degli importanti passi in avanti che vanno confermati e consolidati, avendo portato reali vantaggi per i Pazienti.

A livello Italiano la creazione di una Agenzia del farmaco, rinforzata negli ultimi anni con l'assunzione di personale qualificato in quantità adeguata ed in linea con le altre Agenzie Europee, ha portato e porterà ad una maggiore efficienza e trasparenza della funzione pubblica in questo settore, due doti che sono anche validi antidoti per problemi di gestione quali quelli verificatisi in passato in Italia e recentemente in Francia.

Certamente un mondo sempre più complesso richiede una analisi quanto più possibile profonda , attenta e completa della realtà. Le azioni che ne scaturiscono devono essere severamente valutate in base ad i risultati ed eventualmente rettificate.

In un momento difficile siamo tutti chiamati ad una maggiore responsabilità e ad un maggiore impegno. Nel nostro piccolo, come Associazione di coloro che si interfacciano prima di tutto con AIFA e le altre Agenzie regolatorie ed Autorità pubbliche, vogliamo cercare di portare un contributo di analisi e di proposte: aspettiamo il contributo dei nostri Soci che invitiamo a partecipare attivamente alle iniziative dell'Associazione nonchè al Consiglio Direttivo che si riunisce mensilmente.

WALTER BIANCHI
Presidente SIAR

Note della Presidenza

Con grande tristezza e dispiaciuto di arrecare dolore ai tanti che lo conoscevano, devo segnalare in questo fascicolo lo scritto in memoria dell'amico Alessandro Torsello realizzato da Liliana Di Ciano in nome e per conto di tutti i Colleghi del Consiglio direttivo. La scomparsa di Alessandro ha creato improvvisamente nella SIAR un grande vuoto che sarà molto difficile colmare. Tanti dei progetti avviati per sua iniziativa continuano con successo e rappresentano la testimonianza più tangibile della grande progettualità e concretezza realizzativa di Alessandro Torsello in ambito regolatorio e didattico. Alessandro è stato una delle persone che più si sono prodigate per la crescita della nostra associazione lungo tutti i 25 anni della sua storia. Qui voglio ricordare una delle più grandi qualità di Alessandro e cioè l'amore per il prossimo che lo spingeva a prodigarsi in ogni modo per aiutare ogniqualvolta possibile i colleghi e gli amici in difficoltà o rimasti momentaneamente senza lavoro. Credo quindi che il modo migliore di ricordare Alessandro sia quello di fronte a colleghi o persone in difficoltà di cercare di comportarsi con la stessa generosità con cui si sarebbe comportato lui.

Nel ritornare brevemente allo scopo originario di queste note, mi è molto gradito esprimere al professor Pani le congratulazioni di tutti i Soci della SIAR per il prestigioso e delicato incarico che gli è stato conferito. Per conto della SIAR desidero quindi formulare al professor Pani l'augurio di un pieno successo nell'importante e delicato incarico che ha recentemente iniziato a svolgere. Sono certo che SIAR persevererà con rinnovato impegno a cercare, per quanto è possibile, di facilitare il raggiungimento degli obiettivi dell'AIFA consapevoli che l'Agenzia presidia in tutti gli aspetti uno strumento, il farmaco, essenziale di difesa della salute e che l'AIFA, in una fase economica particolarmente difficile, si trova a svolgere un compito molto impegnativo e delicato nell'interesse del Paese ed a tutela di tutti gli stakeholders.

Ricordo di Alessandro Torsello

LILIANA DI CIANO
Socio SIAR

"È sempre difficile scrivere della morte di un amico, per Alessandro Torsello lo è in modo più acuto, perché Alessandro era la vitalità fatta persona.

Aveva una capacità, strana per i nostri tempi, di vedere le cose sempre in positivo e di vedere il buono che c'era in tutte le persone che incontrava.

Tanti lo ricorderanno per quella fitta rete di conoscenze che metteva a disposizione, quando si trattava di aiutare qualche collega in difficoltà.

Il suo atteggiamento positivo era contagioso e quando si organizzava qualche attività nuova, ne vedeva sempre un arricchimento, non solo personale, ma di tutta la SIAR, che sentiva un po' come una sua creatura, essendone stato uno dei primi Collaboratori.

L'ottimismo lo ha accompagnato anche durante la malattia che lo ha vinto e qualche volta abbiamo parlato della morte, che sentiva mediata da una fede profonda.

Vorremmo che fosse ricordato con una poesia che gli si addiceva:

Aprire il cuore

Finchè non coltiviamo pensieri
amichevoli verso ogni persona
che incontriamo, giorno dopo giorno,
ci perdiamo la parte
piu' gioiosa della nostra vita.
Se davvero potessimo
aprire i cuori non sarebbe
affatto difficile essere felici.

(Ayya Khema)

Adriana Ceci
Teddy Network Coordinator,
PDCO Member

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population

Welcome session

Introduction

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Introduction to the Course - Adriana Ceci

It's really impossible to start this brief presentation by thanking everybody singularly, because all of you represent a great opportunity for this course. I would like to thank in particular Vittorio Silano because he is the chair of our scientific committee as well Walter Bianchi and Enrico Bosone for the very important support that the professional society of regulatory affairs in Italy is giving to the Foundation.

My presentation is aimed to remind to the people that are here for the first time (and this is very important to us, to have new people participating to this course) who we are and what we are doing.

We are a no-profit organization that is aimed to develop pharmacological research to maintain the important heritage of prof Gianni Benzi, not only in the scientific field, but for his very innovative idea concerning the increasing of knowledge and participation in the scientific and regulatory field. Following this idea he founded the first interdisciplinary and international regulatory science school that was located in Italy, but with the mind to the Europe. The starting point of his activity has been to updating the general knowledge in the field of the European regulatory science, and this is what we are committed to continue to do.

The Gianni Benzi Pharmacological Research Foundation is also developing research activities. In particular we set up a registry of neuropathy induced by chemotherapy and we are granting scholarships and awards in the field of the safe use of drugs.

Two awards have been devoted to the fight against the doping. The next call for project is expected for the first of September, and it will be dedicated to the new approach to the neuropathic pain.

The second call will be devoted to the development of personalized medicines, for rare and pediatric diseases. I will be happy if you circulate this information, all the calls will be available on the Benzi foundation website, and we would like to receive applications from Europe and not only from Italy.

Another activity of the Foundation is to participate to public projects, for example the project founded by European commission. In two FP 7 founded projects the Foundation is providing contributions on concerned regulatory and ethical issues.

We are also involved in structuring a high technology district devoted to the development of red biotechnological products, promoted by the University of Bari, the region Puglia and the Minister of Research in Italy.

Regarding the collaborative projects one important collaboration is with the Sigma Tau Foundation. (I take the occasion to remember and to thank doctor Cavazza that has been one of our best supporter to start with the activity of the Benzi Foundation).

We also have a large collaboration with the consortium in Pavia. We maintain the database of medicines that is called EUOrphan, you can visit this, and finally we are now members of the National Consortium for biological resources (CNRB), involved in setting up a clinical trials facilitating structure.

We will have a presentation tomorrow regarding the activity of the CNRB.

The foresight-training course is one of the main activities of the foundation, aimed to consolidate the existing knowledge, but also to facilitate an exchange of tools and experiences. It is aimed in particular to bridge the existing gap between the academic programs, were there is no mention to regulatory aspects, and the increasing regulatory demands that are coming from regulatory agencies and industries. And all of this is made by staying in touch with the EMA innovation.

We have decided, at the start of the training course experience, which are our specificities. Our specificities have been listed as multidisciplinary, necessity to integrate the point of view of different stakeholders, international expertises, key role of the EMA, possibility to start a comparison among different member states' regulatory procedures, and to address which are the emerging issues in the European regulatory context.

I have just some slides to summarize our work, analyzing whether we are meeting these expectancies or not. These slides demonstrate the effort to integrate the major stakeholders' points of views. As you can see, industries represent both the provider and the receiver of the information that we circulate in these courses, but we have a good presence of university and public health centers, regulatory agencies and no profit organizations, including patients' organizations. Therefore, in my opinion, this integration is possible.

The second question was about the internationality.

This is a presentation of the participation of different individuals from a large list of states in Europe and outside Europe, so this is our expectation at international level of this course.

Another aspect was the key role of the EMA. Surely, the presence of high level experts from EMA is one of the most important results of this course, but we are trying to develop also good relationships with national agencies: as you can see many representatives of national agencies are participating to the course.

Finally, which aspects have been addressed during the course? This is just a list of the principal arguments, and Enrico Bosone will develop better what we are doing for example in this last course.

At the end, my question is: what next? There is no doubt that after 4 years we have to ask what we can do better than before. This is just a first very preliminary idea, we want to continue to promote these models of teaching on field by using experiences where they are, in industries and at the level of regulatory agencies. We are also planning to develop some innovative educational models, for example personal exchange among these different stakeholders, e-learning modules, internship outside Europe for young researcher. At the end of the course I will be very happy if you can offer your suggestions and criticisms to help us to improve in the future.

ENRICO BOSONE
Direttore Editoriale SIAR NEWS

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population

WELCOME SESSION

Introduction

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Introduction to the Course
Professor Vittorio Silano
Thank you very much for this introduction. It seems to me that from your presentation you have offered us the possibility to understand this foundation which honors the memory of Gianni Benzi.
Now, doctor Bosone spent most of his life in regulatory affairs, working in the pharmacological sectors fro companies in the medicinal sector, and I am really interested about learning more about this.

Enrico Bosone
Thank you prof Silano, thank all of you for being here.
Just a few words regarding in particular these activities of the Foundation about the foresight training courses. This one is the fourth one, and the title is "evidences for rational therapies: from new born to elderly population". You know that in Europe we have a very complex situation, because the different Countries in the European Union (made by 27 Countries) have different attitudes, habits in science and in the use of drugs. Considering this complexity, I think that one of the missions of the Benzi foundation is to find a pathway, to find a rational insight this complex situation, in order to help the improvement of the regulatory and possibly science situation in Europe, keeping in mind that patients are our common final target. Therefore, as Adriana told you before, one of the aim of the Benzi foundation is to contribute to advances in pharmacological research, and particularly in those fields where the scientific heritage of prof Benzi is more prominent. Some of the principal fields of activities of the Foundation concern the regulatory aspects at European level, and innovation in drugs' development processes. The key reasons for our efforts on this team are the relevance of the European pharmaceutical system, the long term commitment of Prof Benzi at the European Agency and at European level in different institutions, and the growing role of the regulatory aspects in sciences and society.
The real innovations, during the past years, as advances in medical treatment, technologies, diagnosis and science information, have profoundly influenced the manner in which the drugs can and should be used by the citizens. Regarding the relevance of the European Agency and the European regulatory network, the Agency was created as a catalyst of the national resources, and it has proved to represent a center of collaboration, both from scientific and social points of view.
This is just a slide in order to remind you which where the previous courses.
The **first one, in 2008, regarding centralized procedures and pediatric regulation**. So, the focus of this first course was on the procedures and on laws which were and are in our opinion the heart of the European system.
The second course was about the advanced therapies and orphan drugs, as the best examples of innovative medicines.
The third course, in 2010, last year, in Cracovia, was about the benefit risk assessment of medicines to achieve shared objectives. So, the focus was on the **criteria** of evaluation in Europe, which is an issue very difficult to cope with, not just in Europe but in all the world.

And **this last Course**, finally, regards the evidences for rational therapies for new born to elderly population. In this case, we reach the central issue of the patient, in fact all we are doing, at the end of the day, is for the patient, and we are discussing for the appropriate therapies for the patient. This is the focus of the present Course.
Luckily we have some useful documents in order to help us in finding a rational in this complex situation, and one of the main documents is the Road Map of EMA. Our course today, but also in the past, keeps into account the indications from EMA, particularly in this case for this year, for the **unmet public health needs, for the access to therapies, and for rational use of therapies**. You will find the most important documents in the list provided to you.
I would like just to underline one of the documents, issued by the WHO: "the rational use of medicines". It is a document quite recent regarding exactly one of the main issues of our course this year. So, the idea is to continue with the same intentions prof Ceci told you, trying to have from the regulatory and scientific network as many suggestions as possible in order to improve these activities and possibly to enlarge them, because they are for the moment very restricted to a limited number of people, to a broader number of people.
This is our intention for the next year.
Thank you for your attention.

VINCENZO SALVATORE
Head of Legal Sector EMA

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population

WELCOME SESSION

EMA Road Map perspectives and present status

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Vittorio Silano
Thank you very much doctor Bosone, with these two presentations we have got an overview about some of the foundation's activities, with specific references to the training course. There is an open mind in terms of receiving suggestions, is possible, whenever you consider it appropriate, about these activities of other aspects that could be of interest for the foundation.
We now move to doctor Vincenzo Salvatore. He is head of the legal service at the European Medicine Agency, since 2004. You have the word.

EMA Road Map perspectives and present status
Vincenzo Salvatore
Good morning everybody, thank you professor Silano, and thank you Benzi foundation for inviting me. It's a particular pleasure for me to be here today to represent the European Medicines Agency. That goes beyond the usual thanks that you give to meeting organizers .The reason for being particularly pleased of being here, is that I had the opportunity to meet Gianni Benzi, 25 years ago, when I started my academic career at the university of Pavia. Long before I met him in London, since 2004 where we had the opportunity to work together in the European framework, and I had the pleasure to appreciate his outstanding academic, professional and personal qualities, and so it's a particular pleasure for me to be here.
The task assigned to me is to introduce the debate, and to present you the international scene, and what I have been asked, is a short presentation on the contents of the Agency's Road Map 2015. That is the basic document we are relying upon, in order to identify our priorities and challenges that we will face in the next few years. I will be more than pleased to speak to you and answer any question, because the document is a quite broad document, it addresses a lot of issues, and I will be able to touch just few of them. I will focus tomorrow afternoon, with a more specific presentation, on the legal impact of the new pharmacovigilance legislation on the European Medicines Agency activities.
First of all, as you are familiar with, the EMA in London is constantly facing a changing scenario. These changes are mainly driven by a new part of the legislation, that since the year 2000 have confronted the EMA with new legislations, new scientific committees, new tasks, new organization structure. If you just go through this list, you will see that **since 2000 we deal with orphan drugs**, as medicines to treat rare diseases, with a system of incentives and with a strategy in order to improve pharmacological research in the field of rare diseases, or unmet medical needs. And then we had the **big bang in 2001**, when the Commission decided to codify all the directives and regulations that were issued in the past in order to provide a simplified reference document to rely upon, to set the regulatory scene. The Agency's main **responsibilities were dramatically changed, with the Regu-**

lation numbered 726/2004, that still represents our founding act.

Then we had in 2006 a new pediatric legislation, with the creation of a new committee.

