Risk-sharing schemes: the Italian experience in the field of rare cancers.

Luca De Nigro

May 25th 2012
## Declaration of interest *

The opinions expressed in this topic are personal and can not be seen or mentioned as made on behalf of AIFA or any of its committees or working groups.

FOR THIS WILL NOT RECEIVE PAY; ONLY THE REPAYMENT OF TRAVEL AND HOTEL.

<table>
<thead>
<tr>
<th>Activities for a company in relation to a particular product / product group</th>
<th>NO</th>
<th>Currently or last year</th>
<th>Over a year ago but less than 5 years ago</th>
<th>More than 5 years ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee</td>
<td>X</td>
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<td></td>
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<tr>
<td>Adviser</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Principal researcher</td>
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<td></td>
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<tr>
<td>Member of steering committee, an advisory committee or similar organization</td>
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<tr>
<td>Researcher (not principle) for the development of product</td>
<td>X</td>
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<tr>
<td>Financial interest in pharmaceutical company</td>
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<tr>
<td>Patent on a product</td>
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<tr>
<td>The organization in which I work has a repayment or other funds from pharmaceutical companies (I will not receive individual earnings)</td>
<td>X</td>
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</tbody>
</table>

* Luca De Nigro, DOI 2011, 0044 EMA/513078/2010 about declaration of interest of members of scientific committee and specialist
The Italian context on Orphans

- The ‘traditional’ approach (Regulations and Surveillance):
  - National Regulations
  - National Register of Orphan Drugs
  - National Register of Rare Diseases

- The ‘empowered’ approach: Independent Research and advanced Monitoring
  - Independent Research funded by AIFA
  - Drugs Monitoring Registers
  - Multifaceted pricing and reimbursement approach (Managed Entry Agreements)
# Access to orphan drugs in Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Early access</th>
<th>Access</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>GERMANY</td>
<td>No</td>
<td>Easy</td>
<td>Nothing particular</td>
</tr>
<tr>
<td>AUSTRIA</td>
<td>UC/NP</td>
<td>Slow</td>
<td>Nothing particular</td>
</tr>
<tr>
<td>BELGIUM</td>
<td>UC/NP</td>
<td>Slow ++</td>
<td>Nothing particular</td>
</tr>
<tr>
<td>DENMARK</td>
<td>UC/NP</td>
<td>Complex</td>
<td>Nothing particular</td>
</tr>
<tr>
<td>FINLAND</td>
<td>UC/NP</td>
<td>Complex</td>
<td>Nothing particular</td>
</tr>
<tr>
<td>FRANCE</td>
<td>TUA</td>
<td>Rapid</td>
<td>Coordination at OMS level</td>
</tr>
<tr>
<td>SPAIN</td>
<td>UC/NP</td>
<td>Classic</td>
<td>Nothing particular</td>
</tr>
<tr>
<td>GREECE</td>
<td>UC/NP</td>
<td>Classic</td>
<td>Nothing particular</td>
</tr>
<tr>
<td>IRELAND</td>
<td>UC/NP</td>
<td>Classic</td>
<td>Nothing particular</td>
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<tr>
<td>ITALY</td>
<td>TUA</td>
<td>Classic</td>
<td>Nothing particular</td>
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<tr>
<td>LUXEMBOURG</td>
<td>UC/NP</td>
<td>Classic</td>
<td>Nothing particular</td>
</tr>
<tr>
<td>THE NETHERLANDS</td>
<td>UC/NP</td>
<td>Classic</td>
<td>Improvement to be discussed</td>
</tr>
<tr>
<td>PORTUGAL</td>
<td>Depends on the case</td>
<td>Depends on the case</td>
<td>Special funds awarded</td>
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<tr>
<td>THE KINGDOM</td>
<td>UC/NP</td>
<td>Slow</td>
<td>Considered as expensive</td>
</tr>
<tr>
<td>SWEDEN</td>
<td>UC/NP</td>
<td>Easy</td>
<td>Nothing particular</td>
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</tbody>
</table>

**UC**: Compassionate Use  
**NP**: Nominative Base of Patients  
**TUA**: Temporary Use Authorisation
Complete National Regulations for early access to drugs

- Decreto Legislativo n. 211/2003 (GCPs in conducting Clinical Trials, ex Directive 2001/20/CE).
- Decreto Ministeriale 8 maggio 2003 (so-called Compassionate use, EAPs etc).
- Decreto Legge n. 648/1996 (Governance of some off-label therapeutic indications funded by NHS).
- Fondo AIFA del 5% (AIFA’s Fund for off-label nominative use).
- Legge n. 94/1998; Legge Finanziaria 2007 (Governance of Off-label use, as restricted by the National Financial Law 2007.

