The possibility to turn Concept into Reality?

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Chair, Joint European Industry Task Force on Orphan Drugs (EuropaBIO + EBE)

6th European Conference on Rare Diseases & Orphan Products
Brussels, 23-25 May 2012
Orphan Medicinal Products – a balancing act

• Sense of urgency
  • High, unmet medical need
  • Serious, life-threatening conditions

• But few patients, few data
  • Risk:benefit = positive
  • Acceptance that it is ethical to move forward

• (Regulatory) acceptance, despite overall weight of evidence not so available
  • Compared with more common conditions
Results of the approach = drugs are being developed & approved
“Balancing act” creates uncertainty – and has an impact on all stakeholders

- Governments seeking to understand the value of what they are being offered
- How can we tell?
  - Small datasets
  - Early approval
  - Surrogate endpoints
  - Non-routine clinical trial design
- An[other] area in the field of rare diseases where cooperation can help
 Leads to gap between Marketing Authorisation (EU) & Access to Patients (Country / EU Member State)

Number of available OMPs
Cross-country, European initiatives could address areas of uncertainty

1. CAVOD – Clinical Added Value of Orphan Drugs
   • Information needed to make (informed) decisions
   • Approaches to understand what that information means

2. MOCA – Mechanism of Coordinated Access to Orphan Drugs
   • Way to understand and make value judgements at time of pricing & reimbursement
Where do the CAVOD proposals come from?
CAVOD proposals
= the latest stage in 12+ years of policy...

• EU Regulation 141/2000 on orphan medicinal products
• High Level Pharmaceutical Forum (27 Member States)
• Commission Communication on “Rare Diseases: Europe’s Challenges”
• EU Council Recommendation on a European Action in the Field of Rare Diseases
...building on Experience & Commitment to the need to pool expertise

- 2000: Orphan Regulation – EU Centralised Procedure:
  - “...to provide incentives for the research, development and placing on the market” – based on European cooperation

- 2008: Pharmaceutical Forum: Improving Access to Orphan Medicines for all Affected EU citizens
  - “...exchange of knowledge amongst Member States and European authorities on the...clinical added value of orphan medicines”
...building on **Experience** & **Commitment** to the need to pool expertise

- **2008**: Commission Communication on “Rare Diseases: Europe’s Challenges”
  - “...will set up a Working Party to exchange knowledge between Member States on European authorities...”

- **2009**: EU Council Recommendation on a European Action in the Field of Rare Diseases
  - “...sharing Member States’ assessment reports...at Community level, where the relevant knowledge and expertise is gathered”
2010: European Commission requests external providers to conduct a Study & Report on how

• ...“concerning the creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines

• The aim of these common assessment reports for the scientific assessment of the relative effectiveness of orphan medicines should be to provide a well-informed opinion on the place of the product with the authorised therapeutic indication in the therapeutic strategy of the rare condition, to the best of current knowledge

• Not new reviews, not new data, respecting the roles and responsibilities
What will all this seek to achieve?
Gap between Marketing Authorisation (EU) & Access to Patients (Country / EU Member State)

Timeline graphic courtesy of Ernst & Young, CAVOD study, December 2011
Turning concepts & ideas into a real, functioning system? Where are we now?
EU Committee of Experts to draft recommendations on implementation

- Following publication of external report, Dec 2011
- “Potential ways to facilitate information exchange on orphan medicinal products in order to support the Member States in their processes of making informed decisions on the scientific assessment of the clinical effectiveness of an orphan medicinal product”
EUCERD:
EU Committee of Experts on Rare Diseases

- 27 EU Member States representatives (+ alternates)
- Patients
- Industry
- Academia / representatives of European-funded projects
- European Commission, ECDC
- EMA, COMP – request to be present
- “3rd countries” [non-EU]...

The EUCERD’s role is to **aid the European Commission with the preparation and implementation of Community activities in the field of rare diseases.**
What is in the recommendations?
EUCERD draft proposals for implementation – the CAVOD process is:

• A process for the exchange of knowledge between Member States

• Respecting the [current & emerging] roles and responsibilities of all actors at all levels of the process

• A series of actions and interactions to facilitate seamless exchange of knowledge

• Breaking down silos in the process of an orphan product

• “Oil for the machine” – not a new machine
Making the name reflect what it is

CAVOD becomes

“Improving informed decisions on access to orphan drugs through optimisation of processes via EU collaboration”
Four key time-points in the process of an orphan drug where collaboration could help

1. Early dialogue
2. Compilation Report & evidence definition / generation plan
3. Follow-up of the Evidence Generation Plan
4. Assessment of Relative Effectiveness
1st assessment of Significant Benefit

Confirmation of Significant Benefit

Significant Benefit COMP

EC Marketing Authorisation T0 + 90 days

T0 + \( \Delta T \)
(after 3-5 years, flexible, depending on the disease)

Time

**Early Dialogue**
- EMA
- EUnetHTA
- Sponsor

**Compilation Report & Evidence Needs Identification**
- EMA (Report)
- EUnetHTA

**Evidence generation**
- EMA
- EUnetHTA
- MAH

**Assessment**
- EUnetHTA
- EMA

Could be implemented already
- Actions required?