We had another committee in 2007, with the new **legislation on advanced therapies**.

We had as a Christmas present on 10 December 2008, a new legislative package delivered from the Commission, addressing **a new pharmacovigilance legislation, new legislation on falsified medicines, and new information to patients legislation**.

And then eventually, on the 15 of December 2010, the new legislation of **pharmacovigilance** was finally adopted, and it will enter into force next year, and we are currently preparing for the implementation for the next pharmacovigilance legislation.

A couple of month ago, at the end of June this year, the new legislation on falsified medicines was published.

We don't have only a changing legislative scenario. We are also **changing people and premises**. The mandate of the Executive Director of the Agency expired at the end of last year, the agency is currently governed by Andreas Pott, from Administration, who is currently governing the Agency as acting executive director. A new director has been designated recently, and I'm sure you are familiar with him, Guido Rasi, current director of AIFA, the Italian medicine agency, will take up his duties before the end of this year, and we are all looking forward to his coming to the Agency. With a new chair of the management board, Sir Kent Wood, from the MHRA, and in our book of dream, but now it's becoming reality, we have just signed an agreement to be into new premises, we will move some hundred yards from where we are, and we will have a new building in 2015.

As I said, top of agenda is the implementation of a new pharmaceutical package. We have different kinds of priorities: of course we are currently concentrating on the implementation of pharmacovigilance. For pharmacovigilance and information to patients, we will have two sets of legislation. We have regulation, which is addressed mainly to the European Medicines Agency and European institutions, governing centralized procedures and directives, which are sources of binding rules addressed to national competent authorities, to Member States, that have to be implemented in order to enter into force. And that will be the case also for the information to patients. The history of information to patients regulation has been a difficult one, because the "information to patients" package was presented under the sponsorship of the D.G. Enterprise, where the focus was put on the right of industry to inform patients, rather than the right of patients to be informed. Now the perspective has changed with the passage of responsibilities from D.G. Enterprise to D.G. Sanco, we are waiting for a new proposal, which is there, they are exchanging opinions within the international consultation procedure of the Commission, but it will arrive shortly, and it is mainly focus on the point of view of the patients.

And then we have a directive, so no regulation, on **falsified medicine**. It is corrected to address it as "falsified medicines legislation", rather than counterfeit legislation, because it addresses the control of the distribution channel, rather than dealing with intellectual property rights infringement. Therefore it does not address issues about the use of trademarks, but about avoiding the introduction onto the market of medicines that have been tempered. These major responsibilities will be major responsibilities for Member States but of course the role of the Agency will be significant in coordinating inspection activities, and in strengthening the harmonization of procedure to minimize the risk that falsified medicines being introduced into the market. So, all these items make a must, rather than a need, to plan our activities not only to face new challenges, but also to motivate the change, and to create a new stimulation in order to increase the coordinating role that have been assigned to the EMA. As you know the EMA doesn't replace national competent authorities, but we are some sort of virtual agency in order to optimize the resources available at a national level. This is the reason why also our planning cannot depart from inputs that we receive from Member States, and it should be a joint strategy, and that's the reason why all our planning documents are based on HMA strategies, on Heads of medicines agencies discussions, and outcomes of their discussions, in a joint effort to achieve better public health results.

And here the targets that are identified: set priorities, ensure consistent approach, strengthen the role of networking. I have had few opportunities to talk with Guido Rasi in this interregnum period, but I know that one of his focal points for the next year of activities of the EMA, will be to focus on strengthening the network, so working together with national competent authorities. And

also, improve communication and increase transparency, providing more information, granting a better access to the repository of information we receive or we generate in the public health interest, not only in the pharmacovigilance sector. And then of course this relates to the general approach that is to encourage a joint strategy with national authorities.

What are the planning tools we are relying upon? We have a Road Map which is a long term instrument, because it addresses 5 years of activities. We are also working currently on an implementation plan that is pompously identified with a title "from vision to reality", so the road map set the scenario whilst the vision to reality document identifies the tools and timeframes for implementing this vision. And then, based on the "vision to reality" document, we will have a multiannual work program that will set the list of priorities for every single year, and then we have the annual work program that is the traditional document we rely upon to drive our activity.

The Road Map is a complex document, 30 pages document, and can be downloaded from the Agency's website. It's not the first time that we issue this kind of document. This is the second Road Map. We had the first one adopted in 2004. The main reason for identifying this call to promote information and set targets of the Agency was to follow some sort of proactive approach in order to present in advance to our stakeholders our major objectives and to discuss with them about the way of implementing it, the best way to do it. The idea behind it is thus the major involvement of our stakeholders, and as you know our stakeholders are industry, health care professionals, patients' organizations, and then of course our partners in the system, which are national Competent Authorities and of course Regulators.

The Road map 2015 identifies 3 major areas of activities we will have to focus upon in the next few years. **The first one is addressing public health needs and new public health needs**. **The second one is to identify tools in order to facilitate a better access to medicines, and the third one is related to the pharmacovigilance scenario, and relates to the optimization of the safe use of medicines.**

With regard to the **first** of the task that has been identified, we wanted to improve the scientific advice function of the Agency, and to strengthen the role of scientific advice, in particular investigating reasons for discontinuing research development in pharmaceutical industries. There are a lot of information that are currently lost, because industry discontinues research when a project fails, and these kind of information can be of public interest. We will have to work with industry associations and with our stakeholders in order to identify incentives, because of course there are specific information that must be protected and we have legal obligation to protect this. However even when a project fails, if you identify the right balance between the interest of industry to protect their proprietary information and the interest of the general public, or the scientific environment, or academia, to have access to some of the information, which may be of public interest, that would be a step forward. We are currently working also on a project which in the USA they call "staggered approval", in order to differentiate the single steps of development to create some sort of research tools between industry investigating on particular therapeutic areas, and to make available to a broad community of investigators, of academic researchers, some of the results in order to make it faster. The objective is to have the product available on the market, and then as you will see, reading the Road Map, we will have a new approach, "one world, one health". We are aware of globalization, we have to work closely with other national regulators, we have to **harmonize** the approach for human and veterinary medicines, which are currently not always so harmonized. We will have for instance to devote more attention to environmental risk assessment, as a consequence of the use of medicines not only for veterinary use, but also for human use. And then we will have to launch initiatives, together with our stakeholders, we are planning to launch a consultation in order to address the lack of development of antibiotics. And also the potential treat of antimicrobial resistance, due to the misuse of improper use of antibiotics in the population. And then we will have to devote and pay more attention to lessons learned. During these years, in fact, we have faced very critical situations, from pandemic emergencies, to pharmacovigilance urgent issues to be addressed, and we have put in place some measures. These measures could be fine tuned in the period when the waters are not so troubled, and we can reflect on how to improve our actions and reactions, rather than reacting on the spur of the moment with very tight deadlines.

The **second** objective that is linked to the first one is related to identify measures to facilitate the faster access of medicine onto the market. This is also to increase the role of the Agency in perspective with

regard to the activities in the health technology assessment exercise, in order to identify with our stakeholders and national competent authorities, which is the impact of the approval of a pharmaceutical therapy, vis-à-vis alternative measures.
Another aim is to **readdress the current benefit-risk balance assessment model**, by introducing some sort of relative assessment, in order to ensure updates of a continuous benefit-risk assessment of products that have been on the market for a long period of time, and in order to improve the quality and the consistency of regulatory assessment, trying to streamline the methodology of the assessment procedures, not only in Europe, but also in the dialogue with other international regulators. You know we have clusters in place, for specific sectors of activities, with the Food and Drug Administration in the US. We will never reach a single assessment because we belong to different regulatory systems, if you want to put a product on the market in Europe, you need a European authorization, if you want to place a product on the American market, you need the US authorization. This is valid not just for medicine but also for aircrafts. If you want to land in Frankfurt, you need the approval of the European aviation safety authority, and the same aircraft to land in Washington needs the approval from the Federal Aviation Authority. So we will never have a one world of regulatory system, but the more we harmonize the methodology for the assessment, the more likely you will have the same outcome, so that will save money, make the old procedure faster and probably improve public health protection.
And the **third** objective is to optimize and improve the safety of medicine, that's clearly linked to the pharmacovigilance new tasks that have been assigned to the Agency. The pharmacovigilance system is very complex. One of the targets addressed by the new pharmacovigilance legislation, and we will enter into this tomorrow afternoon, is to simplify the system to reach a better distribution of work-sharing with national competent authorities. Another aim is to provide accurate and timely information on adverse reactions, to have an ad-hoc scientific committee able to address pharmacovigilance issues both from national competent authorities and for centralized procedures, the new pharmacovigilance risk assessment committee, that will start its activity next year in July, and to increase transparency. Because we are overwhelmed by requests of people asking for information on adverse reactions linked to the use of medicines.
And we have to avoid the information shopping, because freedom of information acts around Europe are very different, so people tend to address their queries to the authorities which are more generous or more open to provide information, but this would undermine the efforts made by other national authorities to protect this information.
Then we are working on this implementation plan, which is currently under revision by the management board. We had the first draft delivered in June. The implementation plan, the objective is to identify responsibilities (who has to do what?), timeframes (when does it have to be done?), identify resources – and unfortunately the Commission informed that we will have no additional resources for implementing new tasks –, we will have to optimize the available resources. And then, we are simplifying this vision to reality plan, it was too complicated and ambitious, it was a 53 pages document compared to the 27 pages Road Map, so it was more complicated. We will have a short document, easier to read and to implement, but we are still working on that and you will know more on the 7th of October, after the EMA management board meeting. The vision to reality document that will become the road map implementation plan. We will then have multiannual work program and annual work programs.
I'm aware that I'm abusing of the time that I was given, I apologize for that and thank you for your attention, and I will address you to our new website. Now it's one year old, it's still a baby. It's a very good website, you have some search tools where you can include the name of the active substance and you will get immediate information on the product, you will have a green or red light, if the product is affected by regulatory decision, or a green light if it has been authorized and put on the market. It's not only a maquillage operation, we had the website before. This is a tool to facilitate the retrieval of information. More or less the same information was already there, it was much more difficult to find information you were looking for, now it's more user friendly, and we have different information targeted to different stakeholders, in different languages, with different styles of information the stakeholders could be interested in.
Thank you for your attention, I look forward to discussion.

IAN HUDSON
CHMP UK Member

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population

WELCOME SESSION

How the Regulatory System can be attuned to Science

We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Vittorio Silano
Thank you very much for your very interesting presentation, I'm sure that this subject is of tremendous interest to most of the presents, and I hope we will have more time to go back during the discussion but also during private conversation.
We are now approaching the end of the first part of our section, the next speaker is doctor Ian Hudson. He is the director of the licensing division, regulatory agency in London, and he is also Member of few scientific committees of the EMA, in particular the Committee for medicinal product for human use, and the pediatric committee. You have the word.

How the Regulatory System can be attuned to Science
Ian Hudson
Thank you, and good morning every one, and thank you very much for inviting me to his very interesting meeting.
My task is to talk about how the regulatory system can be attuned to science. The first thing to say is that there is a good recognition within the regulatory network that , as sciences evolving rapidly, it is very important that the regulatory system evolves to keep up with emerging science. Our regulation is all about safety, quality and efficacy, but it's about much more than that, it's also about allowing safe innovation, so appropriate products involving new technologies can come to the market for the benefit of public health. So I see one of our key roles as having a regulatory regime that allows safe innovation being able to take into account evolving science.
Regulation must be proportionate; it's no good putting a large number of regulatory barriers that are not necessary, given that all they would do is to inhibit innovation. I think another important aspect is that **science should come first**. We can't put in place a regulatory framework before science has evolved to sufficient maturity, otherwise it may inhibit innovation.
So, what tools do we have to try to keep the regulatory system attuned with developing sciences?
Well, a normal regulatory framework is based on regulations, there are directives, which are transposed into national law, and there are many guidelines, at the European and national level, many of which come through the working parties of CHMP and applicable across the Community. These guidelines set the standards and can change more rapidly as science emerges; it's much more difficult to change directives or regulations, but the **expected requirements are described in guidelines and this can be change relatively easily with the development of science**. Of course, guidelines are not legally binding as regulations are, but the guidelines can be adapted relatively quickly and easily.
Historically, driver to regulatory change can come both from major events but also from more minor keeping in tune with what's happening,. I've listed some of the events on the slide here: The thalidomide tragedy drove the medicines act in the UK . We have also add over the years high profile, safety issues that have resulted in changes to regulatory requirements for registration of products.. Another example was the clinical trial TG14-12, a number of years

ago which resulted in re-evaluation of the approach to be taken in first in man studies with novel products. We have seen new emerging diseases, eg TSE and as consequences of that regulations came to be changed. Other examples are Concerns about the supply chain; concerns over of neglected population that the market alone is unable to address, so, regulation has then stepped in to provide **incentives** in the case of **orphans and also a requirement in the case of the pediatric legislation, to address neglected populations.**

Another area where regulation has been introduced is in the area of Advanced Therapies, dealing with **stem cells, gene therapy, tissue engineered products, that are starting to emerge.**

And we have seen some very high profile concerns about drugs in the market place, and that has resulted in a number of changes over the years, introduction of risk management plans, and more recently the pharmacovigilance package that we are implementing

At a more routine level, there are a number of ways in which the regulatory system does keep in touch with evolving sciences.. Scientific advice working party see a lot of new approaches, Companies coming along with new approaches, new developments, are seeking advice in terms of what the regulatory requirements may be, and advice on how to develop the product,. In addition, CHMP has a number of working parties/ drafting groups, which may also have informal meetings with industry, like the pharmacogenomics working party, to talk about new developments in pharmacogenomics and personalized medicine.

When guidelines are developed, they always go out for public consultation to allow industry academia and others, to comment on. When new products come for assessment, regulators may choose to seek advice from external experts on novel areas. CHMP has scientific Advisory Groups which are groups of external experts, who can advise CHMP on specific points related to specific applications where perhaps the expertise is not sufficiently available within the system.

At a national level, there are various ways that regulators can keep in touch with developments in science: we have a large number of highly qualified experts in the national agencies, about a thousand people work at the MHRA. We have got a very active continuous professional development program which allows our staff to keep up to date. We have got extensive external links with the academic and clinical community at a national agency level, in the UK we have the Commission for Human Medicine, we also have around 200 external experts, we regularly interact with, seeking advice on applications, on scientific advice requests, where we feel it would help to have some external input in reaching our decisions.

The MHRA has about **250 scientific advice meetings every year**, again to advise companies on aspects of development of products. We also have other informal meetings with industries when they tell us about the development programs, portfolios , these meetings help us plan for the future.

We also establish special groups of external experts to consider specific topics. We put in place a program a number of years ago a mechanism for having scientific meeting involving relevant experts to consider areas of emerging science.

