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Ligand Binding Assays That Meet Compliance with Octet® BLI Systems

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Abstract

Octet® Bio-Layer Interferometry (BLI) systems enable analytical assessment of biologics in various stages of the development workflow beginning with discovery and early selection to validation, manufacturing and quality control. The instrument's configuration and sample plate format coupled with real-time analysis allows for rapid assay method development. In the last couple of years, Octet® BLI systems have been used by multiple organizations to generate supporting data submitted to various regulatory bodies for the approval of different biologics drug candidates. In addition, Octet® BLI systems have been cited in the United States Pharmacopeia General Chapters as an appropriate technique for ligand-based Fc-receptor binding studies.[1]

Analytical instruments that offer simplicity and speed can greatly enhance operations under compliance requirements as they reduce the risk of errors while enhancing productivity.

Sartorius offers Octet® GxP packages to support complete GMP compliant implementation. The packages include a GMP qualified Octet® BLI system, 21 CFR Part 11 software with audit trails, software validation package, installation, and operational qualification (IQOQ) protocols and kits, user guides, performance qualification (PQ) protocols and kits, and biosensor validation support. The Octet® platform's design and configuration coupled with its ease of use allows for enhanced productivity. The capacity to test for instance QC potency samples increases to 40X more samples over manual ELISA and up to 16X more samples per day compared to the majority of SPR platforms.[2]

Benefits of the Octet® BLI Platform in GMP

- **Parallel processing of samples — reduced assay development time**
  Faster analysis across many samples allows for faster decision making and is especially useful in assay method development when multiple conditions must be investigated for method qualification.

- **Direct binding assay — minimal sample prep, automated assay without manual steps**
  Assay setup is easy and fast; complete walkaway while experiment is running and minimal manual intervention reduces the risk of human errors.

- **Few moving parts that require maintenance — QC environment ready**
  Octet® BLI systems instruments require very low maintenance. There are no microfluidics that need to be guarded against clogs, contamination, or leaking. Preventive maintenance is recommended annually for the Octet® R8 instrument and bi-annually for the Octet® RH16 and Octet® RH96 instruments.

- **Off the shelf biosensors such as Protein A (Pro A), Protein G (ProG), Anti-human Capture (AHC) and Anti-mouse Capture (AMC) are available for direct capture of ligands. High precision streptavidin (SAX and SAX2) biosensors deliver enhanced precision for GMP applications**
  Octet® Bio-Layer Interferometry (BLI) systems offer an advanced, fast, robust and fluidics-free approach for screening and characterizing molecular interactions such as protein-protein and protein-small molecule analysis. The Octet® BLI platform enables a huge variety of applications performed at various stages of biologics development - from early selection to validation to manufacturing and quality control, e.g. concentration determination of the active analyte, ligand binding, or contaminant testing for lot release and in-process testing. To read more, please refer to the Application Note: **Octet® Potency Assay: Development and Validation Strategies.**

It is estimated that for a typical ligand binding method, an Octet® R8 system will be 2X faster for method development than traditional ELISAs or 4-channel SPR instruments. The sample plate format coupled with real-time analysis and high-throughput readout allows for a more rapid assessment of different assay conditions, that in-turn help speed up assay optimization. Qualification parameters such as ligand immobilization concentration, assay shake speed (similar to flow-rate evaluation in SPR based methods) and effects of temperature are first assessed before the method is evaluated for robustness around more typical parameters such as biosensor and reagent lots, different analysts and day-to-day variability amongst other parameters. Sartorius provides a biosensor lot reservation service for select biosensors which is reserved only for GMP assays method validation.

Examples of Approved Drugs Using Octet® BLI Technology

Octet® BLI is continuously being used to generate supporting data for various drug regulatory submissions including new drug applications (NDA) and biologics license applications (BLA). Applications range from specificity assessment to affinity characterization and binding epitope confirmation in blocking assays.

