Regulatory pathways to expedite drug development – focus on innovative methods and drug development tools

Maria Isaac, MD PhD, MFPM, Psychiatrist

CORS - Copenhagen
Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood nor quoted as being made on behalf of or reflecting the position of EMA or one of its committees or working parties or any of the national agencies.

Other positions:
• Vice Chair of the Psychopharmacology Special Committee of the Council of the Royal College of Psychiatrists, UK.
• Previous : Consultant Psychiatrist & Co-Director of Psychopharmacology Evaluation Unit at the South London & Maudsley NHS trust in London and Honorary Senior Lecturer in the Department of Forensic and Neurodevelopmental Sciences at the Institute of Psychiatry, Kings College London, UK.
Goals of this session:

**Regulatory strategies to expedite drug development and effective access to patients in the EU**

- Qualification of novel methodologies: Voluntary, scientific pathway for innovative methods or drug development tools (e.g. biomarkers) not yet integrated in the drug development and clinical management paradigm
- Parallel FDA-EMA qualification procedure
- Qualification examples: Alzheimer’s disease, e-technology

Adaptive pathways
Outline

1. Regulators
   - phase 1
   - phase 2
   - phase 3
   - framework tools

   EMA scientific advice
   EMA qualification + FDA
   EMA-HTA scientific advice
   adaptive pathways pilot

2. HTA
   - Acc
   - Std
   - principles variability outcomes
   - align – early dialogue

3. P&R
   - EMA scientific advice
   - FDA

European Medicines Agency
EMA structure & functions

decentralised body EU

- headquarters scientific secretariat and coordination (London > 1995)
- network of national agencies from 28 EU countries and > 5000 experts internal & external – scientific committees (multidisciplinary)

& working parties

<table>
<thead>
<tr>
<th>centralised (EMA)</th>
<th>national</th>
</tr>
</thead>
</table>
| registration      | price & reimbursement  
|                   | (access NHS, WTP)    |
| guidelines        | clinical trial approval |
| scientific advice | (national EoP2 meetings?) |
| (opt)             |                      |
|                   | (impact on          |
|                   | review?)            |
| orphan drug       | devices incl. IVDs, coDx |
| designation       |                      |
| paediatric studies|                      |
| EU pharmacovigilance |                  |
| coordination      | inspections          |
|                   |                      |
**EMA committees**

- **SAWP**
- **CHMP** (Committee for Human Medicinal Products)
- **COMP** (Committee for Orphan Medicinal Products)
- **HMPC** (Committee for Herbal Medicinal Products)
- **PDCO** (Paediatric Committee)
- **CAT** (Committee for Advanced Therapy Medicinal Products)
- **PRAC** (Pharmacovigilance risk assessment committee)
Centralised review procedure

for marketing authorisation application (MAA = BLA, NDA) evaluation by multidisciplinary committee for medicinal products for human use (CHMP)

active review time max. **210 days** legislation (excluding ‘clock-stops’)

- **not ‘rolling’ submission** (exc.); wait to file extension until initial MA granted

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**Clock-stops**

- Oral explanation
- ≤ 6m

**Primary evaluation**

- d12
- 0

**Secondary evaluation**

- d12
- 1

**CHMP opinion**

- d180
- d181

**EC decision**

- ≥ 67d

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**2006-14: oncology 23 requests**

- 11 granted (rev), no overlap

**CMA**

- mind the gap: monthly & multidisciplinary, voting 1/MS ± 5 co-opted
Scientific Advice Working Party

• standing WP of the CHMP (Reg. 726/2004)

• multidisciplinary expert group (28) selected by expertise (not MS)
• 16 NCAs, 12 academia; members of EMA committees 3 COMP, 1 CAT, 2 PDCO

• CHMP peer-review, ad hoc discussions, adoption final advice letter
• CMC: starting materials, specs, comparability, bridging…
• non-clinical: overall toxicology plan registration, innovative models…
• clinical pharmacology: PK/PD, modeling & simulation, BE…
• clinical therapeutic areas: endpoints, population, comparator…

• methodology, statistics: interim A, adaptive/seamless design…
• network of external experts
Scientific Advice main activity so far:

- Scientific Advice and Protocol Assistance for orphan drugs
<table>
<thead>
<tr>
<th>Scientific advice/Protocol assistance</th>
<th>Qualification advice/opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product and indication specific</td>
<td>Broader scope – may concern several indications or products</td>
</tr>
<tr>
<td>Fixed timelines – 40 or 70 days</td>
<td>Flexible timelines and proceedings</td>
</tr>
<tr>
<td>Applicant can intervene only if requested by the SAWP, mainly in case of disagreement with the proposal</td>
<td>Always face-to-face meetings, applicant can raise issues for discussion during the procedure</td>
</tr>
<tr>
<td>SAWP “looks” into the data but focuses on methodology</td>
<td><strong>Assessment of the data!</strong></td>
</tr>
<tr>
<td>Always confidential until drug approved</td>
<td>Public if a positive opinion is issued (after agreement with the applicant)</td>
</tr>
</tbody>
</table>
EU Guidance for Qualification of Novel Methodologies