As an example of a more major event that trigged changes to the regulatory guidance there was a clinical trial on a compound TGN1412 a number of years ago. This was a first in man clinical trial and TGN1412 had a novel mechanism of action via the immune system. A group of 6 healthy volunteers all received the first dose, and all 6 of these healthy men volunteers experienced a severe cytokine release syndrome, with multi-organ failure, requiring intensive care unit treatment. They all survived but they were gravely sick, The preclinical data that had been evaluated had failed to predict these events. , As a consequence to this, the UK establish an expert group, chaired by Professor Sir Gordon Duff, from The University of Sheffield, to review the approach that should be taken with certain high risk novel products in the first introduction to men. He produced a report with 22 recommendations to improve the safety profile of first in man trials, particularly with these high risk areas where the preclinical data were less likely to predict the safety in men. Recommendations covered preclinical studies, the application process, interaction, between companies and regulators, and regulators and academic community, the need for access to external experts for regulatory agencies, the calculation of and administration of the first dose: The group also made recommendations in relation to clinical environment for novel studies in man with certain high risk type products and in relation to skills and training for people doing this kind of trials in the future.

As a consequence of these recommendations we put in place a different mechanism for reviewing this particular type of high risk

trial. We established an external advisory group able to advise us. We also put in place a mechanism for a accrediting phase one units.
We also took the recommendations into a European environment, and subsequently a European guideline was produced covering first administration into men with this type of high risk products.
On a more mundane level, certainly the ministerial industry strategy group meetings where we bring together regulators, industries, academia, patients' representatives, to debate topics where science is moving on, but perhaps regulation needs to keep up with it, has been a useful forum. These meetings result in a series of recommendations. We have had a series of these meetings now. The first one we had was novel imaging techniques to measure efficacy of cardiovascular treatments, and we took a number of recommendations forward in the European guideline that was being produced. We have also discussed earlier the access to medicine, then we started to develop a scheme to **allow earlier access to certain very promising medicines in the area of high medical needs before formal regulatory approval.**
Another topic was Benefit risk decision making, we looked at that at a national level and then that fed into the European group that's looking at that, as was mentioned earlier on, where we are looking at "how far can we go" in terms of introducing a more structured way in taking the regulatory decision at the end of the day. We also had meetings on safety biomarkers, personalized medicines, clinical trial design. All of these meetings are published on the MHRA website,
There are a number of other regulatory initiatives that happen at the EMA that keep regulators in tune with developing sciences, trying to prepare for the future. The **biomarker qualification process:** I think today we have had three procedures going through to successful qualification, one in the area of cognitive impairment, pre-Alzheimer disease. **The innovation task force** has spent a lot of time talking with companies and thinking about what is coming along. Regulators, both at a national and European level, are a part of the innovative medicines initiatives. There are also special groups in other areas, like nanotechnology, pharmacogenomics and personalized medicine. We are also looking into novel methodologies and statistical approaches
So to conclude, science is rapidly evolving, I think it's important that regulations evolve with it, but science should precedes regulatory development, however I do believe that regulators have many mechanisms in place to assure regulatory thinking does remain close to advances in science.
Thank you very much

VINCENZO SALVATORE
Head of Legal Sector EMA

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population

WELCOME SESSION

Discussion at the end of the Welcome Session

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Vittorio Silano
Thank you very much doctor Hudson for this very stimulating and challenging presentation.
We are now very much on time with our schedule, and we have the opportunity of a 20 minutes discussion, so the four presentations we have been offered are now open for questions and comments.
Well, maybe just to break the ice, I could start. I must confess I have several questions, perhaps I could set with one very particular and specific. The environmental risk assessment of the drugs, mentioned by doctor Salvatore, I'd like to ask: are there any regulatory innovation, regarding this, or is this more something we are preparing to face?

Vincenzo Salvatore
Well, there is a general need to harmonize the approach with regards to human medicine information related to environment, the environmental impact. The European Union it's also part of the Aarhus convention, on environmental information, so based on the access document regulation, 1049/2001, we are likely to receive a lot of requests concerning documents that we have generated and received, addressing the impact on the environment of the use of medicines. So far, the legal binding obligations stands from veterinary point of view, but we are aware that we will be facing with an increased pressure from lobbyists, corporate organizations, concerning the impact of human medicines on the environment, so we are trying in a way to anticipate things, and to tackle the issue before. Currently we have some basic sources of legislation, which are not clearly addressing the issue of environmental risk assessment of medicines for human use, but we know that we have to be prepared, to move forward before being forced by European legislation.

Silano
Another question concerning this new pharmacovigilance regulation. Is there any specific impact of such a regulation on pharmacovigilance also on herbal medicinal products?

Salvatore
Not really, also because as you know herbal medicinal products are not subject to centralized assessment. The role of the Committee on herbal medicinal products is to contribute to promote monographs national competent authorities may rely upon, but there isn't an assessment procedure as for other medicines. This has been criticized as a potential gap of the legislation, but this reflects the approach that has been followed so far dealing with herbal medicinal products at a centralized level, so without assigning to the Agency any responsibility in the assessment of this kind of products, and this is based on different traditions for different member States, and also on the reluctance of member States to transfer these responsibilities at European level. So as we don't have a responsibility in the assessment, we cannot have any role in pharmacovigilance.

Walter Bianchi
May I ask a question? In February this year I read a paper published

on the new England journal of medicine, concerning the Sentinel initiative, and my question is related to the fact that FDA people said that they are able to query 60 millions health information, 60 million people, so the storage of health information is now quite common and it will be much more common in the future. The question is: the EMA could, in the legal regulation nowadays available, could start a similar initiative? And in case the answer is yes, are you considering such a similar initiative, a similar project?

Salvatore
Of course we are aware of this initiative; we don't have a similar initiative in place. We have a broader initiative, which is called transparency initiative, that addresses single issues of communication. And with regard to pharmacovigilance, we know that we are establishing a system that will grant access – sometime selected access - to some sort of information. We are aware of the sensitiveness of the information that we receive and store. And we are also aware that we have to identify the right balance between the need of disseminating this information and the need to protect personal data affecting single categories of patients, and that could be particularly sensitive in the case of orphan drugs, or rare diseases. However, you will see more in the next few months, because actually Noel Whation, the Head of Unit atthe European Medicines Agency responsible for patients' protection, is currently coordinating this transparency initiative. We are working closely, as I said before, with FDA in order to have a similar approach, but for the time being we don't have a similar tool. We are also forced by the new legislation, as we will see tomorrow afternoon, to promote additional information on data that we will see regarding the use of medicine.

Bosone
Regarding the early access of the drugs, a question for doctor Hudson, just to have more details if possible: what is the current situation in UK for this? And for the future, I have seen that there is a special group studying this topic; do you think to move towards a French regulation, as the ATU, or like in Italy or other kinds of regulations?
And the same question for dr Salvatore: I wonder if the European agency has in mind to make an overview of the early access legislation in different countries in Europe, in order to make public and inform particularly the patients' association of this initiative.

Hudson
Yes, in UK there is the name patient supply currently as a mechanism for enabling patients to receive drugs, and their physicians can prescribe basically any medicinal product, licensed or not, to patients, to fulfill the individual patient's needs, on their own responsibility, it's obviously a higher responsibility if it's a non licensed product. We have been considering whether to go beyond that, to provide a regulatory opinion on the potential risks benefits of the use of certain unlicensed medicines in areas of high unmet need, similar to the ATU scheme in place in France. This scheme is not in place at present, but we are in the process of considering whether to introduce it. It had been put back as there were a lot of other reforms ongoing. However this scheme, if introduced, would not replace the named patient scheme.
We do have other regulatory tools in terms of a notification scheme for importation of unlicensed medicines. There is also a prevision that CHMP level, for a scientific opinion, compassionate use and scientific opinion at CHMP that has been used very occasionally particularly in relation to pandemic flu, and the use of antivirals.

Salvatore
It's a very interesting proposal, and I think it would be very helpful, to have the outcome of this monitoring exercise, some sort of survey, what's happening in a different member States. Unfortunately, we don't have any prevision to do it as an Agency, and we don't even have tools or resources to do it. I think the Agency would be happy to support this kind of initiative, if agreed at the Heads of Agencies level. Therefore, it should be the head of each single competent authority to propose this issue for discussion at one of the next meeting of the HMA. If partner competent authorities agree to that, we would join this forum as observer and of course we would be more than pleased to support this initiative, but it's out of our responsibilities, so we don't have any hook in order to impose it.

Mirella Franci, Sigma-Tau
I have a question for dr Salvatore. I'd like to know, regarding the falsified medicine new legislation that came out in June 2011, considering the possible high costs for the various countries in terms of the new requirement for the active ingredient suppliers, and the new trace-

ability need. If this new legislation will have to come out within 18 months, from June 2011, in all the countries, or it is possible to have a gradual implementation in the various markets? Because there are a lot of very important economic expenses, that may come out due to this new law, which are partially implemented in some countries. For example in Italy we have a partial implementation, but not complete, but I don't know in other markets what is the situation.

Salvatore
Thank you for asking this embarrassing question. What I can say is that legal obligation are binding, and Member States have to implement by the set deadline, by transposing the directive into national legislation. The legal responsibility is to the Member State, because in case Member States fail to implement within the set deadline, there will be no obligations for industries, apart from obligations that are included in provisions, that are self- executing and don't need any specific national measure, taken by national competent authority. If you promise not to quote me, I will tell you that the European Commission is responsible for triggering infringement procedures against Member States when directives are not implemented in the right way or in the due time. The European Commission is also aware that sometime it could be very difficult, for different reasons, to meet the deadline set by the directive, which will be the case for pharmacovigilance implementation. We already know that some of the targets will be reached at a later stage, because we are still waiting for implementing regulations from the Commission, and until the Commission issues the regulation, member States will not have the parameters to refer to for implementing the directive. So, what I want to say is that we saw it, also with regards to access of new Member States to the EU, upgrading current marketing authorizations in order to make them complying with the *acquis communautaire*. In principle the Commission can trigger an infringement procedure the day after the expiry of a deadline. It's not always the case, so it may be the case that there will be some sort of tolerance period, if there are good reasons that have to be reported to the Commission and have to be duly assessed for justifying the delay in the implementation. If you ask me the question as a legal advisor, I would say: you have to implement the obligation by the set deadline.

Ceci
I have a question for Ian Hudson. You cited these biomarkers qualification process that I believe it's a very interesting fact. My question is: are these first assessed biomarkers dealing with both adult and children, or they are only for adults? And, there is a special attention to identify and qualify pediatric biomarkers, since this is a particular and very important point to do now?

Hudson
There is a huge amount of excitement and interest in biomarkers but unfortunately a lot of the evidences isn't there, relating to using novel biomarkers in monitoring in preclinical studies, and early clinical studies in men. So, we are not really at the point of adults versus children, more use preclinically versus clinically. However the third biomarker qualification actually relates to pre-Alzheimer cognitive impairments selection of trials, so this would be adult orientated. Sso unfortunately there is a lot of excitement and hope, but in reality this hasn't yet translated in terms of solid evidence for the use of a lot of new novel biomarkers.

DANIELE ALBERTI
Medical Director – Novartis Oncology

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population
How to provide scientific Evidences
Specific Diseases: haematology-oncology

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

I thank very much the organizers of this foresight course. I'll try to be short.

In my presentation, I'm going to give you an overview about which are the new development strategies for the target therapies in onco-haematology, giving an example coming from my company, Imatinib, not describing what Imatinib cures, but to show how this model changes the organization over research development in a Company.

Before Imatinib there was in many companies an empiric drug development, so generic drugs are to kill every cell including the mutated cells, and this approach was carried out according to a traditional drug development, which was driving the entire organization of pharmaceutical companies, but also the regulatory parties of the research units. As soon as you get results, you may adjust the development strategy, modify a molecule, having a continuous possibility of improving the outcome, and one point I want to underline is that the biomarkers, in addition to the usual aspects of drug development, may play a critical role.

With Imatinib we moved from empirical to a selected drug development which was successful, because the survival of these patients reacted more or less the expected survival at the same classes. However, having understood that not all the patients were responding to this approach, there was an improvement of the molecule of a new drug which was more able to respond to a specific ematochinase, and that resulted in results even better than those obtained with Imatinib. We hope to reach the eradication of the disease.

As a result of this, this example of the ability of effectiveness of personalized therapy, the company changed its organization completely. What I'd like to underline in this slide is that we set up a unit of authorization of medicine, which was a bridge between traditional research and clinical development. However, it was accompanied by a unit focused on molecular diagnostic and more importantly, using thousands of cells lines, in order to get inputs to continuously improve the outcome for the patients.

Our unit is located in FloranPark, and this morning some colleagues spoke about the multidisciplinary of this. This unit is bridging all of the knowledge, not only inside the company, but being in Cambridge in Massachusetts, it's interacting with the MIT, Harvard University and other units, because even a big pharma is enable to take care of all the aspects in the target therapies.

Why do all this? For many reasons: patients are higher in the list, but also there is a pharmaco-economic outcome, because we pay only for effective drugs, and we are not trying to get drug in general way, hoping that somebody will respond and that should be taken in account by the regulatory agencies in order to change this model of drug evaluation also at the level of the stakeholders.

Is it true? One of the main consequences of this is that we are moving to trials on preselected patients, which have signals, a pathological pathway and some biomarkers. As

the result of this approach, we will have the possibility to reduce the number of sample size in trials and also shortening the overall time of development. That is important in a situation of limited resources. Does it work? I don't want to speak only about my company, ask to De Santo whether this approach is validated outside Novartis. It works well, because if they had followed the traditional approach of unselected patients for Trastuzumab, they would have needed 2000 patients, evaluated for many years. Preselecting the population, they are able to show effectiveness with the patients with this type of disease.

In conclusion, we are moving not choosing a drug but a target, preselecting patients with this target, testing the designed drug for this target and checking whether it works or not.

As I said, a better requires a huge organization, using biomarkers experts, using cells lines as incubator to develop the drug, and the pre-selection is no longer made in any way, but using the different DNA profiling.

Does it work? Yes, and just showing that having followed this approach we are no longer haemato-oncologist treating indications, according to the anatomy, the location of a disease, but we are selecting patients according to their target, and checking which is the best drug to be given. Just to give you an example, which could be used for any type of drug, you see that a move-inhibitor, initially developed for basaliomas. You see that even if it is a benign disease, it could work in patients with such huge implications for the skull, but this pattern is also present in some patients with mejulloblastoma, and you see after 2 cycles what could be the outcome. Where should we follow this approach? Of course, when there is a single pathway, as in leuchimia, it's the easier model. However, in those mall cellular cancer where we have many pathways, it would be an approach worth to explore. Just 3 days ago in the web I found that a new target therapy for non small cellular cancer and health inhibitor was able to get the approval with only 2 trials, and phase 1 trial extension, plus a phase 2, with of course the commitment of doing all of the series of steps necessary.