Octet® BLI data was used as a part of supporting data for the assessment of functional activity of pembrolizumab (Keytruda; EMEA approved in 2015). Keytruda as a monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. The active substance of Keytruda is pembrolizumab, which is a humanized monoclonal antibody that binds to human PD-1 and blocks the interaction between PD-1 receptor and its ligands. It is an IgG4 monoclonal antibody with Class-II mechanism of action (binding to cell-bound antigen not involving Fc effector function). The Octet® together with ELISA were used for in vitro binding studies of pembrolizumab.[3]

Tecentriq, on the other hand, was approved by the EMA in 2017 and later by the FDA in 2018. Tecentriq's active substance is atezolizumab which is an Anti-PD-L1 monoclonal antibody. It is used in the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy and other cancers. The Octet® system was used for supporting data in the binding characterization of the drug to its receptor PD-L1 amongst other studies.

In addition to these approved drugs, there are multiple instances where the Octet® system has been used along

with other techniques to provide supporting orthogonal data for various drug applications. For example, Theramex Ireland Limited applied for marketing authorization with the EMA for Livogiva in 2019 with a positive opinion of granting the same provided in 2020. Livogiva is a biosimilar to Forsteo and is used for the treatment of Osteoporosis. The active substance is Teriparatide, PTH (1-34) the biologically active 34-amino acid N-terminal fragment of the 84-amino acid native parathyroid hormone, PTH (1-84). The Octet® BLI platform was used to verify biosimilarity between the two drugs in functional binding assays.[4]

STADA Arzneimittel AG filed an application for marketing authorisation with the EMA for Oyavas in early 2020 with a positive response obtained in January 2021. Oyavas has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Avastin, which contains bevacizumab as the active substance. Bevacizumab is a recombinant humanized monoclonal antibody, which specifically binds to human vascular endothelial growth factor (VEGF), preventing its interaction with VEGF receptors (VEGFRs) on the surface of endothelial cells. In this case, the Octet® system was used for confirming specificity of the biosimilar through functional binding assessment with irrelevant antigens.[5] Many other examples of drug development with Octet® BLI data used for supporting characterization data exist in literature (Table 1).

Table 1

Examples of Approved Drugs Utilizing Octet® BLI Data in Their Applications

Drug Name	Target	Drug Modality	Sponsor	Indications	Application	Regulatory Agency	Year of Approval
Keytruda | Pembrolizumab	PD-1	mAb	Merck	Non-small cell lung cancer	Affinity Characterization	EMA	2015
Tecentriq | Atezolizumab	PD-L1	mRNA Vaccine	Roche	Non-small cell lung cancer	Specificity	EMA	2017
Comirnaty | BNT162b2	COVID-19	mAb	Pfizer	COVID-19	Affinity Characterization	EMA	2020
Ultomiris | Ravulizumab	Human C5	Peptide Biosimilar	Alexion	Paroxysmal nocturnal hemoglobinuria (PNH)	Affinity Characterization	EMA	2019
Livogiva | Teriparatide	PTH	mAb Cocktail	Teva	Osteoporosis	Affinity Characterization	EMA	2020
Atoltivimab, maftivimab, and odesivimab-ebgn	EBOV glycoprotein	mAb Biosimilar	Regeneron	Ebola virus	Competititon studies	FDA	2020
Oyavas | Bevacizumab	VEGF-A	mAb	Mabxience	Non-small cell lung cancer	Specificity | Affinity Characterization	EMA	2021
Jemperli | Dostarlimab	PD-1	mAb	GSK	Endometrial cancer	Affinity Characterization	EMA	2021
Regdanvimab	S protein	mAb	Celltrion	COVID-19	Affinity Characterization | Blocking Assay	EMA	2021
Xevudy | Sotrovimab	S protein	mAb	GSK | Vir Biotechnology	COVID-19	Affinity Characterization	EMA	2021
Nuvaxovid	COVID-19	Vaccine	Novavax	COVID-19	Affinity Characterization	EMA	2022
Kimmtrak | Tebentafusp	CD3 | gp100	TCR	Immunocore	Uveal melanoma (UM)	Specificity	EMA	2022
Tixagevimab | Cilgavimab	COVID-19	mAb Combination	AstraZeneca	COVID-19	Affinity Characterization | Blocking Assay	FDA	2022
Opdualag (nivolumab | relatlimab)	LAG-3 | PD1	mAb Combination	BMS	Melanoma	Blocking Assay	EMA	2022