- Voluntary, scientific pathway for innovative methods or drug development tools (e.g. biomarkers) not yet integrated in the drug development and clinical management paradigm
- One procedure with three outcomes:
  - Qualification Advice, OR
  - Qualification Opinion
  - Letter of support

Long-term benefits from EMA perspective: Speed-up the time to regulatory acceptance of novel approaches and time to new marketing authorisation applications
Qualification of novel methodologies

**CHMP qualification opinion** on the acceptability of a specific use of the proposed method (e.g. use of a BM) in a R&D context (non-clinical or clinical), based on the assessment of data, not product-specific. Qualification team, peer-review, public consultation, publication

**CHMP qualification advice** on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted, confidential

The procedural route is not fixed but will follow the assessment of the data

**Aims:** SAWP/CHMP early involvement in the design of the strategy, with commitment to evaluate data from agreed studies and to provide opinion

**Scope:** Focus on acceptability of specific use of the proposed technology/BM developed for a specific intended use in the context of pharmaceutical R&D (Context of Use)

They will be included in the future CHMP guidance
New procedure

- Regulatory requirements evolve as we gain experience
- Multi-stakeholder (e.g. Regulators, Payers, Learned Societies, Patients, Notified Bodies)
- Multidisciplinary (Analytical Scientists, Pharmacologists, Toxicologists, Modellers, Clinicians, Statisticians)
- Qualification procedure is a platform for dialog:
  - Opening new communication channels
  - Involving different stakeholders whenever possible (e.g. FDA, HTAs, patient representatives, device experts, learned societies, GCP inspectors)
BM qualification procedure

Qualification of novel methodologies for drug development: guidance to applicants
Documentation needed:
- letter of intent
- briefing document
- Supportive documents (e.g. study protocols/reports) and scientific literature

Applicants:
- Consortia, networks, public/private partnerships, learned societies, academia, pharmaceutical industry

Fees:
- Same fee reductions as in scientific advice for paediatric, orphan conditions and SMEs (small and medium-sized enterprises)


Qualification team

2 Coordinators (SAWP or CHMP)

Adding external experts if CoI assessment allows

Experts multidisciplinary, min 4

therapeutic areas

statistics

context of intended use: e.g. non-clinical safety testing, translational research

technology platform supporting the development of the novel methodology: e.g. genomics, proteomics, ultrasound, MRI imaging

Experts

Project Manager (EMA)

01 December 2016
Role of SAWP and CHMP

Scientific Advice Working Party (SAWP) –
Serves as primary scientific group, allows extensive networking within the Agency (Committees, other working parties and expert groups will be involved as appropriate)

Committee for Medicinal Products for Human Use (CHMP) involvement -
- CHMP member can be team member, peer review, discussion and adoption of final responses (Advice Letter or Qualification Opinion) by CHMP plenary
- Helpful for future CHMP interactions, also in the context of Marketing Authorisation Applications
Joint FDA/EMA Letter of Intent (LOI)
Submissions for Biomarker and Clinical Outcome Assessment Qualification Programs

A joint Letter-of-intent (LOI) template to enable efficient parallel submissions to the US FDA and EMA for Drug Biomarker Qualification or Clinical Outcome Assessment Qualification.

Update: Letter of intent

To facilitate parallel submissions of applications for drug biomarker qualification or clinical outcome assessment to EMA and to the United States Food and Drug Administration (FDA), the two agencies launched a joint letter of intent (LOI) in December 2014.

The joint LOI allows the two agencies to share scientific perspectives and advice. The agencies are also able to provide the same response to submitters.

With the joint LOI, the agencies intend to reduce the time taken by applicants to prepare LOIs. However, applicants do not have to submit jointly to EMA and the FDA - they can send EMA or FDA-specific LOIs separately if they wish.

Some sections of the LOI are specific for EMA or the FDA. See the template for details.
• Encouraged by both Agencies
• Voluntary, at request of sponsor
• Discussion between FDA-EMA and tripartite meeting with sponsor
• Alignment of procedural flow between agencies is important and challenging: preparatory interactions with all agencies should start early
• Each Agency will issue separate responses to sponsor’s questions in line with their usual procedures

→ Increased dialogue between Agencies and sponsor from early stages of development
→ Exchange views, share expertise
→ Optimise and facilitate global development, meeting both agencies requirements
Qualification opinion of Alzheimer’s disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment for use – in predementia AD clinical trials

<table>
<thead>
<tr>
<th>Agreed by Scientific Advice Working Party</th>
<th>27 October 2011</th>
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</thead>
<tbody>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>17 November 2011</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>22 December 2011</td>
</tr>
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</table>

Comments should be provided using this template. The completed comments form should be sent to Qualification@ema.europa.eu

Keywords | Qualification opinion, PET Biomarker, Pre-dementia Alzheimer’s disease
4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

AMYVID is a radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) and other causes of cognitive impairment. AMYVID should be used in conjunction with a clinical evaluation.