I think we are leading a revolution, because when I joined many years ago the pharmacological company, it was impossible to think about this. Remember last century, it was written that kinesio-inhibitors are something which we don't know what do they mean. Now there is a total change of this paradigm.

What are the consequences? That biomarkers and molecular targeting of cancers to design new drugs is a key factor, and these biomarkers are developed for many purposes, to monitor the pharmacodynamic effect, the safety, to predict the clinical outcome. So, this is something that we are trying to do, many other companies are trying, in parallel to the traditional drug development, in order to present to the agencies not only the results of a trial, but the biomarker which is able to pre-identify the patients able to respond to the new drug.

These slides are coming from prof Rasi, he presented these 2 years ago in Pavia. Also the agencies are looking to this approach of personalized medicine in order to identify drugs able to respond, tools able to identify the patients, in order to have a more focused scientific approach but also to save money, because the money, especially in this period, is not so available to everybody.

To conclude, what are the consequences of this approach and for who, the companies, the physicians, the hospitals, the patients? The trials could be much smaller than in the past, focused on patient subpopulations, and the one of the consequences would be that doing smaller trials in these patients. In addition, fewer centers would be involved, so we would respond to the issue of competition between clinical centers, which would become attractive for everybody, industries, agencies, appealing to attract resources and investments in clinical research. Another consequence is that the centers, with pathologists, imaging facilities, should be able to run in parallel trials in the same pathological indication, but on different pathways in order to have a single trial on a specific pathway. This is something, which requires a total different approach. An ethical review board should authorize a pretrial diagnosis of a pathway in order to allocate the patient to the right compound, which could be of benefit for the patient.

Another consequence is that in phase 1 studies we are not looking only to the safety or the kinetics, but we are looking for activity. In phase 2 trials we look for the register, and in phase 3 trials in the subset of populations could be part of a post-marketing surveillance to prove and confirm the activity of the drug. All of this should be acknowledged by the agencies, which should change their roles. I'm very happy to listen about flexibility, but companies require not only flexibility, but also new rules

to drive the decision making processes and investments.
Thank you very much for your attention.

Discussion
Bosone
A new paradigm. Do we expect that it will be possible to expand this new methodology with the personalized medicine to the other diseases, for example in my mind I have the Amiotrophic lateral sclerosis, which is a disease without any valid treatment for the moment. I've seen that for example in multiple sclerosis natalizumab is a target therapy, and interferon beta wasn't, so can we expect that this paradigm can be used also in other fields?

Alberti
I think that we need to be sure that we have the true target, and once we have identified the target we have to make an attempt. I'm not used to be very optimistic. We have started a new approach, we are at the beginning, we are very lucky to live this situation, but we have to be prepared to some frustrations, because we don't know exactly all of the molecular basis of most of the diseases. As soon as we have a better knowledge of the specific or unique, or more targets working together, then we can try to develop a new pharmacological agency.

Ceci
I understand that the model you proposed is the future model, and it may be for many cases. It's able to reduce the sample size, and I understand this is possible to do if efficacy is the goal. But how can you reduce the sample size without lowering the power for acquiring safety data with this new approach?

Alberti
I've focused my presentation on activity in onco-haematological indications. For safety we need to keep open all of the present approaches, for the post-marketing surveillance, we haven't just passive reports but specific programs of sentinel studies, observational studies, in order to have enough numbers to get information also on the rare adverse reactions. For sure.
One point if I can add a comment prof Ceci. We have a small sample size on patients who have the mutation pathway, but what I didn't mention, I forgot: we have to screen many more patients. And that could have an impact on the cost of development. We are doing a trial on an ak-inhibitor. To get one patient, we have screened 45 patients, with all the analyses to identify a pathway.

Rossi
I'd like to add something to this topic because I think it's extremely important when we are trying to develop innovative medicine. Of course safety is extremely important, but with innovative medicines it's very unpredictable what kind of safety signals you have to follow, and we have some interesting examples from Miriam this morning, even a vaccine was associated with something that was totally unexpected.
So, it's not on the basis of the classical clinical trial that we will be able to follow the effect of therapies that are targeting molecular mechanisms, but the same type of model that Miriam was showing this morning. So, I don't think that just clinical trials will address this.

Paolucci
I want to reinforce the consciousness I mentioned, because we are concerning target therapies at a very first part of a very interesting learning curve, but we cannot step forward in this field without making clear concepts. So, if we have one interluchine, and we try to inhibit that interluchine, it's one thing. If we have a monogenic disease, we know what it is, and one gene it's involved. As I showed in that colored cartoon, cancer is a genomic disease. The tumor cell is not a tumor cell because it prevents apoptosis. Period. So, you have an anti-apoptotic targeting and we solve the problem of cancer. It's not the way it works. It has apoptotic inhibition, capability of making metastasis to resist to whatever. There are ten marks in this picture, and it's very simplycistic to think that you interact with one gene and you have solved the problem. We must be aware that we have to go step by step toward this direction, but we must cool down a lot of enthusiasm, because it will take ages before we can have in our hands all the target therapies able to froze down a tumor cell. And indeed, the second point will be, and we have a very negative issue about this, when we try to associate only two target therapies, all the trials have been stopped after few months because of toxicity. So, we have to be very cautious. We don't want to deny a scientific progress, that's the way to go, but we have to be very well aware that it will take time, and so enthusiasm is a good thing, but in the relationship with the patient we have to take into consideration this aspect.

IAN HUDSON
CHMP UK Member

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population

ROUND TABLE I: THE FUTURE EUROPEAN LEGISLATION FOR CTs

Are the Clinical Trials and the GCP Directives to be changed?

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

I would like to start with some background about the clinical trials directive: prior to the directive, Member States operated their own regulatory system. In the UK we had our own regulations, a well established regulatory and ethics committee review, independently from other Countries, we didn't review healthy volunteers trials at all.

Then along came the clinical trials Directive, which was transposed into national legislation, this is our version transposed into the medicines act in the UK in May 2004, subsequently additional Directives on GCP and GMP came along, and also d detailed guidelines, which is now in volume 10 of Eudralex. At the time of first implementation of the Directive, detailed guidelines were not available and that was one of the problems.

The aims of the clinical trial Directive were to harmonize the rules for conducting trials across the EU, trying to have one common set of rules that would both protect the rights of subjects in clinical trials but also provide the good environment for running clinical trials and the valuable data coming out the clinical trials processes. The hopes, the aspiration, the expectations from clinical trial Directive were the rationalization of all the documents, the administrative procedures, and one set of documentation could be developed and used in all the member states. A **Single process**, a single set of rules regarding safety reporting, timelines, assessment decision, hopefully to get as close as possible to **harmonized decisions**, whilst recognizing that the individual Member States remain responsible for the assessment decision. Some of the definitions that had to be agreed include what a clinical trial is, or more important on what a clinical trial isn't, particularly what constitutes non-interventional clinical trials. Also what the investigational medicinal product is, and what it isn't? Also agreed definitions of sponsors and amendments. Hopefully, reducing any national variation, reduce the burocratic burdens, and overall improve the environment for clinical research in the EU. These were the aspirations.

But there have been some issues with the Directive. A number of things were happening around the clinical trial Directive coming into place: the EU enlarged from 15 to 27 member states, and that added a level of complexity. Given that the transposition of the Directive into international legislation does allow some scope for variation in interpretation, there has been some local interpretations during the transposition process into national legislation. The guidelines weren't there yet at the time when the Directive came in, Member States didn't all bring it in at exactly the same time, so people trying to do a multinational trial had to operate through the CTD in some countries and not in others. Some countries were a year or two longer in terms of bringing the Directive in.

Across the Community, Member States had different approaches to clinical trials, some had a lot of experience, some had very little experience, some had a lot of interest and wanted to give it a lot of priority, other Member States really didn't want to give it high priority or were

less interested in it. And the need of resources available in the Member States to be able to run clinical programs and to assess CT, the infrastructure was variable across the Community. Another issue with the directive, and probably the most important issue is that the approach taken was basically "one size fits all", there was a lack of proportionality in terms of implementation.

The clinical trial Directive has however achieved a number of things. There is legislative harmonization across the Community where there wasn't legislative harmonization before, we just heard about the EUDRACT and the single submission into a single database across the community for clinical trials, we now have clear identified roles for sponsors, for competent authorities, for ethics committee. We have common timelines for applications across the Community , that has been achieved. And there is a much better networking between the regulatory agencies across the community looking at clinical trials, and also between regulators and ethic committees, for example in the UK we have a memorandum of understanding between the MHRA and the ethics committees, and we have frequent dialogue about individual protocol and policy issues.

And it improved confidence in the standards of clinical research related publications in the EU. But, there is always a, some issues remain. We have seen some reduction in trial numbers – in the UK from 1100 to 900 over the past year or so. Similar reductions have been seen in Europe.

So, what can be improved? There are a number of areas that can be improved. We have seen some divergent interpretation and national implementation directive, in transposition into national legislation, and indeed in the interpretation subsequently, some national differences. I've listed some areas of improvement: definition, the application process, safety reporting, use of the databases, the competent authorities, review process, and difficulties faced by non-commercial sponsors.

We haven't been entirely consistent across the Community in relation to what an investigational medicinal product is, or more importantly what can be excluded from the definition of an investigational medicinal product. We have now got the concept of non-IMP, but it doesn't have a legislative base. The clinical trials facilitation group has worked very hard to resolve as many of these issues as possible.

In relation to clinical trials, exactly what is a clinical trial and what isn't? Interventional clinical trials are within, but non-interventional clinical trials are excluded from the directive,? We need a common interpretation of this. There has been some difference in interpretation of what a substantial or not substantial amendment to a clinical trial is, after the CT has been approved, what is substantial needs review by agencies, whereas a non-substantial one does not ,. Again the clinical trials facilitation group is trying very hard to come out with guidelines on that, but this has come late in the day, and there have been some difference of opinion between the member states.

There is also been a difference of views about sponsorship for multi-countries trials, whether you must have one sponsor among a number of people, clearly defined, or one sponsor for the all trial across member states. **If it is a collaborative academic trial applied in different states, this is a big problem**. In the UK we decided that the role of the sponsor, as long as we are informed and can agree on who is responsible for what, can be taken by a number of people.

In terms of the CTA process, I think we can improve by having harmonized requirements for exactly what needs to be in the clinical trial authorization.

And the timelines were often written in the legislation and not always as transparent as it might be.

Safety reports. This was one of the great benefit of the clinical trials Directive: everyone must report to the eudra-vigilance, all the Member States reviewed the data, with a single annual safety report template, and shared assessment across the Community. In reality it didn't quite work out like that, there was variety in the ability of sponsors to report, and some of the academic groups have not been able to do it directly but via the Member State Competent Authority. Member States have added their additional requirements, a variety of different requirements, some of them on paper, some electronic, in different forms, etcetera. Not all Member States have fully supported the eudravigilance clinical trial module, not everything have been uploaded in time, and so we had some different approaches there, and so in reality the european database has not been kept as up to date as it should be. There have been some progresses, but there are still issues.

Inconsistent data entering by Member States into the EU-database, meaning that it has not be as useful as it might have been. For example, some trials have been stopped, but the decision has not been entered on the database. It's improving but it has not been as reliable as it might be,. And also, it hasn't been as searchable and usable as member states would have liked to see, to make it a very useful database.

In terms of the assessment process, we have in the past reached **different decisions on clinical trials**. The CTFG has put in place various initiatives to try to provide training for the assessors across member states, trying to facilitate consistency in approach. In recent years there has been a higher coordination among the Member States, and there has been a **harmonization procedure** over the last few years, where for multi-countries trial applicants can select a country to take a lead in the process, and there is a single lead country to assess across the community. It's moving towards a more decentralized procedure type approach to clinical trials, it hasn't been very used by industries, but I think it's definitely an advantage to have that in place.

National requirements: there have been different national requirements in terms of the application process, local translation and certain national application form, specifically national information requirements, and many member states dealing with the problems for the development of multi-countries trials.

So, these have been the problems that have been highlighted, and many of these have been, or are being addressed, through the work of the clinical trial facilitation group, trying to reach harmonization. So the commission is thinking about changing the Directive and they consulted on this and they prepared some proposals for consultation in 2010, and a number of areas they are thinking about changing, and they are on this and the next slide.

The first relates to multiple divergent assessment, offering a number of option for streamlining the assessment, **including a centralized process, or something more like the decentralized process, a number of options were outlined.** They highlighted the inconsistent implementation of the directive in terms of substantial amendments, suspected adverse reactions, and the scope of the directive, what is in, what is out, non-interventional trials, etcetera.

They also commented about the regulatory framework not always being adapted to practical requirements, it's not always risks commensurate, basically one size fits all, so if it is the first in men immunological targeting monoclonal versus a phase four study with a well known substance within indication, the same requirements pretty much are applied in terms of the documentation, etcetera. And of course the risks are completely different in those two scenarios. The Commission, in their proposals, recognize the needs to move towards a risk based approach.

They also commented on some of the difficulties particularly in certain areas, such as pediatrics and emergency situations, where the normal procedures for consent is much more difficult, and the fifth area they consulted on is compliance with GCP in countries.

So, they have consulted, we have seen some of the responses coming back, I think generally we would welcome the proposals offered from the Commissions. Next steps are proposals for a legal text next year, to be negotiated by the Council and the parliament. Hopefully all of this will be before we arrive to the EU parliamentary elections. ,

Finally I would like to mention a couple of things we did in the UK within the scope of the existing directive, and there are actually a lot of things that can be done within the scope of the existing directive. We have applied a much more risk based approach recently, in relation to low-risk trials. We have introduced an notification scheme for low risk trial, for example a phase 4 trial within indication, all you need to do is to notify the MHRA that you are doing it, with minimal documentation, and if you don't hear anything within 14 days (we have 14 days to object), then you can go ahead. We are also separating piloting a risk proportional monitoring approach to clinical trials, where the extent of monitoring is based on an analysis of the trial, not a " a one size fits all" monitoring program, but if it is high risk, critical data, then you have much more extensive monitoring. The applicant and regulator need to think about the risk assessment with the drug, the trial, the procedures, the data etcetera. Then think about the monitoring that needs to be carried out. This is currently being piloted at the moment. We have also adapted our inspection program to be much more risk based as well, so that will focus our resources on the higher risk areas.

In summary, the clinical trials directive has achieved some benefits, but it has only been partially successful in reaching the harmonization it set out to achieve in Europe, there are a number of issues remaining across a number of areas. There is a need to change to ensure that EU remains an attractive place to do clinical research, recognizing that we have seen a decline in the amount of clinical research that has been carried out in Europe.

Thank you very much.