- Report could be implemented immediately
- Involvement with PRAC requirements needs more work

- Evidence generation plans & follow-up would need to be defined
- Other?

- Appropriate methodologies / tools for OMPs to be developed

Period 1:
- For EMA / EUnetHTA coordination

Period 2:
- For simple Compilation report & evidence generation plan

Period 3:
- For follow-up of the evidence generation plan

Period 4:
- Relative effectiveness assessment
1. Early dialogue

• Early exchanges between EMA + EUnetHTA members (HTA bodies)
• Starting at time of Orphan Designation
  – Assumption of Significant Benefit
• Continuing through Protocol Assistance
• Discussion between all stakeholders from the earliest stages:
  – “What do we have in our hands here?”
1st assessment of Significant Benefit

Orphan Designation

Protocol Assistance

CHMP Opinion T0

EC Marketing Authorisation T0 + 90 days

T0+ΔT (after 3-5 years, flexible, depending on the disease)

Period 1:
For EMA / EUnetHTA coordination

Period 2:
For simple Compilation report & evidence generation plan

Period 3:
For follow-up of the evidence generation plan

Period 4:
Relative effectiveness assessment

Early Dialogue

Compilation Report & Evidence Needs Identification

Evidence generation

Assessment

- EMA
- EUnetHTA
- Sponsor

- EMA (Report)
- EUnetHTA

- EMA
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- Appropriate methodologies / tools for OMPs to be developed
2. Compilation report & evidence definition / generation plan

- Between CHMP Opinion and Marketing Authorisation
  - But building on on-going dialogue already taking place
- Taking into account input from all parties with interest in follow-up
  - Including the new Pharmacovigilance legislation – PRAC Pharmacovigilance Risk Assessment Committee
- In collaboration with the Sponsor
### Significant Benefit

**Confirmation of Significant Benefit**

**Significant Benefit COMP**

**CHMP Opinion T0**

**Protocol Assistance**

**Orphan Designation**

**1st assessment of Significant Benefit**

**Time**

#### Period 1: For EMA / EUnetHTA coordination
- Early Dialogue
  - EMA
  - EUnetHTA
  - Sponsor
  - Could be implemented already
  - Actions required?

#### Period 2: For simple Compilation report & evidence generation plan
- Compilation Report & Evidence Needs Identification
  - EMA (Report)
  - EUnetHTA
  - Report could be implemented immediately
  - Involvement with PRAC requirements needs more work

#### Period 3: For follow-up of the evidence generation plan
- Evidence generation
  - EMA
  - EUnetHTA
  - MAH
  - Evidence generation plans & follow-up would need to be defined
  - Other?

#### Period 4: Relative effectiveness assessment
- Assessment
  - EUnetHTA
  - EMA
  - Appropriate methodologies / tools for OMPs to be developed

**EC Marketing Authorisation T0 + 90 days**

**T0+∆T**

(after 3-5 years, flexible, depending on the disease)
3. Follow-up of the Evidence Generation Plan

• By the Marketing Authorisation Holder after Marketing Authorisation – on-going basis
• Objective: a coordinated approach for Sponsor / MAH
• Studies should be:
  – Defined, relevant, aimed at building understanding of the role of the drug in therapeutic strategy
  – Do not pre-empt requirements of individual Member States
• BUT...voluntary process, uptake will depend on the ability of the system to indeed deliver a more streamlined approach
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<tr>
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<td>EMA</td>
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**Period 1:**
- Orphan Designation
- Protocol Assistance
- Confirm Orphan Designation
- Significant Benefit
- CHMP Opinion

**Period 2:**
- Compilation Report & Evidence Needs Identification
- Period for simple
- Evidence generation plan
- Time for follow-up of the evidence generation plan
- Evidence generation assessment

**Period 3:**
- EAC Marketing Authorisation
- T0 + 90 days
- Time for relative effectiveness assessment
4. Assessment of Relative Effectiveness

• Under the EUnetHTA framework
  – And future permanent network of HTA agencies
• Will require:
  – The availability of appropriate methodological tools to evaluate orphan drugs
  – Their use!
• Flexible, tailored
• Multi-stakeholder involvement – development and execution: patients, clinicians, industry, MAH
Time

1st assessment of Significant Benefit

Orphan Designation

Protocol Assistance

CHMP Opinion T0

Significant Benefit COMP

Confirmation of Significant Benefit

EC Marketing Authorisation T0 + 90 days

Period 1:
For EMA / EUnetHTA coordination

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T0+ΔT
(after 3-5 years, flexible, depending on the disease)

Early Dialogue

- EMA
- EUnetHTA
- Sponsor

Could be implemented already
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Compilation Report & Evidence Needs Identification

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Evidence generation

- EMA
- EUnetHTA
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Evidence generation plans & follow-up would need to be defined
- Other?