A negative scan indicates sparse or no plaques, which is not consistent with a diagnosis of AD. For the limitations in the interpretation of a positive scan, see sections 4.4 and 5.1.
Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer’s disease

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tr>
<td>Draft agreed by Scientific Advice Working Party</td>
<td>6 June 2013</td>
</tr>
<tr>
<td>Adopted by CHMP for release for consultation</td>
<td>27 June 2013(^1)</td>
</tr>
<tr>
<td>Start of public consultation</td>
<td>19 July 2013(^2)</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>27 August 2013(^3)</td>
</tr>
<tr>
<td>Adoption by CHMP</td>
<td>19 September 2013</td>
</tr>
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</table>
IMI - EPAD

European Prevention of Alzheimer’s Dementia Consortium
What is EPAD?

- EPAD brings together a trial ready cohort of well-characterized subjects evaluated at highly qualified sites running a standing adaptive proof of concept trial in AD.
- 8 Work Packages including our delivery cluster
- 35 Partners (Academic, EFPIA and non-EFPIA commercial entities)
- 30 Trial Delivery Centres

www.ep-ad.org
EPAD Objectives

- Develop a Platform to test treatments for the **Secondary Prevention of AD**:
  - Including
    - Delay in onset of symptoms in people with preclinical evidence of AD pathology; and
    - Delay in onset of clinical dementia in people who in addition to biological evidence of AD also show symptoms (ie, MCI due to AD or prodromal AD)
  - Excluding
    - Subjects with dementia and subjects who have no symptoms and no evidence of disease (primary prevention population)
**Key Events:**

2013 Dementia Summit and follow-on events: London/Finance, Ottawa/PPP, Toronto/Big Data, Tokyo/Care, Lausanne/Regulation

Mar 2015/WHO: Review global actions to date and plans going forward


**Global Funding:**

Europe/IMI-EPAD: Committed public investment of ~E25M across 5yrs (+ IMI EMIF and AETIONOMY)

Canada/CCNA: Application for ~$12.5M Canadian public investment over 5 yrs

US/GAP: Seeking minimum of $25M public investment over 5 yrs
Draft qualification opinion on the ingestible sensor system for medication adherence as biomarker for measuring patient adherence to medication in clinical trials

Document details

<table>
<thead>
<tr>
<th>Download document</th>
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<tr>
<td>Reference number</td>
<td>EMA/CHMP/SAWP/513571/2015</td>
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<tr>
<td>Status</td>
<td>draft: consultation open</td>
</tr>
<tr>
<td>First published</td>
<td>16/09/2015</td>
</tr>
<tr>
<td>Last updated</td>
<td>16/09/2015</td>
</tr>
<tr>
<td>Consultation start date</td>
<td>16/09/2015</td>
</tr>
<tr>
<td>Consultation end date</td>
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</tr>
<tr>
<td>Email address for submissions</td>
<td><a href="mailto:qualification@ema.europa.eu">qualification@ema.europa.eu</a></td>
</tr>
</tbody>
</table>

Summary

Proteus Digital Health Inc. intends to have its Proteus technology approved as a ‘qualified method’ for measuring adherence to medication in clinical trials by associating relevant physiologic and behavioural parameters, such as indications of therapeutic response. The Proteus technology is an ingestible event marker, a platform technology that can be co-formulated with active pharmaceutical compounds into drug/device combinations, integrating measuring of medication adherence into oral pharmacotherapy. The ingestible event marker is approved for marketing in the European Union and the United States as a medical device.
Wacean
A patient-driven innovative tool for data capture
Why PROMs?

- They are the reflection of patient-centeredness in clinical research;
- Patient Reported Outcomes are measurements based on data provided by patients regarding their health condition without amendment or interpretation of the patient’s response by a clinician or anyone else;
- Such as the other types of Patient Relevant Outcome Measures, they have to be convincing to satisfy the requirements of both regulators and HTA during the assessment of a product.
- However, appropriate and validated outcome measures of disease activity, or disease progression, still do not exist for the vast majority of rare diseases, even diseases for which medicines are already approved, or for which therapies are under development.
14 Qualification Opinion and 76 Qualification Advices finalised to date
Important considerations for Qualification studies

- **Endpoints** → Demonstration of diagnostic and prognostic performance (sensitivity and specificity), predictive value for drug response, likelihood ratios

- **Statistical plan** → Will study design and data analysis support targeted CoU?
  - Prospective vs. retrospective, pre-specified cross-validation possible?

- Impact of methodology on **diagnostic thinking, patient management and clinical outcome** → demonstration of clinical utility

- **Standard of truth** → Assessment of true state of a patient or true value of measurement might not exist or is invasive and unethical
  → Surrogate standard to be justified

- **Analytical platforms:**
  Technical/performance characteristics to be defined and justified, fit for purpose;
  Software used should be reliable and testing procedures should be available
Links

**EMA guidance for companies requesting SA or PA**

**Qualification of novel methodologies for drug developments**

**Scientific guidelines**

E-mail: maria.isaac@ema.europa.eu

European Medicines Agency | 30 Churchill place| Canary Wharf | London | E14 5EU| United Kingdom  Tel: (44-20) 3660 7153 | Fax: (44-20) 3660 70 40
Thank you for your attention

Further information

Maria.Isaac@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
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