LEONARDO SANTI
NCBR, President

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population
ROUND TABLE I: THE FUTURE EUROPEAN LEGISLATION FOR CTs
Which role for EUDRACT to cover unmet needs

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Leonardo Santi
Thank you Adriana for the invitation at this important meeting and especially at this round table. In Italy the Minister of Health is fully aware that there are many legal, ethical and regulatory obstacles to clinical research. Presently MoH is preparing for parliamentary approval a new bill which incorporates the suggestions from the European Commission. The proposed law will require authorized centers carrying out clinical trials respecting precise requirements during all experimental procedures. For example, the reorganization of the local ethical committee with added strong and effective health coordination trough the centers for clinical trials. A project leading to the establishment of the national clinical research network has been proposed by the "centro Nazionale per le risorse biologiche", and will be presented in depth by prof Dino Amadori during the course of this round table.
I'd like to empathize that our understanding and treatment of diseases have always and heavily relied on parallel development in clinical and biological research. At a time where increasing number of biological drugs are available to clinicians, integration between the laboratory and the clinical has become critically important. In addition, the exchange of data and materials among bio-banks will play a fundamental role in acquiring new knowledge for the development of therapeutic strategies. Bio-specimens from clinical trials represent a valuable source of samples for translation in research, whether in clinical trial patients care has taken priority over research goals and the specimen collection is still principally carried out for diagnostic purposes. Sample collection is very different, not only among various organizations conducted in clinical trials, but it may also characterize the variability of a given institution. Relevant clinical information associated with the sample is often poorly recorded. Moreover, due to financial restraints and the lack of specific founding, clinical investigators are encouraged only to collect a minimal number of samples. Regulatory and legal requirements offer often a complicated access to relevant information. The result is that sample is frequently not sufficient for research purpose. Collectively, these issues create a fundamental problem for the use of clinical trial specimens for transnational research.
In my opinion, this problem is necessary to be taken into consideration.
I will leave the word to my colleague professor Brasseur.

Brasseur
Ok, thank you very much and good morning everybody, it's my pleasure to welcome you for this round table discussion, and we have a number of discussant already prepared.
But before this we will have two presentation, the one from Galluccio and the second from Ian Hudson.
So, without delay I will leave the

place to doctor Galluccio for the EU database of clinical research.

Galluccio

Thank you very much mister Chairman, thank you for the invitation to this very interesting round table, a very challenging title. The future of EU legislation for clinical trials.

There is a huge discussion ongoing and maybe next year the new Directive will be presented.

So, my presentation will be on the existing clinical research database in Europe. We have databases that operate at EU level, many of you know EudraCT, the EU database that was established to exchange information between the competent authorities in the Member States, the EMA and the EU commission.

EudraCT is a very large database of interventional clinical trials, that captures the protocol data included in the clinical trial application form, eventual amendments to the clinical trial application, the data of the authorization by the national competent authority and the ethics committee opinion, the details of the GCP inspections carried out in the EU.

Recently it has been launched the EU clinical trials Register, a public Register, designed to benefit the general public by expanding access to trial information, but there are also many local initiatives, at Member States' level. These databases have different aims, they are a research application system for improving the application process for regulatory and ethical review. For example, the Italian "Osservatorio" and the UK IRAS, but there are other initiatives in other EU Member States.

The website of the EudraCT database states that the database is confidential, the EU clinical trial Register, to search clinical trials protocols data is of public domain. Some words on the legislation, registration and results of reporting from clinical trials in the EU.

According to the clinical trials directive 20/2001, launched in May 2004, EudraCT is an instrument to exchange information about ongoing clinical trials between the Member States, the EMA, and the EU commission.

Further, it could be a tool to coordinate at EU level the assessment process, but I'll explain later the initiatives in this field.

Since march 2011, following changes to the EU pharmaceutical legislation, some information held in the EudraCT database have been made public through the clinical trial register, that is the protocol data in adult phase II, III and IV clinical trials, where at least one investigator site is in an EU Member State, and the description of any pediatric clinical trial, with the investigator sites in the European Union, and also any trial which is part of a paediatric investigational plan, including those where investigators are in third countries, outside the EU.

The EU clinical trial Register is a Register containing information on investigational medicinal products. It doesn't provide info about non-interventional clinical trials on medicines, or clinical trials for surgical procedures, medical devices or psychotherapeutic procedures and other kind of clinical research.

Next step within the current legislative framework is to expand EudraCT to include report of clinical trials results. Therefore, the results will be included in a database hosted by the EMA, with the support of the Member States; we are waiting for the publication of a technical guideline by the EU commission and then it will start the process of developing the results database.

Some words about the importance of public reporting of clinical trials' protocols and their results, in a common EU repository. Of course, the suppression of selective publication of results is based on the interest of sponsors. Increase of transparency on a public level in clinical research, avoids unnecessary application of clinical trials, favors promotion of social value of research, allows trend analyses in the clinical research by the policy makers and can be a work tool for authors of systematic reviews.

And last, but not least, fostering the integrity of reporting within the requirements of a prospective registration, for example of endpoints and endpoints time-points registration, addressing the problem of partial publications on such measures, or acknowledgments of eventual amendments in the prespecified measures.

Now I want to give a short presentation of the Italian database, that is the Osservatorio. It was launched in December 1999, many years before the EudraCT. At the beginning it was an interventional clinical trials database. Recently, in March 2010, it has been launched the non-interventional CT module, and on December 2010 we have published a portal of clinical research with medicines, interventional and non-interventional.

Further, we have the Osservatorio public site, containing data of clinical trials with investigational clinical products, and complete information for the health care professionals and the public in general. Every year AIFA publishes an annual report on CT research in

Italy, and since December 2010 we have started distributing a clinical research newsletter addressed to the users.
What about the Osservatorio secure site? It has another objective, of course, it is an integrated research application system for the request of the ethics committee opinion and the competent authority authorization, and it has a link with EudraCT, there is a semi-automatic data upload from OsSC to EudraCT , so we are feeding the EudraCT from the Osservatorio's database.
Osservatorio ongoing developments. AIFA has established a telematic implementation group, the TIG, including representatives of the the ethics committees, the sponsors and CROs and the ISS. It has the following mandate: define the user requirements with respect to each submission, validate software development, actively participate in the pilot phase of the project, provide support to other initiatives to promote administrative harmonization of guidelines in compliance with applicative regulations. In June 2011 the first user acceptance has been completed. The aim is to deploy a validated submission system, capable of speeding up the application process for both regulatory and ethical review, harmonizing procedure and shorten the timeframes in the review process of clinical trials.
There is a new legislation under preparation, under discussion. In 2012 the proposal will be presented, a public consultation on a concept paper was held from October 2009 to January 2010, stakeholders have been invited to comment on this consultation.
Item 1 of the public consultation was about cooperation in assessing and following applications for clinical trials.
The proposal will be for the sponsors to send the documentation for requesting a CT authorization to all Member States concerned, through a single EU portal and a single submission. The EU portal will subsequently distribute the info to the Member States concerned.
The EU has collected some replies to the public consultation concerning this issue. A large number of responses supported this unique submission, stressing the idea of including the ethics committee in the portal was a challenge.
Several responses referred to existing national portals, in particular the Italian Osservatorio and the IRAS system in the UK. Some responses focused on the fact that the unique portal should replace the national portals. Several responders raised the issue of languages of course, and many responders stressed that setting up a single EU portal was challenging in terms of functionality, compatibility, performance and reliability. For me this is the major point, but of course it's a very complex project.
My conclusion: EudraCT was launched in 2004, and it has been evolving in response to various policy initiatives. As a consequence, a prospective registration and publication of protocol data has become standard practice in Europe. In the near future and in the framework of the new legislation, the public report of clinical trials results will be achieved, probably within the next year.
At a national level, some Member States continue to manage their own database in order to improve the application processes from both regulatory and ethic point of view. The so-called e-submission.
The need of a public reporting in a local language and to have information on the state of the trial in every clinical site support the role of national registers. Future regulation should take into account the proposal discussed in the EU Commission public consultation regarding the single portal for the management of the all clinical trial application processes. The new legislative framework should considerate the existing national registers, and take the opportunity to include the ethic committees in the single EU portal.
Thank you very much.

Adriana Ceci
Teddy Network Coordinator,
PDCO Member

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly PopulationRound Table I: The future European Legislation for CTs

GRIP (Global Research in Pediatrics) & TEDDY

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Directive 20/2001 is of fundamental importance in pediatric field, because it introduced for the first time the word "children" in a legal, ethical contest declaring that ' We have to devote to children a special attention, and children are entitled to be subjects of clinical trials in a specific manner'

Before this Directive, children and people that were not able to give consent were put in the same category while we know now that this is completely different situation. So anytime we speak about modification of Directive 20/2001, we have to take into account that the level of guarantee for children that we have reached with the Directive and with the subsequent legislative acquisitions , should not be lowered in any case. In particular, we consider that some very important document , like the ethical recommendation published in 2008 to complete the ethical framework opened by the 20/2001 Dir and that represents in our opinion the high level standard for children clinical trials in EU, shouldn't be touch.

For this reason the 20/2001 Dir. represents the basis of the activity of TEDDY, the first clinical pediatric Network of Excellence, and then of GRIP, sharing the same interest on pediatric clinical trial. A common objective of the two projects is to address the methodological issue connected with pediatric trials, as well the ethical issue and the current practices in this field, and to collaborate in recommendations and other documents to be shared with the EU Authorities and other stakeholders. Very briefly, the basis of our position on the Directive modification under the methodological point of view, is summarized in a Methodological TEDDY position paper published at the end of the TEDDY project.

In addition to elucidate specifically the paediatric trials procedures followed in Europe, we have performed two different surveys. The first one has been done in 2007, at a legislative level, and has enquired about the rule governing the approval of the pediatric trial in the different Member States. This survey has enabled us to identify important differences among EU. First of all the number of ethic committees is very different varying from 300 ethic committees (Italy) to only 2 or 3 like in other countries. Other differences have been detected in experience, in capacities to deal with specific problems and in particular with pediatric problems, etc.

So, through this first survey, we identified that the legal framework is very much differentiated in Member States, and we concluded this survey with the idea that what is important is not to modify the Directive, but to implement it in a more coordinated manner. This was our message at this point.

So, the last survey has been done 2 years ago, and we reached a consistent number of ethic committees in Europe, being specifically devoted to identify which are the feelings of the single ethic committees, not the Member States, regarding the approach to pediatric trials. The principal conclusion has been that the crucial point are the same points that are now part of

the revision of the Directive, like the issue related to insurance, the issue related to risk assessment and minimization procedure, the complexity to evaluate the risk benefit for pediatric trials, the burden of the administrative problems. So, at the end of this survey, we concluded that an approach that proposes to modify some points of the Directive can be accepted, but this approach is related to what I said before, about not touching the guarantee and the level of children protection.

So, in an official GRIP document to the Commission we have suggested the following:

- the proposed revision should only be considered in the light of pediatric specificity , that means not only the general GCP, but the pediatric GCP including the ethical recommendation
- the existing pediatric procedure should be updated according to the PDCO process of the PIP approval,
- the competence of ethic committees in pediatric that are very low at the moment, should be redefined
- the current prevision in the clinical trial Directive would be maintained for single country clinical trials while a single approval should be considered for multinational trials.

This position regarding the single submission to the European portal is quite different from others circulated even today, in the sense that our opinion is that both the central and coordinated appraisal can be acceptable, and even in different cases. For example, all of this can reduce the number of procedures, having the effect to facilitate the assessment of trials, but in particular a central assessment can be considered for: rare diseases, emergency situations, advanced therapy and those pediatric trials requiring a high level of knowledge and expertise, which is difficult to identify in all the European countries.

Another point is that when a coordinated assessment procedure (that seems to be the most supported approach at the moment) is considered, we have to integrate what is proposed at the moment with some aspects specifically devoted to pediatric , that are derived by the existing rules that we should not neglect in this moment. In addition to the cited ethical aspect, we suggest to include the need to appoint a data safety monitoring board (not mentioned at the moment), the provision of the medicinal product to patients involved in trials after the conclusion of the trial where appropriate, to provision of appropriate pediatric expertise at any local level and more generally speaking the necessity that ethic committee and competent authorities have a specific awareness about kids' problems, and the obligation to guarantee children's health and well being.

Finally, in case of non-interventional trials, we remember the great importance of this sector in pediatrics so we completely agree that this kind of studies should be performed at an high scientific and medical level, and that clinical trials academic non-commercial should be also harmonized with proportionate requirements, in order not to go in opposition to the feasibility of this kind of trials.

In conclusion, our position is that modifications aimed to simplify are in principle acceptable. Centralized procedure for approval is not considered by us unfeasible, on the contrary should be preferable in some specific cases, but anyway the current level of children protection shouldn't be lowered, and the pediatric specificity should be integrated in any proposal for modification.

SPEAKERS AND AUDIENCE

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population
ROUND TABLE I: THE FUTURE EUROPEAN LEGISLATION FOR CTs
Final Discussion

Brasseur
Ok, thank you very much again, I think we had very interesting presentations, some information to feed the debate. Maybe for the sake of clarity, since we had at least 2 different approaches, the one concerning the databases, and the other one concerning the revision of the Directive, we could start the discussion with the databases.
One question to dr Galluccio: at the end of the day, when I see that the confidential databases are falling into the public domain, is anything left that should be kept confidential, in these different databases, or do you think the information should become fully available to the public? And if not, what would you believe should remain within, for instance, regulators only?

Galluccio
Well, as I said during my presentation, we have lots of information that have been made public. What is excluded from the public domain are phase one trials in adults. Phase one trials in children are publically available.

Brasseur
Why? Is there any reasons for maintaining adults' confidential and not children's one?

Galluccio
I'm sorry, we should ask to the Industry representatives, because I am available for the publication of adults trials too. I think in the future also phase one adults trial may be made public. Everybody, you can search information about phase 1 trials, and have all the information available. Personally, i don't see any problems in publishing phase 1 trials...

Dehlinger-Kremer
I don't have a different view, but according to the regulation is mandatory to make the data of trials public, so...

Brasseur
No, but my question is the other way around: what could be maintained confidential and why, is there any reasons to maintain something confidential in the databases?

First question
The only binding obligation that stands from current legislation is to protect, so not to disseminate, commercial confidential information, and in principle in clinical trials you shouldn't have a confidential information reflected in the document itself and personal data protection. That means that sensitive personal data concerning patients should be kept confidential unless you have got the informed consent of the patient, or of parents, to disclose this information. These are the only current restriction to disseminate information reflected in clinical trials. In principle, information concerning patients have been authorised to be disclosed.
For the paediatric, there is the concern concerning the identification of the patient, unless the parents gave the consent to disclose this information.

