Interactions with FDA and EMA: The LITMUS experience from qualification advice on biomarkers in NASH

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Background

There is a need for non-invasive diagnostic and prognostic biomarkers to replace the liver biopsy in NAFLD. The BEST[1] glossary is a taxonomy for classifying and developing biomarkers for different context of use (COU).

2 pathways can lead to approval of a new biomarker for use in clinical development:

1) Drug-specific development and approval – the use of a biomarker as part of a development of a specific new drug, eventually approved for that use.

2) A biomarker qualification – approves a biomarker for a particular COU in a specific patient population which can be used in drug development for regulatory approval (e.g. plasma fibrinogen is qualified for use for enrichment in clinical trials of chronic obstructive pulmonary disease (COPD) patients at high risk for exacerbations and/or all-cause mortality). The qualification pathway is available in EU and US.

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Regulatory Pathway

First step in a qualification is to determine the COU. The COU includes two components: the biomarker category[1] and the biomarker's proposed use in drug development[2].

In EU, the EMA qualification process[2] is implemented through Scientific Advices including a project lead from the qualification 'group' the interaction leads to either a qualification advice, or a qualification opinion (approval) of the biomarker. As the scientific knowledge may change with new data the qualification process may encompass an ongoing interaction between the CHMP and the applicant. Prior to final adoption of an EMA qualification

In the US, the FDA CDER qualification process [3,4] includes three submissions: the Letter of Intent (LOI), the Qualification Plan (QP), and the Full Qualification Package (FQP). The qualification process ends with FDA issuing an FQP Determination Letter indicating whether the DDT is qualified or not.

Qualifying a biomarker does not result in the endorsement of a specific measurement method. If a manufacturer is interested in pursuing the development of a specific biomarker test for marketing as a device, the test should be submitted to and approved by CDRH in US and by notified bodies in the EU. A biomarker qualified for a specific COU will be publicly available and announced as a guidance which can be applied to any drug development program for which the COU is appropriate.

Methods

The biomarker qualification requires a technical and a clinical validation

The evidence for the clinical validation comes from the "LITMUS registry" that includes NASH patients from the EU and US. Data from other registers, and from placebo groups in NASH clinical trials, can be used as supporting evidence.

Technical validation of imaging and serological biomarkers is performed according to regulatory guidance.

See below example for required protocols for an IVD[5,6] (see table 1).

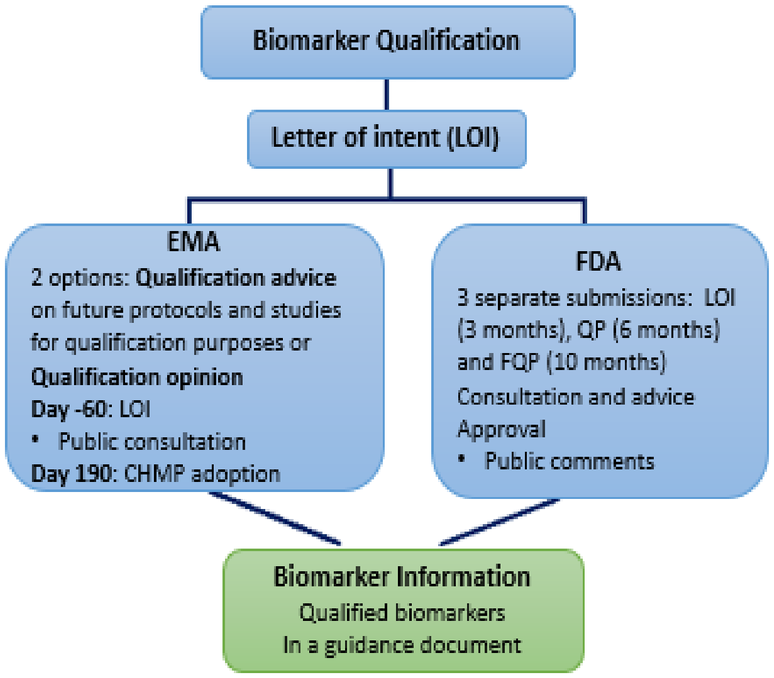

Table 1 Technical protocol required

Analytical Specificity	Reagent Characterization	Sample Stability
Linearity	Reference Range	Reproducibility
Detection Limits	High Dose Hook Effect	
Assay Dilution Parallelism	Accuracy against Reference Method	Carry-Over and Cross Contamination

Results

Insight into the disease is mandatory to select COU

When selecting COUs for biomarkers in NASH, the regulatory NASH guidelines from FDA[7] and EMA[8] should be considered. This is required for the definition of the COU, the clinical data and the statistical analysis.

Biomarker qualification requires two sets of clinical data, one for defining a cut-off and one for validating the cut-off.

The technical validation of the biomarker and real-time stability are essential.

The type of documentation and the timing of feedback differs between the FDA and EMA qualification pathways.

The LOI submission to EMA requires a complete briefing document, whereas the LOI to FDA only requires a description of the biomarker, patients and the proposed COU.

FDA/EMA Feedback is related to integrity of clinical data[9], quality of data, statistical assumptions, COU, and technical performance of the biomarker

Conclusion

LITMUS is a private public partnership to facilitate the development and validation of biomarkers, and to advance them towards qualification as DDTs.

As qualification of biomarkers requires knowledge of the different qualification needs, early interaction with EMA and FDA provides advantages

Experience from regulatory interactions regarding qualification of DDTs needs to be shared to facilitate future qualification of biomarkers.

References: 1) Biomarkers, EndpointS, and other Tools glossary https://www.ncbi.nlm.nih.gov/books/NBK326791/ 2) Qualification of novel methodologies for drug development: guidance to applicants, EMA guideline, November 2014, 3) Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff, FDA guidance, December 2019, 4) Biomarker Qualification: Evidentiary Framework, Draft Guidance for Industry and FDA Staff, FDA guidance, December 2018, 5) Guideline on bioanalytical method validation, EMA guideline, July 2011, 6) Scientific and Regulatory Considerations for the Analytical Validation of Assays Used in the Qualification of Biomarkers in Biological Matrices, Steven P. Piccoli and John Michael Sauer, 2019 7) Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment - Guidance for Industry, FDA, 2018. 8) Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH), EMA, 2018. 9) Draft Guideline on registry-based studies, EMA, 2020.