Octet® BLI 21 CFR Part 11 Software Frequently Asked Questions (FAQ)

Stuart Knowling, Ph.D, Sartorius, Fremont, CA

Correspondence
E-Mail: octet@sartorius.com

Introduction

GxP Compliance Tools for Octet® BLI Systems
From antibody quantitation, ligand binding characterization to potency assays, Sartorius offers a wide range of GxP compliance tools for developing validated assay methods on the Octet® BLI platform, including:

- Comprehensive tools for GxP compliance
- Simplicity in operations for analytical development and regulated quality control labs

Availability of a comprehensive tool set for compliance makes the Octet® BLI platform an ideal analytical instrument in regulated quality control (QC) labs for lot release and in-process testing for ligand binding, concentration, and impurity analysis in both upstream and downstream processes.

Installation Qualification (IQ)

Operational Qualification (OQ)

Analytical Instrument Qualification

Maintenance: Compliance Assurance (PMOQ)

Performance Qualification (PQ)
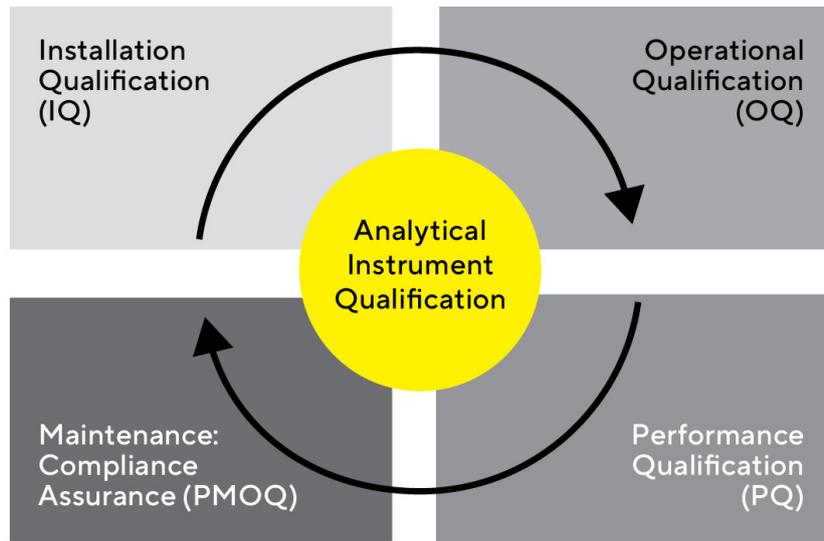
Sartorius Solutions for GxP Compliance

Compliant Installation and Operational Qualification (IQ/OQ) Kit and Services

The IQ/OQ kit provides comprehensive documentation to verify the Octet® BLI instrument, accessories and computer system are supplied and installed per Sartorius's guidelines by certified personnel. It also provides documented verification that the Octet® BLI instrument operates as intended at the user site by inspecting the critical components. These tests verify that the various key operational parameters, such as the optical system, plate temperature, system alignment, lamp performance, and shaker speed meet stipulated specifications.

Performance Qualification (PQ) Kits

PQ kits provide rapid and convenient methods to verify the performance of your Octet® R8 and RH16 systems. PQ can be performed using one or two tightly controlled assays, depending on the instrument's intended use. The PQ-Kinetics and quantitation assays verify accuracy and precision of the assays are within specifications for a well-characterized model system pair.

Octet® CFR Software and Software Validation Package

For researchers working in GLP or GMP laboratories, the Octet® Software Validation Package provides the most comprehensive documentation and tools available to validate the Octet® GxP server Monitor and Octet® CFR Software features and functions. It trims validation time to just three days using a fully integrated manual that mirrors the validation process in a regulated laboratory and provides sample data sets to authenticate analysis within Octet® software to traditional programs including Microsoft® Excel, and GraphPad Prism.

Biosensor Validation

This service enables Octet® BLI system users to sample multiple lots of a biosensor during assay qualification and validation and reserve a well-characterized lot for purchase. The service is available for the following biosensor types: Octet® ProA, Octet® SA, Octet® SAX, Octet® NTA, and Octet® AMC. Customers can order up to five different biosensor lots, up to 20 trays from each lot for evaluation, and reserve up to 40 additional trays for future purchase.

Software and Compliance – Frequently Asked Questions

1. How is the Octet® GxP software package different from the regular Octet® BLI software?

The Octet® 21 CFR Part 11 Software package includes all features available in the regular Octet® BLI Discovery and Octet® Analysis Studio software package but Octet® 21 CFR Part 11 Software has features to allow users to produce electronic records that meet the requirements of the FDA 21 CFR Part 11 Final Rule. This includes features such as administratively controlled application access, user group with defined access and roles, an audit trail, and electronic signatures of artifacts.

All Octet® R-Series BLI systems can use the Octet® 21 CFR Part 11 software package with basic Installation Qualification and Operational Qualification (IQ/OQ) and Performance Qualification (PQ). However, the Octet® R8 and Octet® RH16 (beginning SN 20325+) systems are better suited for a GxP environment due to the availability of extended IQ/OQ, and PQ packages that add more tests and documentation to verify the functioning of the systems and QC assay kits that generate automatic reports in the Octet® Analysis Studio Software.