Peuvrelle
My personal feeling is that there is almost nothing left which isn't disclosed, in the current databases, so of course it's also something about changing mentality, but already in the USA there was a great deal of disclosure that was done with clinical trials information. So, i think it

goes into the vast transparency which is probably a very good thing. In the past there was the tendency to only communicate, disclose results when they were positive, i think it's also a good thing that now there is the need for disclosure.

Brasseur
Any comment?

Egger
Just a very quick comment, i agree with the other speakers, that i don't think there is anything preventing phase 1 trials becoming public, in the future it will go in that way.

Hudson
I support that, I personally see no reasons not to make results from phase 1 trials available.

Brasseur
Just staying for a second on the databases: they do not all concern CTs, we have different databases concerning different information. I also understood that on a national basis there are lot of information that is "lost" for Europe, so you mentioned that some of the data are picked up automatically in European databases, but how to integrate that residual information that is not picked up and useful for the other european citizens? Is there a way out? Are there some efforts?

Galluccio
Well, i think there is a legal problem, because the commission issues the guidelines with the dataset to be reported into the EUDRACT database. So, there has been a discussion between Member States to identify those data elements that can be shared between Member States. Secondly, there is a technical problem to guarantee that the data interchange can be an automatic upload of data from local databases to European databases. So, two problems: first, to decide which common data elements should be shared, secondly to create a gateway to transfer information from national databases to the EUDRACT database.

Brasseur
Ok, so it's more a technical problem for the time being.

Criscuolo
Let me offer another analysis of the situation. Usually, when i'm analysing a system that is not working, or a way to improve it, I tend to refer to a system which is working, in the clinical trials setting. We know from the beginning that USA, despite it's a Country that is more expensive, it's really taking the leadership of clinical trials. Despite that cost of clinical trials in the USA are usually 150% up to 200% of the average, they still keep around 30% of the global clinical trials. What is the reason? My personal analysis, is that USA consider research and pharmaceutical industries as a very strategic area. Europe has lost this vision in the '80. So, in my opinion, i think it's useful to discuss an implementation or a modification of the clinical trials Directive, that is fine, but in my opinion we are only working at the extreme end of a long process, and Europe has not yet understood that we should invest in research and we should support better pharmaceutical Industries. If we are not working in these strategic areas, we are just introducing little modifications, maybe we will get 1% more clinical trials, which is useful. We should change the mentality, we should insist with our politicians that research and pharmaceutical industries should be better supported, and this is not happening and I don't even see it as a vision in the future.
Some people in Europe have understood this problem. We have seen the innovative medicine initiative starting and trying to support this, but in my opinion is really a small drop. Even if there was a long and significant support to the initiative, in my opinion it is just a little drop that will produce a small change, so we should have more and more investments at the beginning, and not working at the extreme end of the process.

Brasseur
Ok, thank you for the comment.

Second question, Alberti
I don't agree totally with you. We, Novartis oncology, have made analyses on Europe, against the states, but more importantly, take into account what is happening in the developing countries which will become much more appealing attracting investments, I'm referring to the Far East. And to be challenging, i think we shouldn't complain. It's easy with 27 countries, industries, health authorities, to complain. We should work together. Working together, as a mind-set, will per se attract investments, and we have set up a plan in Novartis oncology, and now we are attracting many more trials, including phase 1, than in the States, because we are focusing in key centres, we are going in Countries very important and setting up a network we can with the present situation attract investments.

Brasseur
Thank you. Of course the future of the research can lead to much philosophical discussion and they are important, but for today the discussion is more focused on a technical level.
I would like to come back to the panel and quote Kerstin when she said "we have often central designation, a central designation, a central pharmacovigilance, so we would like to go in central clinical trials". Does it apply to all types of medication, paediatric, geriatric, adults and so on? Is that the vision, that we should go central once for all?

Hudson
I think the difficulty is that a centralised procedure is necessarily quite bureaucratic, it involves all the Member States. Whatever we come up with, we must be sure that it doesn't become a bureaucratic nightmare. To set up some sort of centralised committee of 27 member states, to review clinical trials, isn't going to workfor the majority of trials that are in a single or few countries . Also, if you think about the total volumes of clinical trials that go through the system, such an approach isn't going to work. However some scheme such as a modified decentralised system along the lines of an extension to the current VHP scheme that is in place may be an appropriate option. .
I think this apply to all trials, whether paediatric or not,.

Ceci
Yes, thank you, you know my position is quite different, but I would like to underline that, in my opinion, it's easier to have an homogeneous participation of all Member States and all scientific groups in a centralised vision that in a decentralised one, because the experiences with the decentralised marketing authorisation procedure is that some Member States acquire a position of leadership while others remain on the corner. This position cut the participation of some Member States. I believe that, under a scientific point of view, it's important that all Member States can participate with their Experts, their scientific communities, their patients. This is why i would prefer to have a centralised procedure, where the key expertise can be better express itself.

Foà
I apologise, i came in just now, so maybe i didn't hear all the discussion, but I just heard the comment about USA, and i would like to express some minor disagreements on the fact that USA is so far ahead, speaking on behalf of haematology. In the past it was a reality for the phase 1 trials, but if you look now, the last years, Europe has been leading the way. Many of the advancements and major studies came from Europe.
This is something that we are witnessing. What is happening it's obviously that Industries are mainly across the Atlantic, that's the key point.
The other thing which is very important: although Europe is very heterogeneous and we are trying to do everything to destroy it, but having say that, there is a great collaboration between Member States, for example with transnational and multi-countries studies. This is happening: the key point is to improve the regulation. We just organised at EHA, at european parliament for two days of meeting, between the EHA and members of parliament in Brussels exactly on this topic. How can we improve the possibility to run trials in Europe? Running a clinical trial has become very complicating, penalising also academic clinical trials. If you look at the number, the number of trials in Europe is dramatically decreasing. We'd like in the ideal world that patients entered in clinical trials from first to the third phase, but the regulations are very complicated, making trials very difficult, and they have to be simplify.
The problem is the legislation, we should take up some changes to make the clinical trials Directive much simpler, at least in certain area. But the key issue is: where should it be approved, at a central or at a local level?
If you have to go through 6 ethics committees in 6 countries, this is the problem. But if we manage to consolidate what Europe is doing, we will improve.
Another thing to say is that if you look at the States, there is a high university competition. Paradoxically, conducting studies is easier in Europe. But we have to improve the rules and simplify the legislations. I think Europe is leading the way in hematologic pathologies.

Westermark
A short comment. We have the voluntary harmonisation procedure that is already going on and the CTs facilitation group. So, one suggestion might be to make a feasibility study built on that and just from talking to people that are participating in this business they are very positive, it's a way that could be explored.

Brasseur
That leads me to the next question: many of you have been alluding to the CAP. Can someone explain me

what do you mean by that? Because that' a nice word, but what would be the procedure behind that? How is it organised? Is there some view on that, or it is just a way to hide the difficulties?

Peuvrelle
The coordinated assessment procedure. Only the big lines of it have been put in the concept paper, but basically it is a decentralised procedure, so there is a Member State that makes the first application and the others are accepting it, so to that regards it constitutes an acceptable option, and to come back to your previous question regarding the central approval which is always what seems to be the most appealing and interesting. I think we have to be pragmatic, someone was talking about the Parliament, I also had the possibility to discuss with some Members of the European Parliament, and they clearly estates that they will block it. So, even though it may be an interesting way, we should find some other options, and that's why i was showing different documents. We have to be pragmatic, centralised will not be pushed forward, and we have to find something else, and i think the CAP is an interesting start.

Brasseur
What is the difference between the centralised and decentralised, at the end of the day? If you have a rapporteur or a Member State, if you have everybody being involved, and if you have a consensus of common opinions, what is the difference?

Peuvrelle
To put it blindly, i think it's a very certain way to go around people's feelings and that they will loose their national independency.

Hudson
To me, the main difference is that if you think about the centralised procedure, if it were to resemble the the centralised approval procedure, to have 27 member states around a table considering the 5 thousands clinical trials that happen in Europe every year, it will be a bureaucratic nightmare. Something more like the VHP procedure being translated into a DCP type procedure, would be much more feasible, involving coordination amongst those Member States that are involved in the clinical trial, so if it involves 7 countries, those 7 member states can be involved, as currently happens in DCP. If you want to go to an eighth member state, it should either recognise that approval or withdraw from the trial.

Brasseur
But allow me to be pragmatic. We know that very often, when you have 8 member states, you have to include 2 more, because recruitment is not as fast as it should, so don't you think that having the view of the european citizens as a whole is important? I'm very interested in knowing what happens in the UK, as a Belgian citizen. I feel concerned. So, why shouldn't it be an European voice as an whole, and few member states in a corner in their secrecy?

Hudson
Well, in the UK we have around 1000 trials per year. Three quarter of those trials will be UK only. I see no advantage, all I see is bureaucracy, if non-involved member states have somehow to be involved in deciding if those trials should go ahead. We need something like mutual recognition, but something very simple, like "yes, we accept the approval", otherwise, we say no and opt out from doing the trial in that country.

Dehlinger-Kremer
I think Ian offered the same comment i wanted to give: should we really use the resources of 27 member states to evaluate a trial? But for the centralised procedure, you start with 8 member states, you have to include 2 others and establish a mutual recognition. Wouldn't the others states start excluding some countries?

Brasseur
Yes, but don't forget that not all the products resulting from the centralised procedure are marketed in every country. Of course, the numbers, we are speaking about 50 products a year and not 500, but it's not because you are going through a centralised procedure for a medicinal product that you will find it in 27 member states. It's a philosophical approach by stating that as a whole, all European citizens feel concerned.

Dehlinger-Kremer
Nevertheless, there is a little difference between having a market authorisation valid for all Europe, and having just one piece of the research. It's a marketing decision, to sell it in one country or all of the 27.

Brasseur
We have to stop here, thank to all the discussant and presentations.

ANTONIO GALLUCCIO
AIFA

4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population

SESSION II: BEHIND REGISTRATIVE CLINICAL TRIALS

The Registrative use of non-interventional and/or non sponsored studies: is it allowed? How to regulate it?

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Bosone
The title of the session is: behind registrativo clinical trials, how to use different tools to increase different evidences. Because in the last session we have spoken about the clinical trials mainly for the approvals in Europe, which is the core of the activity of the course in the clinical environment. But , as already discussed also yesterday, there are many cases in which other tools are also very useful in order to improve and increase or to substitute the evidences in specific cases, and we have the opportunity to discuss these different tools now in this session.

Dorica Dan
I have the pleasure to introduce the speakers for this morning session, so first of all I'd like to invite doctor Galluccio to return to the podium to speak us again, from the national monitoring Center of clinical research in Italy. Thank you

Galluccio
Thank you mister Chairman. My second presentation will be on the non-interventional studies from the perspective of the regulatory authority, as I'm representing the Italian agency, AIFA.
My first slide will focus on the definition of a non-interventional clinical trial, because we have a very detailed legislation on interventional clinical trials and very little on non interventional studies. However, the definition of a non-interventional clinical trial, can be found in the directive 2001/20: the medicinal product is prescribed in the usual manner, according to the terms of the marketing authorization; the assignment of a patient to a particular therapeutic strategy isn't decided in advance by the trial protocol, but falls within current practice; and the decision of the prescription of the medicine is independent from the decision to include the patient in the study. Another point is that no additional diagnostic monitoring procedures shall be applied to patients, and epidemiological methods shall be used for the analysis of collected data.
EU Commission gave some clarification in its questions and answers, version 9, august 2011, specifying that those requirements must be cumulatively fulfilled, and in the questions and answers it's written that purposes for excluding non-interventional clinical trials from the scope of directive 2001, is that such trials are typically of a lower risk than interventional trials.
The European Commission, in the pharmacovigilance guidelines for medicinal products for human use, volume 9a, specifies that it's important to clarify that interview, questionnaires and blood samples may be considered as normal clinical practice. Based on this definition, a fundamental distinction can be made between non-interventional, or observational, and interventional post-authorization studies. The latter

are considered clinical trials falling under the scope of the directive 2001/20. But the first point I want to discuss with you is if there is the possibility to give a definition of current clinical practice. We can define it with respect to the diagnosis and/or the follow-up of a specific medical problem, and we know that current clinical practice can vary between healthcare professionals, and can differ depending on the setting eg outpatient versus inpatient clinics, district hospitals versus universities, and between member states. So, there could be different approaches at the level of hospital, ethics committees or regional health authority, or member states, and these different approaches could influence the conduct of international, multinational and even national non interventional clinical trials. Maybe you are aware of the EU network of centres for pharmaco-epidemiology and pharmacovigilance, which is drafting a position paper to provide common interpretation of the current definition of non-interventional trials, in the context of the current legislative framework, that is the EU directive 2001/20. This document has been presented to the clinical trial facilitation group, of the heads of medicine agencies, on July 2011, to start a discussion. Well, definition is very important as classification within the framework of interventional trial has huge consequences. In fact interventional clinical trials are generally very expensive and highly regulated: investigational medicinal product, according to the directive, shall be made available free of charges by the sponsor; there is the need for a mandatory insurance; and the trial must and should be performed according to the full GCP.

Therefore, there is the need of harmonization at the EU and national level, for example a common approach, a common procedure to be adopted by the ethics committees that review this kind of research, in the evaluation of non-interventional clinical trials, to avoid delays in the start-up, or sometime the withdrawal of the application and the failure of the clinical research project.

I'll show you some example of retrospective and prospective non-interventional clinical trials. For example, retrospective observational database of research review, of records, where the events of interest have already happened, case control, cross sectional, etc. Or studies in which the prescriber later in time becomes an investigator, but prescription has already occurred. Retrospective data collection of individual medical methods at the site of the investigator. Some common examples of prospective non-interventional studies are registries, in which data collection derives from routine clinical care, or studies which evaluate the pharmacoutilization, the impact of usage of medicines, or measuring the effectiveness, or risk management measures, or therapeutic intervention in current practice.

Let me say some words about how Italy regulates the non-interventional clinical trials. Guidelines have been issued by AIFA on March 2008. According to these guidelines prospective studies must receive a favourable opinion by the ethics committee, retrospective studies are simply notified to the ethics committees. There is a tacit approval at day 60 if no objections are raised by the ethics committees. A national register managed by AIFA has been established for non-interventional studies starting from 1st March 2010 onward.