- Decreto Legislativo n. 279/2001 (Governance and surveillance of known Rare Diseases).
National Register of Orphan Drugs

Registro Nazionale Farmaci Orfani

Il Registro Nazionale Farmaci Orfani contiene dati sulla diagnosi e sul follow up dei pazienti trattati con i farmaci orfani autorizzati a livello centralizzato dall'Agenzia Europea di Valutazione dei Medicinali (EMA) e rimborsati dal Sistema Sanitario Nazionale (SSN).

Il Registro Nazionale Farmaci Orfani, istituito presso l'Istituto Superiore di Sanità, predispone le schede di rilevazione per ogni patologia rara e relativi farmaci, raccoglie, verifica e analizza i dati inviati dai Centri regionali autorizzati all'erogazione dei farmaci.

Tale registro si prefigge di avere una copertura totale del territorio nazionale ovvero di riferirsi a tutti Centri in Italia abilitati all'erogazione e alla prescrizione dei farmaci orfani.

In tutte le fasi della raccolta, elaborazione e archiviazione dei dati sarà garantita la tutela della riservatezza dei dati personali secondo la normativa vigente (DLgs 196/2003).

Per accedere al registro clicca sul farmaco di interesse sottoposto al monitoraggio:


Aldurazyme - Fabrazyme - Replagal - Revatio - Thelin - Tracleer - Ventavis
Il Registro Nazionale Malattie Rare è istituito presso l’ISS in attuazione dell’articolo 3 del D.M. 279/2001.

Il Registro ha come obiettivi generali di effettuare la sorveglianza delle malattie rare e di supportare la programmazione nazionale e regionale degli interventi per i soggetti affetti da malattie rare (art. 2). Il Registro mira infatti ad ottenere informazioni epidemiologiche (in primo luogo il numero di casi di una determinata malattia rare e relativa distribuzione sul territorio nazionale) utili a definire le dimensioni del problema; si tratta, inoltre, di uno strumento utile per stimare il ritardo diagnostico e la migrazione sanitaria dei pazienti, supportare la ricerca clinica e promuovere il confronto tra operatori sanitari per la definizione di criteri diagnostici.

L’attività del RNMR è iniziata nel 2001 e, per aumentare la copertura e l’efficienza della raccolta dei dati epidemiologici il Centro Nazionale Malattie Rare (CNMR), a partire dall’inizio del 2007, ha messo in atto una nuova modalità di raccolta dati che include un nuovo software; uno strumento che può essere utilizzato sia dai singoli presidi/centi abilitati alla diagnosi e al trattamento dei pazienti affetti da malattie rare sia dai Responsabili dei Centri di Coordinamento Regionale che coordinano le attività e fanno da tramite tra il CNMR e i singoli presidi/centi.

Il software è sviluppato su piattaforma web, di semplice utilizzo, realizzato rispettando gli standard di sicurezza e di riservatezza per il trattamento dei dati sensibili.
The promotion of independent research on drugs (started 2005, ongoing 2012) represents one of the strategic tasks of AIFA to support clinical research in areas of interest for the NHS and where commercial support is normally insufficient.

The call for proposals (first cycle) was aimed at investigators working in public or non-profit organisations (e.g., scientific foundations, patient associations, etc.). Three main areas of drug research were included in the first program (2005-2008):

Area 1. **Orphan drugs for the treatment of rare diseases and drugs for non-responders.**
Area 2. Head to head comparison of drugs and therapeutic strategies.
Area 3. Strategies to improve the appropriateness of drug use and pharmacoepidemiology studies.
<table>
<thead>
<tr>
<th>Area</th>
<th>Call for proposals 2005</th>
<th></th>
<th>Call for proposals 2006</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Letters of intent</td>
<td>Study</td>
<td>Funded protocols</td>
<td>Letters of intent</td>
</tr>
<tr>
<td>Area 1: Orphan drugs</td>
<td>150</td>
<td>31</td>
<td>20</td>
<td>184</td>
</tr>
<tr>
<td>Area 2: Head to head comparison of drugs</td>
<td>80</td>
<td>25</td>
<td>13</td>
<td>121</td>
</tr>
<tr>
<td>Area 3: Pharmacovigilance and appropriateness</td>
<td>172</td>
<td>45</td>
<td>21</td>
<td>149</td>
</tr>
<tr>
<td>Total</td>
<td>402</td>
<td>101</td>
<td>54</td>
<td>454</td>
</tr>
</tbody>
</table>
Drugs’ Monitoring Registers