Assessment

- EUnetHTA
- EMA

Appropriate methodologies / tools for OMPs to be developed
Key Considerations

• Each actor playing their role – each actor “owns” their part of the process

• Multi-stakeholder involvement
  – As all elements in the systems to date acknowledge – COMP, EUCERD

• Implementing all elements
  – The elements of the system should promote uptake where appropriate

• Taking what steps can already be taken
  – At time of Marketing Authorisation – prevalence of the approved therapeutic indication
Situating the implementation of the “CAVOD process” in the wider external context

- 2008 ≠ 2012 (≠ 2015…)

1. New Pharmacovigilance legislation
2. Evolving cooperative environment between HTA bodies

Provide tools, opportunities, elements to build on
1. New Pharmacovigilance Legislation

• ...“post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed”

• PRAC requirements captured in CHMP Opinion
• Post-Marketing Authorisation data-gathering
• Coordination vital – building on early dialogue
2. A framework of broadening, deepening EMA + HTA collaboration in active exploration

- EUnetHTA
- Cross-Border Healthcare Directive permanent network
- Already working together on key elements
  - Beyond cooperation on improvement of the EPARs;
  - Early dialogue and scientific advice – including multi-stakeholder pilots;
  - Post-launch collaborative data collection; and
  - Cooperation on guideline development, including assessments and Clinical Trial design
Situation the implementation of the “CAVOD process” in the wider external context

• 2008 ≠ 2012 (≠ 2015...)

1. New Pharmacovigilance legislation
2. Evolving cooperative environment between HTA bodies
3. Legislation: Transparency Directive, ...
4. Policy: Mechanism of Coordinated Access to Orphan Drugs (MOCA), ...
But ingredients need to be correctly mixed together!

- Data capture – notably Timepoint 4
  - Registries?
- In context of other EU collaborative initiatives
  - ENCePP – European Medicines Agency
  - EUenetHTA database(s)
  - Orphanet
  - Others…? Managed Entry Schemes in-country…
- Fitting into existing systems – financing by those who intend to use data?
Starting to do this?
Pilots for the Process?

• Several timepoints already identified
• Sharing knowledge could help
• Objective to facilitate understanding of the appropriate role of orphan drug in national healthcare systems

➡ EUCERD recommendation that these should be the starting points

➡ Where more work is required, steps can be implemented later
A. Early Dialogue / Shared Advice

• [Voluntary] process already exists – being further developed

• Propose that representatives of EUnetHTA invited to Protocol Assistance
  – Case-by-case, 2-4 procedures
  – Experience in orphan drugs / the orphan drug

• Early access to EMA documents

• Building on EUnetHTA core HTA information package

→ Sponsor’s agreement
B. Single, usable document at time of Marketing Authorisation

• Single report based on existing assessments by experts from Member States
  – Available at time of Marketing Authorisation
  – COMP, CHMP, PDCO, [CAT], PRAC (2012 onwards)

• Building on:
  – EPAR
  – Orphan Designation Reports
  – Confirmation of Significant Benefit at time of MA
  – Paediatric Investigation Plan (PIP) – if applicable...
Will it make a difference?
What is the CAVOD for?

“Bundling the fragmented know-how to assess the clinical value of orphan medicines would allow the timely production of well-informed opinions, based on more data, shared information, experiences and in-depth discussion.”

High Level Pharmaceutical Forum Conclusions
“Improving Access to Orphan Medicines for all Affected EU Citizens”
What is the CAVOD for?

“This collaboration could lead to non-binding common clinical added value assessment reports with improved information that facilitate the national pricing and reimbursement decisions, without pre-empting respective roles of the authorities.”

High Level Pharmaceutical Forum Conclusions
“Improving Access to Orphan Medicines for all Affected EU Citizens”
“To facilitate Member States informed decision…”
Will it help Access?

- Consolidated Common Report
- Data – MA & COMP revision of criteria
- Agree on “Post-MA research activities”
- Compilation of post-MA data – registries, etc.
- Updated consolidated Common Report
- Data – In-use

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<th>60-90 days</th>
<th>3-5 years</th>
<th>Re-evaluation</th>
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<tr>
<td>CHMP Positive Opinion</td>
<td>European Commission Marketing Authorisation</td>
<td>Second discussion with Member States</td>
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- Patients get access
- Conditional reimbursement schemes?
- Appropriate methodologies
Characteristics to aid success

• Case-by-case
  – Heterogeneous conditions, therapies, situations
• Voluntary
• Multi-stakeholder involvement
• Developing right tools for the job
• Measured
  – Does it work? Periodic reporting
This is a Work In Progress
Formulating Policy into Reality: where in the process and what next?

- 26-27 January 2012: EUCERD Plenary endorsement of general direction
- 9 May 2012: EUCERD Drafting group revises draft
- 19 June 2012: Enlarged drafting group
- 20-21 June 2012: EUCERD Plenary (adoption?) [Or November 2012 EUCERD meeting]
- Next steps from relevant authorities to implement

“Oil in the machine”, not a new machine
“Orphan” & “non-orphan” tools exist to make it possible

Healthcare provision remains a Member State responsibility...but no longer in isolation
THANK YOU!

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http://www.eucerd.eu

EU Committee of Experts on Rare Diseases (EUCERD)