I am going to discuss now figures by the Register, the main therapeutic investigated areas are neurology, oncology and haematology. The most frequent primary objective of non-interventional studies are effectiveness, safety and pharmacoutilization. Until July 2011, there have been 18 post-authorization safety study applications. A large number of non-commercial sponsors are involved. More exhaustive and detailed statistics will be published in the upcoming AIFA annual report of clinical trials on medicines in Italy. This will be the first official report by AIFA dealing with non-interventional clinical trials. With regards to the assessment of any additional diagnostic or monitoring procedures, this issue can can switch a clinical trial from non-interventional to interventional, and we receive a great number of queries by the stakeholders on this issue. According to the Italian guidelines, the following procedures are considered acceptable as they are considered current clinical practice: follow-ups visit, corresponding to clinical practice, or required by current national and international guidelines. The text underlines something we added with respect to the EU definition of non-interventional clinical trials current clinical practice, in the national guideline: it is considered normal clinical practice the administration of questionnaires, interviews, inquiries, subjective evaluation by the patients about state of health, reading scales, blood tests whose use is justified by the rational of the study. The studies where blood tests are performed for pharmacogenetics or pharmacogenomics purposes are not considered observational studies.

We receive often queries by the sponsors or the researchers, I'll give you some examples of studies that could fall within the current definition of interventional clinical trials: a study where the drug to be administered has no market authorization for the medical condition, although this indication is reimbursed by the Italian national health system for off

label use, based on scientific evidence and lack of therapeutic alternatives. We consider the above mentioned clinical trial as interventional because no marketing authorization has been granted, but only a nominal use authorization. Another example is that an intervention is simply further analyses of an already drawn blood, for pharmacogenetics or pharmacogenomics purposes. Another example is about roll over studies: long term extension studies in which patients, previously enrolled in randomized clinical trials, are followed beyond the time specified from the protocol for the observation. There is no intervention but an active collection of data on safety or other outcomes (e.g. death, event free survival, etc)..

My conclusion is that non-interventional studies are gaining increasing importance in the assessment of post-market safety (PASS studies) and effectiveness in the real world and are a resource of scientific knowledge which is necessary when it's not possible to perform interventional clinical trials.

The EU, which has regulated in detailed the interventional trials, is trying to gain harmonization, starting from a milestone, a common interpretation of the definition of non-interventional trials. Few member states, just three, and among them Italy, have set up national registers to analyze and describe qualitative and quantitative aspects of non-interventional research.

Cooperation between the clinical trials facilitation group, of the heads of human medicine agency, the European network of centres for pharmacoepidemiology and pharmacovigilance and the member states is necessary to foster non-interventional research in Europe.

Thank you very much.

Discussion

Massacese

As a neurologist, I have to deal very often with rare diseases and orphan medications. I have a question and a comment. The question is for dr Galluccio about the interventional studies. In the eternal struggle with the ethical committees, we have discussed deeply what is the level of study, which kind of studies have to get preventive approval – I'm talking about non interventional studies. There is no discussion about the need of preventive medical committee approval for prospective studies, by to me many ethical comments would ask for approvals for studying retrospectively data that are already collected and are in a database. It's too much, a work which is not needed. I'd like to have a comment about this, which is requiring more and more work from the investigator, and to me it doesn't help the patients, because they have already given their consent in the time they are entering hospitals and clinics.

I have a comment in addition about the definition of orphan diseases and orphan drugs. It is clear that it is an epidemiological definition, but what about the subgroup of diseases? Can we define a form of orphan disease if it is just a form of a disease, but there are cases for instance in the USA, of medications that have been approved under the orphan drugs act, because they have been studied in subgroup of a disease. And this is something that is critical, because for diseases that are close to the definition, can be orphan or not according if you use the subgroup definition.

Last but not least, what about the definition of an orphan n drug? To me, the definition of an orphan drug as a drug for orphan diseases is to much. I think an orphan drug is a drug which doesn't have sponsors. In other words, a drug whose patent has expired, and still can be developed for the public health needs is an orphan drug. And this kind of definition is not always accepted, and I think this should be discussed.

Galluccio

Just a brief reply on the ethics committee role in the assessment of non-interventional clinical trials. As I have said during my presentation retrospective design protocols should be notified to the ethics committee. In case of no grounds for non acceptance the sponsor can start the clinical trial after 60 days (tacit approval).

I know that sometimes, some ethics committees, in some regions, grant a formal approval, because as I said there isn't a legislation but only a guideline, and every region can emanate further laws, together with local authorities. So we have to build up further guidelines or even legislations to gain harmonization at national level.

Westermark

Concerning the other two questions.

For the subgroups, you can apply for a subgroup of disease, but it's a bilateral evidence that you need to prove. You need to prove that a drug is effective only in this subset of condition, and also the other way around, that it cannot be used in the other conditions. So, in this situation you can focus on subgroups.

And your second question: for a drug that has lost its patent, you can very well develop for an orphan condition. If you do so, you can have the orphan designation and a marketing authorization. This is sometime criticized, hen it comes to old drugs that are well known. But anyway, the important is that you develop the drug for a certain condition, you develop the trial and you promise to offer drugs to the patients.

This is perfectly acceptable.

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4th Foresight Training Course of the Gianni Benzi Foundation - Evidences from Rational Therapies: From Newborn to Elderly Population

ROUND TABLE II : MODELS FOR THE ASSESSMENT OF B/R RATIO, COMPARATIVE B/R RATIO, COST BENEFIT AND HTA EXPERIENCES

HTA experiences at international and national level

Note: We suggest reading this presentation looking also at the slides, available on www.benzifoundation.org

Ceci
It's a real pleasure to have here to present his theme dr. Jommi, he is a friend of mine first of all, but in particular he is one of the oldest individuals who in Italy has begun to develop this expertise, starting from the old term, "pharmacoeconomy", and now it has enlarged in "health technology assessment".
Claudio Jommi is associate professor at Piemonte Orientale University in Novara. He is an economist, but expert in pharmaceutical and health care system analyses and economic evaluation.
Thank you

Jommi
Thanks a lot for your kind invitation. Honestly, the topic that I have to talk about it's a bit wide. I will focus on the most critical issues. I'll start with a very short description of the meaning of health technology assessment, followed by the main critical issues around HTA, the role of HTA in policy making, and discuss whether we are moving towards an European HTA, or national authorities will govern the introduction of new technologies.
There are many **definition of HTA**. The most complete has been given by the international network of agencies for HTA (INAHTA), according to which HTA is a multidisciplinary field of analyses, studying or trying to understand the medical, economic, societal, ethical impact of a new and existing technology into the real world.
HTA has been represented as a bridge between science (collection and systematic review of evidences on a new technology, i.e. assessment), and policy-making, including recommendations that could be either binding or not, and decision on the reimbursement list set at national level, price, inclusion into regional and local formularies if any, of a new technology. The origin of HTA can be traced to the very prominent role of the US Congressional Office of technology assessment, but this discipline has been spread all over the world in the last two decades. The first agencies in Europe were founded in Sweden (SBU), followed by CDT in France, a network of hospitals focused on HTA on medical devices and new technologies, and the TNO in the Netherlands. If we look at the Agencies joining the international network, you can see how much this discipline and the connection between this discipline and decision-making has been spread all over the world.
Economics is one of the most important part of HTA, because it tries to answer to three questions: 1) does the new technology provide value for money (incremental cost-efficacy, cost-effectiveness ratio)? Is the new technology affordable or

sustainable (budget impact analysis, that detects the net incremental cost of the introduction of the new technology)? Which is the organizational impact of a new technology, i.e. does the new technology change the settings of care?
HTA should be put into the general context of health technologies market regulation, which should simultaneously reach this very challenging objectives: equitable and appropriate access to effective and safe products; static allocative efficiency (i.e., resources should be allocated appropriately, according to their impact on health); dynamic allocative efficiency, i.e. producers of innovation should receive enough money to continuously invest into research and development, to find solutions to unmet needs; affordability, i.e. technology should be given to the system at a reasonable cost..

HTA is a very **complex process**, the first phase is "**priority setting**", that is deciding which technologies should be assessed. This is a very critical aspect: if technology assessment is compulsory, and if the technology has acquired a positive opinion, then we should have a rapid access to the system. The second phase is "**scoping**", i.e. converting a general research question into a more specific one, answering to the following questions: which is the relevant population next to be treated? Which is/are the appropriate comparator/s, the appropriate outcome measures, etc.? The **assessment**, which is the most technical part, searches for knowledge and evidences. The **appraisal** is the recommendation, based on assessment. Appraisals could be simply disseminated to the community, or converted into policy making. Once new technologies have been introduced into the market, the system should re-evaluate them. For example, it has been demonstrated that erythropoietin, that was not cost effective at launch, proved to be more cost-effective, thanks to the evidence provided by post-marketing studies.
Which are the main critical issues of HTA?
The first one is **criteria for priority setting**. Criteria has been scrutinized by a research on 11 HTA agencies, according to which priority setting has been mostly determined looking at the clinical impact, the economic impact plus budget impact, and the burdens of disease. Another more practical issue is whether do we have to evaluate all technologies, or just part of them. Technology assessment was born mostly not on drugs but on medical devices. Now, most of the assessment activity has been focused on drugs, because drugs account for the largest budget, and clinical evidence on drugs, when market authorization is granted, is higher than for medical devices. The other question is: do we have to evaluate only new technologies, or do we have to reassess the existing ones? The answer is: a full assessment should be implemented: when a number of alternatives is available, it's important to re-assess them. Should we assess individual technologies or broader clinical practices? The general idea is that we have to move from individual technology assessment at market launch, to a broader analysis of the treatment and practices, once they are many for the same indication.
Another question is: **should we establish an horizon scanning activity**? Horizon scanning is very useful, but it's very difficult to carry out.

One of the most critical aspect of HTA, is that **head-to-head trials** are not frequently carried out. According to a recent review published on JAMA, head to head studies account for 35% of randomized clinical trials and observational studies published in the literature.
Another critical aspect is: which **outcome** should be included in the scoping and assessment process? There is obviously a clear focus on final outcomes (length of life and quality of life), but in many circumstances information on surrogate outcomes or clinical outcomes are the only one available. Most of the HTA agencies, at least in Europe, have adopted a pragmatic approach, accepting surrogate endpoints, provided that they are clinically relevant and validated. In addition, HTA agencies have mostly accepted (an important exception is our Drugs Agency) quality of life measurement. Some of them have also considered other parameters, like acceptability to patients, or ease of use.
Another important issue is that, despite cost-effectiveness should be the most important parameter from an economic perspective, actually **financial budget impact seems to be much more influent** on decision-making in most countries. In Italy, for example, despite an economic evaluation is expected to be delivered in the case of orphan and very innovative drugs, the existence of a drug budget makes our Drugs Agency paying more attention to the impact of new product on drug budget.
Results of economic evaluation studies could importantly change according to **perspective** used. The role of informal care and productivity lost due to temporary or perma-

nent absence from work and early retirement or mortality, may be very important for some diseases (like rheumatoid arthritis). The investment in new technologies (the proportion of drugs costs over total cost of rheumatoid arthritis has dramatically increased in the last ten years, because of biotechnological products), may positively impact on costs sustained outside the health care system. The advantages of a new technology would be underestimated, if the health care system perspective is used.

Another big issue is **stakeholders' involvement in HTA**. The EUnetHTA project is investing a lot on creating a framework for this critical issue. According to a research we have recently carried out on decision-making process in HTA organisations in Europe we have found that (i) the industry is considered an important information source, especially for horizon scanning, economic evaluation analysis. In some circumstances, the industry is authorized to request a prioritization process for a new technology, or an assessment. The industry is rarely involved in technical committees supporting the evaluation process. This happens, for example, in England, where the NICE's Appraisal Committee includes two representatives, coming from the industry; (ii) the involvement of patients shows important differences across countries, ranging from a very structured participation in England, an intermediate level in France and Germany, where only accredited patients associations are generally authorised to participate, and low participation level in other countries, including Italy and Spain, where lobbying prevails on technical support. There is a huge debate on patients' contribution. In England, for example, patient experts are expected to contribute and have been educated to actively interact with other stakeholders on issues, such as patients related outcome, quality of life, impact on informal care, acceptability of a new therapy, etc. (iii) clinicians are obviously involved , because they give information and perform or give important inputs to systematic review. The first question is: how clinicians are recruited? NICE has adopted a very formal procedure, through advertisement on internet. In most countries scientific societies are used to select clinicians to involve. In other countries (e.g. Spain) the recruitment process is very informal. Conflict of interest is another important aspect. In most advanced systems (e.g. NICE), the problem of conflict of interest is pragmatically solved: clinicians are invited to declare conflict of interest on the technology which is going to be evaluated and do not participate in the discussion.

HTA in a regionalised systems is another important aspect. In Spain, where HTA was born at regional level, the Central Government has preferred to coordinate region experiences, sustaining a specialisation process, instead of centralising the process. Sweden has clearly distinguished the role of national HTA, managed by SBU and TLV, and regional / local HTA, In Germany HTA is managed at central level. Despite Länder have an important role in market access for new technologies, they are not allowed to perform HTA.

The last critical issue is **transparency**. We have found huge differences across countries in the level of transparency on reports, report drafts, minutes and meetings agenda. The highest and lowest level of transparency has been respectively found in England and Spain.

There is not time to describe the way **HTA** is **used to decide P&R** in the major 5 EU countries. In France, where reimbursement status is managed by the Transparency Commission of HAS, and price is negotiated with the relevant company by the Economic Committee, market access for new drugs is the priority, provided that the product is useful for the system. Comparative evaluation, that does influence price negotiation, is mostly carried out using the best comparator or what has been used in head-to-head , if any, clinical trials. Sustainability or affordability of a new technology is reached through a tough price negotiation and price-volume agreements.

The Italian model is similar to the French one, with two important differences: comparison is carried out considering all products in the same therapeutic categories and risk-sharing agreements, together with price-volume agreements, have been used.

In Germany P&R has been changed in 2011: companies are still free to set prices at launch, bur rebates will be required according to comparative added value. Should there is not any added value, the drug will be subject to reference pricing applied to the whole therapeutic category.

England (and more generally UK) is a typical system that has mostly relied on allocative efficiency, that could be strengthened with the introduction of an explicit value based pricing, scheduled for2014.

The last point: **are we moving towards a European technology**

assessment? The answer is, in my opinion, "no". The European Committee has put the development of HTA as a priority, and stated that the EU should provide to decision makers, third party payers and stakeholders robust scientific evidences of the technology. There are a number of projects at the European level: the most important one is the EunetHTA project. It was created as a European project in 2006, it moved towards a collaboration among HTA Organisation, and became a Joint Action, and expected to become a stable cooperation. The idea is to create a core HTA methodology, but not binding for any HTA Organisations. The Joint Action, WP 5, is working on relative effectiveness: further info can be found on the relevant website. WP 5 is expected to give guidelines on the most critical aspects of relative effectiveness by the end of 2012, thus creating room for a higher homogeneity across countries in the way they assess added value (but not necessarily in the way they manage P&R). Another big step is the European Directive on Healthcare cross border, according to which the EU will sustain the creation of a voluntary network connecting national authorities on HTA, and again should avoid application of assessment: the idea is not to create an European Agency on technology assessment, and not to intervene on reimbursement and price criteria, autonomously chosen by countries.