• The Drugs Monitoring Registers are not:

• Phase IV Clinical Trials (Post Marketing Studies)
• Observational Studies (PASS studies)
• Mechanisms of Restricted Drug Prescription

• The Drugs Monitoring Registers are:

• Telematic tools of the National Health System for drug prescription and administration
Drugs’ Monitoring Registers

Therapeutic areas involved in the network:
Cancer, Rare Diseases/Orphan Drugs, Dermatology, Diabetology, Cardiovascular, Ophthalmology, Neurology...

http://monitoraggio-farmaci.agenziafarmaco.it
New drugs’ main characteristics in clinical trials and practice:

- Precise indication of pathology and treat. phase
- Surr. efficacy endpoints vs hard endpoints in CTs
- Accelerated registration processes
- High production costs, sustainability of NHS
Tracing treatments by Case Report Forms in order to verify:

- Appropriateness in prescription
- Tolerability
- Requirements for Risk Management Plans and off-label use where needed
Treatment no longer supported by NHS for non-responder patients after the first re-evaluation, in case of progression of the disease and/or intolerable toxicity of the treatment, as noticed by the physician.
The AIFA’s authorisation mechanism for monitored prescriptions (Orphans/not Orphans)

- First therapy cycles for eligible patients

  Drug → Response’ evaluation

  - Responders: Treatment continues, supported by NHS
  - Non Responders: Treatment supported by NHS stops
Risk-Sharing contracts with Companies in order to manage:

- Public expenditure and sustainability
- Relevant data for the price and reimbursement policy of NHS
- New models of HTA reporting
- Cost Sharing, special discount applied to the initial cycles of therapy for all eligible patients
- Risk Sharing, special discount applied to the initial cycles for non-responder patients after re-evaluation
- Payment by Results, total refund applied to the initial cycles for non-responder patients after re-evaluation
Potential of Risk Sharing Approach in Reimbursement

Marketing authorisation → Monitoring through Register (2 years min.)

New contract with adaptation of price and reimbursement parameters

Risk Share?

- YES
- NOT

Evaluation of the clinical outcomes and the economic effects of contracts, plus HTA reporting

or both?

Observational study in selected centres, in order to verify safety and effectiveness
Negotiation Procedure

- The procedure involves the Committee for Pricing and Reimbursement of the Italian Medicines Agency (AIFA) and the marketing authorisation holder (MAH).

- AIFA proposes different RSS on a case-by-case basis when the launch of a new high-cost pharmaceutical (ORPHAN / NOT ORPHAN) presents uncertainties concerning value, clinical results and/or the budget impact, and potentially inappropriate use.
The Monitoring Registers – the context 2012

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals connected</td>
<td>about 1,000</td>
</tr>
<tr>
<td>Users, Physicians, Pharmacists</td>
<td>over 20,000</td>
</tr>
<tr>
<td>Registered Patients (cases)</td>
<td>over 400,000</td>
</tr>
<tr>
<td>Profiled accesses to projects</td>
<td>over 90,000,000</td>
</tr>
<tr>
<td>Public accesses to projects</td>
<td>over 110,000,000</td>
</tr>
</tbody>
</table>
Orphan Cancer Drugs under Monitoring

Arzerra®, Atriance®, Mepact®, Mozobil®, Nexavar®, Revlimid®, Sprycel®, Tasigna®, Thalidomide Celgene®, Torisel®, Vidaza®, Yondelis®

... with Risk Sharing scheme applied

Arzerra® (CS), Nexavar® (CS + PbR), Revlimid® (CS), Sprycel® (PbR + CS), Tasigna® (CS), Torisel® (PbR), Vidaza® (CS), Yondelis® (PbR)
The Monitoring Registers - DO THEY FIT?

Institutions, healthcare communities and payers

- Balance between rapid access to market and appropriateness
- Balance between costs and effectiveness
- New sources of relevant clinical data (Publications, OLAP)

Pharmaceutical Companies

- Access to market for the new drugs, supported by NHS
- New sources of relevant clinical data (Publications, OLAP)

Patients

- No real differences in access to orphan or not orphan drugs, with support by NHS
- Monitoring of prescriptions and tolerability
Thank you for your attention...

Luca

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