Approaches used for validating Biomarkers for Use in Drug Discovery/claims in Europe

Section on Pharmacological-Toxicological and Biotechnological Assessment
Medicines Evaluation Board
Utrecht, The Netherlands

Jan Willem van der Laan
Classical biomarkers in cardiovascular field
- Blood pressure
- Heart rate
- ECG-profile

Previous nomenclature:

Surrogate endpoints
Focus on diseases:

- myocardial infarction
- stroke

leading cause of morbidity and premature mortality worldwide

Not on health.
For atherosclerosis surrogate endpoints/biomarkers:

Lipid markers of dyslipidemia

• LDL-C major atherogenic lipoprotein

additionally:

• hsCRP

Focus on Therapy: Sensitive to statins
Log-linear relationship between LDL-C levels and relative risk for CVD

Most important parameters

- Disease symptoms/morbidity
- Survival/premature mortality
- Clinical condition, Quality of life

What is the clinical relevance of changes in biomarkers in relation to therapy or prevention in case of genetic risk factors?
Need for new biomarkers

- For a priori differentiation in patient groups
- Differentiation between therapies. Can a perceived increase in therapeutic being substantiated?
- Biomarkers for diseases with a heterogenous symptomatology. Enrichment of subgroups.
- Early prediction of safety concerns
A New, Voluntary, Scientific Pathway Leading To

CHMP Qualification Opinion and Scientific Assessment (public)

CHMP Qualification Advice (confidential).
Advice or Opinion?

- **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.

- **CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.
**Differences: Scientific Advice-Qualification Advice**

<table>
<thead>
<tr>
<th>Scientific advice</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>Assessment of the data!</td>
</tr>
<tr>
<td>Always confidential</td>
<td>Public if a positive opinion is issued (after agreement with the Applicant)</td>
</tr>
</tbody>
</table>
Experience to date - Qualification Advices

Since the introduction of the procedure 12 Advices have been completed and 5 are ongoing (status 2012):

- 5 CNS
- 3 Nephrology
- 3 Oncology
- 2 Gastroenterology
- 2 Respiratory
- 1 Muskuloskeletal
- 1 Cardiovascular
Experience to date - Qualification Opinions

Since the introduction of the procedure 6 Opinions have been completed and 1 is ongoing

- 4 CNS
- 2 Nephrology
- 1 COPD
Experience to date – current and future projects

Non-clinical - Toxicology
• Assays for early detection of kidney, hepatic and muscular tissue injury

Clinical
• Hippocampal volume by MRI or amyloid deposition in the brain by PET or certain proteins in cerebrospinal fluid in the predementia phase of Alzheimer’s disease:
  – As inclusion criteria for enrichment in clinical trials: Opinion
• Hippocampal volume by MRI or amyloid deposition in the brain by PET or certain proteins in cerebrospinal fluid in mild to moderate Alzheimer’s disease
  – As endpoints for assessing disease modification: Advice
• A Carer outcome scale for dependence in Alzheimer’s disease
Experience to date – current and future projects

More

• CRP for use as a marker of atherosclerotic cardiovascular risk for the purpose of identifying adults at increased risk for cardiovascular events

• A Patient Reported Outcome scale on Physical Activity to be used as an endpoint in COPD

• A Patient Reported Outcome scale for function for brain metastasis

• A combined diagnostic methodology for patient population enrichment in Parkinson’s disease

• Centralised Ratings in clinical trials in schizophrenia to decrease inter-rater variability and increase sensitivity of the trial to detect a true effect
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>
</tr>
</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>
</tbody>
</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
Qualification of novel methodologies for drug development: guidance to applicants

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreed by SAWP</td>
<td>27 February 2008</td>
</tr>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>24 April 2008</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>30 June 2008</td>
</tr>
<tr>
<td>Final Agreed by CHMP</td>
<td>22 January 2009</td>
</tr>
</tbody>
</table>
Experience on Nephrotoxicity Biomarker Qualification

PSTC
ILSI-HESI
PSTC: Why New Safety Biomarkers for Renal Function?

- Histopath/ClinPath failed to predict development of future tubular degeneration (i.e. within a species and across species).

- Current kidney functional tests are either insensitive, variable or non-specific to kidney injury. When changes are detected injury has already happened!

Example:
- Approximately 2/3 of kidney function loss before BUN or creatinine increases.
Selection of Biomarkers
Mapping to the Nephron

Proximal Tubule
- GST-α
- β2-Microglobulin
- NAG
- Kim-1
- Cyr-61
- Lipocalin-2
- Timp-1
- Clusterin
- EGF
- (Osteopontin)

Distal Tubule
- GST-μ
- Osteopontin
- Calbindin D28
- Timp-1
- Clusterin
- EGF

Collecting Duct
- (Calbindin D28)

Unspecific
- VEGF
- Cystatin C

Glomerulus
- Podocin
- β2-Microglobulin (indirect)
- (Osteopontin)
- (Cyr-61)

Loop of Henle
- Osteopontin
Discussion of Qualification Data

Correlation between Histopathology and Biomarker Data.

Performance of Proposed Biomarkers Compared with Accessible Biomarkers in Current Use.
**Non Clinical**

**Urinary Kim-1, Albumin, Total Protein, β2-Microglobulin, clusterin, trefoil factor3 and Cystatin C**

- Are Tools in NC DD to detect acute drug-induced nephrotoxicity
  - tubular
  - glomerular with associated tubular involvement

- Add and complement BUN and, sCr to correlate with histopathology (gold standard)

- Data submitted were generated in short term (up to 14 days) pre-clinical studies *in rat*. 
Clinical

Urinary Kim-1, Albumin, Total Protein, β2-Microglobulin, clusterin, trefoil factor3 and Cystatin C

For early Clinical trials:
- worthwhile as bridging markers for early detection of acute drug-induced renal alteration
- should be explored further as clinical biomarkers for acute kidney injury.

For monitoring nephrotoxicity in clinical setting:
- cannot be recommended
- (further data needed to correlate BMs with the evolution of the nephrotoxic alterations)
There is sufficient evidence to support the voluntary use of

- α-GST,
- RPA-1
- clusterin

along with currently used methods to gain further insight into renal injury when it is seen in preclinical safety assessment studies in rats.
• The novel BMs evaluated have been shown not only to have utility for the detection of tubular injury but some also provide useful information on the tubular site of injury

• **Clusterin** is confirmed to have utility for detection of tubular injury without additional insight as to location. The superiority of clusterin (compared with the reference BMs: BUN and sCr) was evident when regeneration was present.

• **α-GST** was shown to be superior to all of the reference markers for detection of injury to the **proximal tubule**.

• **RPA-1** was shown to be superior to all of the reference markers for detection of injury to the **collecting duct**.”
Clusterin:
- Can be used together with traditional clinical chemistry markers and histopath. in GLP tox. studies used to support renal safety in clinical trials.

Urinary RPA-1:
- Can be included with traditional clinical chemistry markers and histopath. in GLP tox. Studies used to support renal safety in clinical trials.

α-GST:
- Not Qualified yet.
Concluding Remarks

- The Qualification of BM of nephrotoxicity can serve as models for qualification of other BMs.

- The opinions are public and may serve together with guidelines to overcome detected insufficiencies.