To summarise, HTA is becoming ever and ever important for decision making. It's desirable that economic analysis will rely more on the incremental cost effectiveness ratio, and less on budget impact analysis. However , because of budget constraint and short term cost containment imperative, it is more likely that budget impact will diffuse more than economic evaluation. It is recognized a strong added value considering HTA at the European level, as a network between national agencies, pulling expertise, and minimizing the duplication of efforts. For example a systematic review could be carried out by only one national agency and the others, through mutual recognition and integration, may rely on evidence provided by the first one. Within this trend, there are some questions to answer: how much will be binding the conclusion to avoid the application of assessment? How much the industry and the member states will be available to invest into HTA? Which will be the actual involvement of stakeholders?.

Thank you very much for your attention.

VIVIANA MASCILONGO
MAURIZIO GIARACCA
Soci SIAR

Interazioni informatiche per lo Specialista in Attività Regolatorie: websites istituzionali e portali tematici

In Italia negli ultimi 5 anni si è ampliamente diversificata ed intensificata l'attività regolatoria attraverso l'utilizzo di sistemi informatici (Websites Istituzionali e Portali Tematici).

La comunicazione in tempo reale, il dialogo e la gestione della documentazione tra lo specialista in attività regolatorie dipendente o consulente con le istituzioni nazionali regolatorie (Agenzia Nazionale del Farmaco e Ministero della Salute) si sono incanalati in sistemi informatici al fine di garantire:

- tracciatura dell'iter;
- maggiore trasparenza nel dialogo;
- efficienza nella gestione e chiusura della pratica.

I sistemi informatici attualmente presenti in Internet rispecchiano le diverse categorie mercelogiche (es: specialità medicinali per uso umano, dispositivi medici, ecc) ed attività (farmacovigilanza, convegni e congressi) su cui lo specialista in attività regolatorie deve concentrare la propria operatività ed analisi regolatorie.

Ogni sito regolatorio istituzionale (Aifa e Ministero della salute) garantisce l'accesso a diversi sistemi informatici per attività regolatorie di cui esponiamo un riassunto breve ma utile per orientarsi in questa mappa interattiva, in vista della rivoluzione regolatoria attesa per il 2015: eCTD anche per le procedure nazionali.

Dal website Aifa (www.agenziafarmaco.it) (Fig. 1).

I sistema Informatico: AIFA Front End, Categoria merceologica: specialità medicinali per uso umano.

Questo portale è costituito da una parte informativa (news, utilities, ecc...) (Figg. 1, 2), ed una parte ad accesso riservato solo per le aziende farmaceutiche accreditate con Codice SIS (Fig. 3). In accesso riservato con password si gestiscono le aree sensibili e cruciali (Fig. 4): check point, prezzi e rimborso, ricerca e sviluppo, trasparenza (Figg. 5-7).

Gestore: CINECA.

Osservatorio nazionale sulla sperimentazione clinica dei medicinali: è il portale per la gestione della parte

Figura 1:

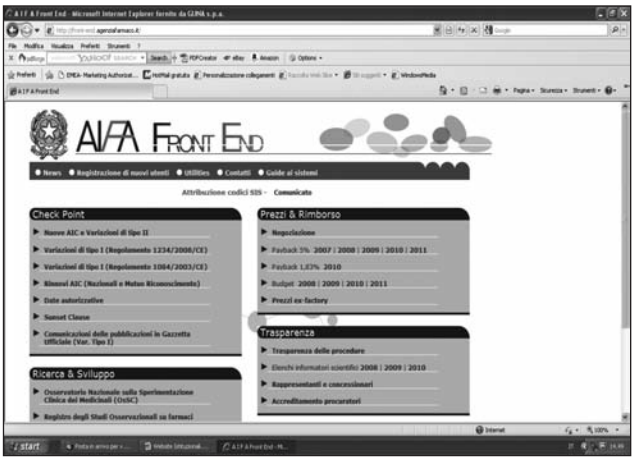

Figura 2:

Figura 3:

Figura 4:

Figura 5:

Figura 6:

clinica relativa alle specialità medicinali per uso umano (Fig. 8).
Il portale NSIS (Fig. 9):
questo portale è il più articolato ed interessante in quanto linkato sia con il website Aifa che con il website del Ministero della Salute.
Queste sono le aree tematiche da cui si può accedere dal website Aifa nell'ambito della gestione delle specialità medicinali per uso umano attraverso accesso con password:

- farmacovigilanza;
- tracciabilità del farmaco;
- convegni e congressi.

Convegni e congressi (Fig. 10)
Trasmissione dei dati tecnici delle specialità medicinali (Circolare 9/97): trattasi di un programma del 1997 creato su base access, il cui utilizzo è mandatorio solo per la gestione delle specialità medicinali per uso con procedura nazionale (richiesta di AIC, variazioni, rinnovi). Per le procedure europee (MRP; DCP, Centralizzata EMA) l'utilizzo di questo programma è escluso (Fig. 11).
Il sistema di versamento delle tariffe (Fig. 12): è il portale al quale devono iscriversi obbligatoriamente le aziende farmaceutiche accreditate con codice SIS per poter procedere con il pagamento delle tariffe (Fig. 13). É un portale costantemente aggiornato e che richiede l'accesso con password (Fig. 14).
Dal website istituzionale del Ministero della Salute www.salute.gov.it (Fig. 15).
Questo website è molto articolato per le informazioni che carica quotidianamente. Una sezione è dedicata al riepilogo di diverse banche dati. Inoltre il Ministero della Salute ha recentemente attivato l'utilizzo della posta certificata obbligatoria per la gestione di specifiche attività regolatorie (es: pubblicità dei dispositivi

Figura 7:

Figura 8:

Figura 9:

Figura 10:

medici, richieste di nuove AIC per le specialità medicinali ad uso veterinario, ecc...).
da cui estrapolare le info richieste. Esempio: dispositivi medici. Questa banca dati è utile per cercare il dispositivo medico per sua classificazione nazionale e/o brandname (Fig. 16).
Il Repertorio dei Dispositivi Medici:
è una sezione del portale NSIS (Fig. 17). Tuttavia si accede tramite un altro portale www.impresa.gov.it (Fig. 18), richiede l'utilizzo di 1 smart card o di una business key (acquistabili presso le poste o presso le camere di commercio) (Fig. 19) con accesso autorizzato per il legale rappresentante (o suo delegato) dell'azienda fabbricante (Fig. 20).
GMDN, www.gmdnagency.com: è il website per la ricerca e l'acquisto dei codici identificativi per i dispositivi medici del nomenclatore internazionale. Richiede la sottoscrizione ad un abbonamento annuale e rilascio di 1 password di accesso (Fig. 21).
Il portale della normativa sanitaria:
la sua finalità è l'accesso gratuito ad un motore di ricerca pubblico e la possibilità di iscriversi ad una newsletter periodica e molto aggiornata (Fig. 22).
ECM: è il portale relativo all'accreditamento degli eventi formativi, gestione di questi con password di accesso (Fig. 23).
Accreditamento Provider (Fig. 24, 25).
Si riportano qui sotto gli accessi ad altri portali dal websites del Ministero della Salute di non utilizzo regolatorio, in quanto destinato ad altri attori del Sistema Sanitario Nazionale (medici, paramedici, infermieri), ma la cui conoscenza può rivelarsi interessante per l'estrapolazione di informazioni utili nell'ambito delle aziende farmaceutiche (Fig. 26).
eHealth (Fig. 27).
Il Sistema NSIS:
dal website del Ministero della Salute l'accesso al Sistema NSIS fornisce

Figura 11:

Figura 12:

Figura 13:

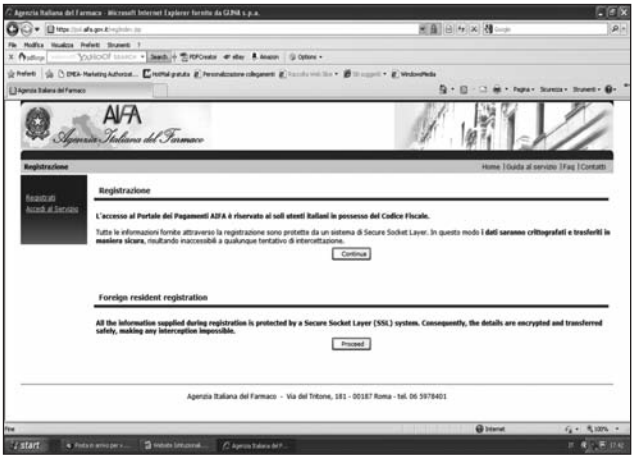

Figura 14:

Figura 15:

Figura 16:

Figura 17:

Figura 18:

Figura 19:

Figura 20:

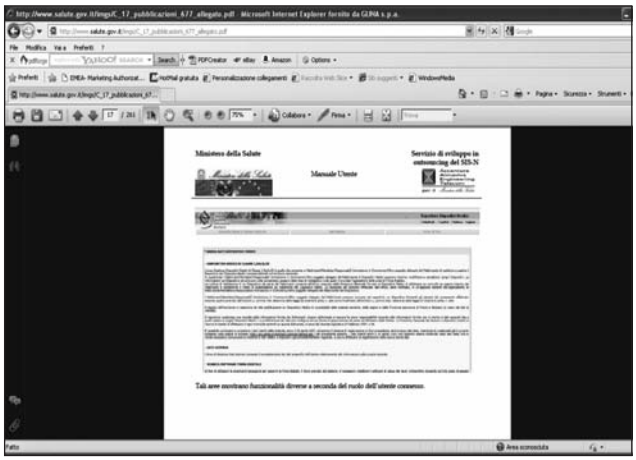

Figura 21:

Figura 22:

Figura 23:

Figura 24:

Figura 25:

Figura 26:

Figura 27:

Figura 28:

Figura 29:

Figura 30:

Figura 31:

Figura 32:

Figura 33:

Figura 34:

Figura 35:

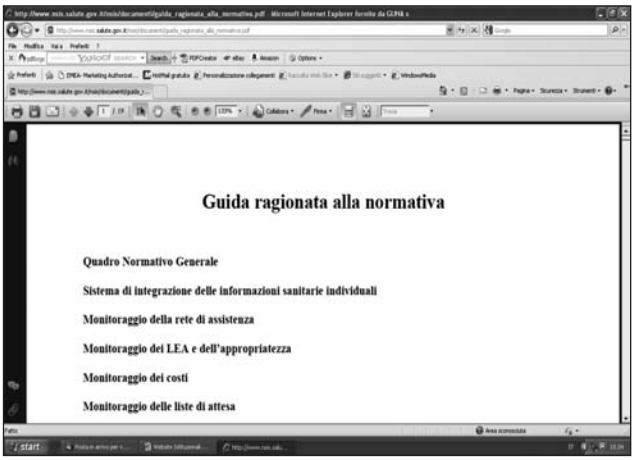

Figura 36:

Figura 37:

Figura 38:

Figura 39:

Figura 40:

Figura 41:

una visione più ampia di questo portale, il cui utilizzo viene finalizzato da diversi attori: enti sanitari pubblici (es: ASL), aziende farmaceutiche, medici, ecc... (Fig. 28).
La sezione linkata con Aifa è la tracciabilità del farmaco con ampio sviluppo delle sezioni "contraffazione" e "sostanze stupefacenti".
Progetto mattoni (Fig. 29-31).
Es: tracciabilità del farmaco (Fig. 32-33). Assistenza domiciliare (Fig. 34).
Da medicinali e dm veterinari (Fig. 36-41): Eudrapharm, Impact, Stupefacente, SIUCS e Portale Salute UE.

SIAR
Società Italiana Attività Regolatorie

SCHEDA ISCRIZIONE SOCI
Anno 2012

Nome e Cognome_____

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Specializzazione_____

Qualifica professionale_____

Indirizzo privato_____

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Ente di appartenenza/Azienda_____

Attività dell'Ente_____

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NOTE_____

_____

Il pagamento della quota associativa dà diritto, per il periodo di pertinenza, al ricevimento della rivista Siar News, all'accesso all'area riservata del sito SIAR, alla partecipazione gratuita ai seminari organizzati da SIAR e ad uno sconto sulla quota di iscrizione ai corsi di formazione organizzati da SIAR.

INFORMATIVA EX ART. 13 D.lgs. 196/2003

Egregio Socio,
desideriamo informarLa che il D.lgs. n. 196 del 30 giugno 2003 ("Codice in materia di protezione dei dati personali") prevede la tutela delle persone e di altri soggetti rispetto al trattamento dei dati personali. Secondo la normativa indicata, tale trattamento sarà improntato ai principi di correttezza, liceità e trasparenza e di tutela della Sua riservatezza e dei Suoi diritti. Ai sensi dell'articolo 13 del D.lgs. n.196/2003, pertanto, Le forniamo le seguenti informazioni:
1. I dati da Lei forniti verranno trattati per le seguenti finalità
a)adempimenti connessi all 'invio della rivista SIARnews o di altra corrispondenza, anche mediante posta elettronica,pertinente agli scopi della SIAR;
b)adempimenti connessi con i rapporti dell 'Associazione con i Soci;
c)aggiornamento ed eventuale distribuzione ai Soci dell 'elenco Soci;
d)gestione amministrativa delle quote associative.
2. Il trattamento sarà effettuato con modalità manuali e/o informatiche
3. Il conferimento dei dati è facoltativo e l'eventuale rifiuto di fornire tali dati comporta come unica conseguenza l 'impossibilità di poterLa comprendere tra i nostri Soci.
4. I dati potranno essere comunicati a:
a)Istituto di credito per l 'invio della richiesta delle quote annuali;
b)Enti ed istituzioni che ne facciano richiesta motivata qualora possa essere nell 'interesse dei Soci. L 'elenco di tali Enti ed Istituzioni è consultabile presso la Segreteria SIAR.
5. Il titolare del trattamento è: SIAR (Società Italiana Attività Regolatorie) con sede legale in Corso Mazzini, 13 – 27100 Pavia
6. Il responsabile del trattamento è il Dr.Walter Bianchi.
7. Rispetto ai dati in nostro possesso,Ella potrà sempre esercitare i diritti previsti dall 'articolo 7 del D.lgs già citato. In particolare,l 'interessato può consultare,modificare,integrare o cancellare i propri dati o opporsi al loro utilizzo rivolgendosi al Responsabile del trattamento.

Il/la sottoscritto/a, acquisite le informazioni fornite dal titolare del trattamento ai sensi dell'articolo 13 del D.Lgs. 196/2003, l'interessato: - presta il suo consenso al trattamento dei dati personali per i fini indicati nella suddetta informativa.

Data: _____ Firma: _____

Da trasmettere a:

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La quota di iscrizione per l'anno 2012 è di € 97,00 ed è da versare mediante bonifico a: CARIPARMA - PAVIA - AG. 2
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