Regulatory enablement of molecular endotypes for drug development. Definition of the context of use (COU) and molecular endotype which most urgently will assist in drug development: Stakeholder alignment under the Clinical Trial Symposium (CTS) & OARSI umbrella

Morten Karsdal¹, Anne Christine Bay-Jensen¹, Ali Mobasheri², Christof Ladel³ and Virginia Kraus⁴

¹Nordic Bioscience, Herlev, Denmark; ²Oulu University, Oulu, Finland; ³Independent consultant, Frankfurt, Germany; Duke University, Durham, VC, USA

BACKGROUND: To enable regulatory interactions to enhance the use of biomarkers in clinical studies

For a biomarker to be considered in therapeutic development, it must navigate various approval pathways. In the US, acceptance for single therapeutic trials is via IND, NDA, and BLA submissions, while for multiple drug development programs, it's through the Biomarker Qualification Program. This program specifically evaluates the biomarker itself, not the measurement method.

Alternatively, in the US, a biomarker test can be approved by CDRH, leading to a legally marketable In-Vitro Diagnostic (IVD). The De Novo classification offers a pathway for novel medical devices, based on risk classification. Additionally, the 510(k) submission demonstrates equivalence to predicate devices, while PMA evaluates Class III device safety and efficacy. In the EU, approval is through CE marking, aligning with US FDA pathways.

A biomarker for general drug development can be qualified by CDER through the Biomarker Qualification Program, resulting in a tool usable under specific COUs. This process involves collaborative efforts with regulatory agencies and stakeholders, often in consortia, to streamline qualification. Monitoring biomarkers play a pivotal role in medical product development, furnishing tangible evidence of treatment impact, while predictive biomarkers serve to mitigate trial risks and minimize failures by pinpointing responsive patient subgroups.

Meetings/reports/discussions

METHODS – Identify the need & COU



Daniel Guldager Kring Rasmussen^{1,*}, Quentin M. Anstee^{2,3}, Richard Torstenson⁴, Bruno Golding⁵, Scott D. Patterson⁶, Clifford Brass⁷, Paresh Thakker⁸, Stephen Harrison⁹, Andrew N. Billin⁶, Detlef Schuppan^{10,11}, Jean-François Dufour¹², Anneli Andersson¹³, Ioan Wigley¹³, Elizabeth Shumbayawonda¹³, Andrea Dennis¹³, Corinna Schoelch¹⁴, Vlad Ratziu^{15,16}, Carla Yunis¹⁷, Patrick Bossuyt¹⁸, Morten Asser Karsdal¹

Regulatory scrutiny

RESULTS

A Qualification of novel methodologies for drug development (EMA)

		_	Meetings/reports/discussions
Optional: Innovation	n Task Force meeting]	Briefing meeting report
	sion of draft dossier f of Rapporteurs and QT	}•	Possibility to have an informal teleconference with the EMA scientific
Day -15: Prepa	aratory meeting]]•	officer and relevant experts Preliminary feedback may be provided
Day 15-30: Evaluation	f the procedure] 	List of questions sent to applicant
Day 60: Discussio	n with the applicant	,],	Discussion with the applicant Additional meeting may be requested by
Day 70-90: SAWP		}•	the qualification team
Day 100: CHMP discussion of Qualification Opinion	Day 100: CHMP ado	ption of Qualification Advice	Report: Suitable for Qualification Opinion or Qualification Advice
Day 130-190: Public consultation	1	,	Draft Qualification Opinion shared with applicant and released for public consultation (6 weeks)
Communication and training]	······,	Guidance document
Drug Development Tool (DDT) qualif	ication process (FDA	N)	

	-1	
Optional: CPIM or pre-LOI meeting		Meetings/reports/discussions
<u> </u>		Report with feedback
Submit Letter of Intent (LOI)		
•		
LOI acceptable for review?		
✓ ~2 weeks		Reviewability memorandum
LOI review		
	*	Determination letter with feedback
Submit Qualification Plan (QP)		
+		
Acceptable for review?		
✓~2 weeks	*	Reviewability memorandum
Qualification Plan review		
🗸 6 months 🛛 🚽		Determination letter with feedback
Submit Full Qualification Package (FQP)		
+		
Acceptable for review?		
✓ ~2 weeks		Reviewability memorandum
FQP review		Determination letter with feedback
🖡 10 months		or acceptance
Qualification (decision)		



Enrichment or Stratification?



Prognostic enrichment for endotype?





Contact: Morten Karsdal, MK@nordicbio.com

NORDIC BIOSCIENCE

CONCLUSION

Define the COU – real life or clinical studies population? Use CLSI guidelines to allow technical robustness Evaluate the risk benefit Regulatory is your friend to help drug development