Drug Name	Target	Drug Modality	Sponsor	Indications	Application	Regulatory Agency	Year of Approval
Briumvi | ublituximab	CD20	mAb	Propharma Group	Relapsed Multiple sclerosis	Specificity | Bridging	EMA	2023
Elrexfio | elranatamab	BCMA | CD3	bsAb	Pfizer	Relapsed Multiple myeloma	Specificity | Bridging	FDA	2023
Leqembi | lecanemab	Aβ aggregates	mAb	Eisai	Alzheimer's Disease	Specificity	FDA EMA	2023 2024
Ahzantive | aflibercept	VEGF-A | PlGF	Recombinant fusion protein biosimilar	Klinge Biopharma	Retinal disorders	Specificity | Blocking Assay	EMA	2024
Baiama | aflibercept	VEGF-A | PlGF	Recombinant fusion protein biosimilar	Formycon AG	Retinal disorders	Specificity | Blocking Assay	EMA	2024
Epruvy | ranibizumab	VEGF-A	mAb fragment biosimilar	MIDAS Pharma	Retinal disorders	Specificity | Blocking Assay	EMA	2024
Tuznue | trastuzumab	HER2	mAb biosimilar	Prestige Biopharma	Breast and gastric cancer	Specificity | Blocking Assay| Bridging	EMA	2024
Anktiva | Nogapendekin alfa inbakicept	IL-15 Receptor	Recombinant fusion protein complex	ImmunityBio	Bladder cancer	Specificity | Agonism | Bridging	FDA EMA	2025
Dazublys | trastuzumab	HER2	mAb biosimilar	CuraTeQ Biologics	Breast and gastric cancer	Specificity | Blocking Assay| Bridging	EMA	2025
Exdensur | depemokimab	IL-5	mAb	Glaxosmithkline	Asthma	Specificity | Blocking Assay	FDA EMA	2025
Gotenfia | golimumab	TNFα	mAb biosimilar	STADA Arzneimittel AG	Rheumatoid arthritis	Specificity | Blocking Assay| Bridging	EMA	2025
Teizeild | teplizumab	CD3ε	mAb	Sanofi Winthrop	Type 1 diabetes	Specificity | Agonism	EMA	2025
Usymro | ustekinumab	p40	mAb biosimilar	Elc Group	Plaque psoriasis	Specificity | Blocking Assay	EMA	2025

Bio-Layer Interferometry (BLI) in USP General Chapter <1108>[1]

Regulatory bodies such as the FDA, EMA, NMPA and others do not typically recommend or refer to specific product, brand, or vendors in their guidance on analytical technologies. References are however typically made of certain technologies in some USP chapters as a general guidance. These references are based on general concepts around the application in question. The United States Pharmacopeia (USP) has recently released a new general chapter <1108> which for the first time cites the use of biolayer interferometry in key ligand binding applications, specifically in *in-vitro* assays that assess complex Fc domain interactions with molecules such as C1q (a subcomponent of the C1 complex of classical pathway of complement activation that is involved in antibody dependent immune function) and Fc-receptor molecules that act as regulators of immune response amongst other functions. BLI is further cited as a label-free technique that provides more precise kinetic data and that can measure a relatively wide range of binding affinities. It can incorporate the use of a reference material to express relative equilibrium dissociation constant (K_D); a useful parameter in comparing a reference material and a new lot during manufacturing.

References

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3. **https://www.ema.europa.eu/en/documents/assessment-report/keytruda-epar-public-assessment-report_en.pdf**
4. **LIVOGIVA, INN-teriparatide** (europa.eu)
5. **Oyavas - INN-bevacizumab** (europa.eu)

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