EMA Qualification of Novel Methodologies – Streamline DDT development for regulatory Qualification

C-Path DDT-KD Consortium September 2015

Presented by Thorsten Vetter on 25 September 2015

'Science Advice Office
Guidance for Qualification of Novel Methodologies

• ...on the regulatory validity and acceptability of a specific use of a proposed method in R&D context

• Voluntary, scientific pathway for innovative methods or drug development tools not yet integrated in the drug development and clinical management paradigm

• **One procedure with two outcomes:**
  - Qualification Advice, OR
  - Qualification Opinion

Long-term benefits from EMA perspective: Speed-up the time to regulatory acceptance of novel approaches and time to new marketing authorisations, improve public health

The proactive regulatory approach: “Be part of it and shape it together.”
Qualification of novel methodologies

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

**Qualification opinion** on the acceptability of a specific use of the proposed method (e.g. use of a BM) in a R&D context, based on the *assessment of data*, not product-specific. CHMP discussion and adoption, public consultation, *publication*

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

**Aims:** early and preferably iterative involvement to support the design the development strategy and during the project at key milestones, with commitment to evaluate data from agreed studies and to provide opinion
Clear proposal for a Qualification claim (Context of Use, CoU)

• **Technical aspects**: e.g. Analytical platform, biological matrixes, timing for evaluation

• The relation of the **marker response** with normal biological processes, or pathogenic processes, or pharmacologic responses to a therapeutic intervention and the expected **quantitative response-threshold**

• The **intended use of the DDT in drug development and clinic** (e.g. exploratory vs. confirmatory, prognostic vs. predictive: preclinical, translational, toxicity biomarker, inclusion criterion, stratification factor, enrichment tool, therapeutic drug monitoring, primary endpoint, secondary endpoint, initiation of treatment in clinic or change of intervention)

**Final CoU** will be informed by assessment of submitted data
Qualification team

Coordinator
(SAWP or CHMP)

Experts
multidisciplinary, min 4

Adding external experts if CoI assessment allows

therapeutic areas

statistics

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

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

Project Manager
(EMA)

28 September 2015
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
- SAWP/CHMP commitment to evaluate the data obtained from studies agreed during Qualification Advice and to provide a Qualification Opinion regarding the use of the method in R&D.
- Helpful for future CHMP interactions
<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>Broad scope – may concern several indications or products, novel methodologies for specific R&amp;D requirements, safety signal detection tools, etc.</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, can provide additional data/analyses</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 public consultation and check for commercially relevant information)</td>
</tr>
</tbody>
</table>
• **Applicants:** Consortia, Networks, Public/Private Partnerships, Learned societies, Academia, Pharmaceutical industry

• **Fee incentives:** Same fee reductions as in scientific advice for paediatric use, orphan conditions and SMEs (small and medium-sized enterprises)

• **Initiation, Consultation and Qualification Advice:** Confidential

• **Qualification Opinion:** Public consultation prior to final publication ensuring scrutiny of and alignment with scientific community and external stakeholders

---

<table>
<thead>
<tr>
<th>Document(s)</th>
<th>Language</th>
<th>Status</th>
<th>First published</th>
<th>Last updated</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final conclusions on the pilot joint European Medicines Agency / Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers</td>
<td>(English only)</td>
<td>22/01/2009</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Document(s)</th>
<th>Language</th>
<th>Status</th>
<th>First published</th>
<th>Last updated</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease (ADPKD)</td>
<td>(English only)</td>
<td>draft: consultation open</td>
<td>22/07/2015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Qualification Opinions to date

• Paediatric Ulcerative Colitis activity index (PUCAI)

• Ingestible sensor system for medication adherence testing in clinical trials

• Total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease (ADPKD)

• Qualification of exacerbations of chronic pulmonary disease tool (EXACT), and EXACT-respiratory symptoms measure (E-RS) for evaluating treatment outcomes in clinical trials in COPD

• In-vitro hollow fiber system model of tuberculosis (HFS-TB)

• MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase-II dose-finding studies under model uncertainty
Qualification Opinions to date

• A novel data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer’s disease

• Alzheimer’s disease novel methodologies / biomarkers for the use of cerebrospinal-fluid amyloid beta 1-42 and t-tau and / or positron-emission-tomography amyloid imaging (positive / negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer’s disease

• Low hippocampal volume (atrophy) by magnetic-resonance imaging for use in clinical trials for regulatory purpose in predementia stage of Alzheimer’s disease

• Novel methodologies in the predementia stage of Alzheimer’s disease: cerebrospinal-fluid-related biomarkers for drugs affecting amyloid burden

• Alzheimer’s disease novel methodologies / biomarkers for BMS-708163

• ILSI / HESI submission of novel renal biomarkers for toxicity
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: preparatory interactions with both 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
Letters of Support

Letters of support

Based on qualification advice, the Agency may propose a letter of support as an option, when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data.

Letters of support aim to encourage data-sharing and to facilitate studies aimed at eventual qualification for the novel methodology under evaluation.

These letters include a high-level summary of the novel methodology, context of use, available data, and on-going and future investigations. The Agency publishes letters of support on this page, if the sponsors agree.

<table>
<thead>
<tr>
<th>Document(s)</th>
<th>Language</th>
<th>Status</th>
<th>First published</th>
<th>Last updated</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter of support for skeletal muscle injury biomarkers</td>
<td>(English only)</td>
<td></td>
<td>19/03/2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter of support for microaneurysm formation rate (MAFR) biomarker</td>
<td>(English only)</td>
<td></td>
<td>21/01/2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter of support for Predictive Safety Testing Consortium translational drug-induced kidney injury biomarkers</td>
<td>(English only)</td>
<td></td>
<td>07/11/2014</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Novel Methodologies procedure numbers
Services seen

- Clinical (87%)
- Pre-Clinical (13%)
- Pre-Clinical safety (13%)
- Patient selection (32%)
- Clinical efficacy (38%)
- Clinical Safety (11%)
- Tools for trial design (6%)
Thank you for your attention

Further information

Thorsten Vetter

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 7475 Facsimile +44 (0)20 3660 5555
Email thorsten.vetter@ema.europa.eu

Follow us on @EMA_News