2. Is the Octet® CFR software package compatible with Windows 10?

Yes, Octet® CFR Software versions 10 and above are compatible with Windows 10 32-bit and 64-bit beginning with Windows 10 version 1607, the "Anniversary Update." Windows 10 versions 1507 and 1511 are not supported. We recommend Windows 10 64-bit Professional or Enterprise. Windows 7 is no longer supported. Octet® Software version 13 is also compatible with Windows 11.

3. Is it possible to install the software on a terminal server or remote desktop server if users cannot install the applications on individual workstations ?

For Octet® BLI Discovery Software when recording data, the files should be stored to the local computer and after recording, the files can then be moved to a network drive for backup. The Octet® Analysis Studio Software can be installed on a server or workstation and then users can remote desktop to it.

4. How many user accounts can be registered on an GxP server?

There are no enforced limits. The practical limit is the space available on the computer hard drive.

5. How are detailed histories recorded on the GxP server?

Audit trails are recorded in the database managed by the Octet® GxP server software. Each experiment has a unique identifier, and all data-specific audit trails are logged with the experiment identifier. Audit trails can be filtered by experiment, user, machine, project or date for viewing and printing.

6. Can Octet® BLI data be integrated onto Watson LIMS?

We currently don't formally integrate with any LIMS systems. Depending on how your system works, you could potentially upload Excel, CSV or PDF reports created by the analysis software. If the LIMS allows arbitrary file upload/attaching, you could archive method files and even raw data as well.

7. Can you turn off specific feature(s) of the 21 CFR Part 11 software?

21 CFR Part 11 features cannot be disabled. However, a user with the permission "Set commenting requirement" (see "Viewing and Changing Group Settings" in Octet® BLI Discovery User Guide 13) – can disable the commenting requirement in the Octet® Analysis Studio Software. All activities will still be logged to the audit trail, but this turns off the "enter reason" dialog that pops up whenever a change is made.

8. Is it possible to install the Non-21 CFR Part 11 software on the same PC as the 21 CFR Part 11 software?

Yes, it is possible, but this is not recommended as a compliance best practice.

9. Can an audit trail be Deleted? If so, will that leave a trace in the GxP server?

Specific entries in the audit trail cannot be deleted by any means in the Octet® software.

Uninstall/reinstall also does not delete the audit trail. If you really need to delete the entire audit trail, you can do so if you are an IT administrator on the computer running the GxP server. It is important note here is that here that "Administrator" refers to the Administrator to the PC (Windows PC), not the GxP server. Only the IT administrator can delete the audit trail database and there is no scheme for the GxP server administrator to delete the audit trail file.

The location of the file is provided in our documentation as it is desirable to create backups of the audit trail database. This is also why it is recommended that the GxP server is installed on a separate computer from those running the Octet® BLI Discovery or Analysis Studio Software, this ensures that IT can safeguard any accidental deletion of the audit trail files.

Each organization must develop controlled, documented procedures for compliance with this requirement. It is the customer's responsibility to administrate these documents.

10. What are the allowed user privileges?

The following default group selections are available, and in general (Table 1):

- Administrators—can manage Users and Group settings including add, delete, edit and view all events
- Supervisors—can review data and events
- Developers—can create methods, run experiments, adjust analysis settings, and export data
- Lab Users—can run experiments, view and export data
- Guests—have no explicit privileges, these must be assigned by the administrator

See Octet® BLI Discovery User Guide 13 for more information on user privileges.

11. How can we authenticate Excel workbooks?

Octet® Analysis Studio Software generates a password-protected excel report sheets in which cells are protected and cannot be changed. However, in general we don't provide a means to authenticate Excel workbooks. Once you export data to Excel you are outside of our CFR umbrella of data integrity. Sartorius does not consider this a data integrity defect.

Default Group Privileges	Administrator	Supervisor	Developer	Lab User	Guest
Administration					
Manage users and user settings	Yes				
Analysis and Change					
Create and edit method template			Yes		
Build multi-dataset			Yes		
Edit preprocess settings			Yes		
Edit analysis settings			Yes		
Edit annotation/display properties			Yes		
Convert Kinetic step/step type into Quantitation			Yes		
Edit report pages			Yes		
(LEGACY) Change			Yes		
Review					
Sign Document		Yes			
Set commenting requirement		Yes			
Review Audit Trail for any user		Yes			
Remove signature from document					
Default Group Privileges (continued)	Administrator	Supervisor	Developer	Lab User	Guest
Plate Settings					
Edit experiment info			Yes		
Edit sensor and sample plate info			Yes		
Include/exclude wells and sensors from analysis			Yes		
(LEGACY) Plate			Yes		
Run Experiment					
Run Experiment				Yes	
Import analysis settings template to new dataset				Yes	
Export data and Excel report				Yes	
Choose repository directory when running an experiment					

Table 1. Default User Privileges.

12. Are the audit trails on the GxP server, Octet® BLI Discovery, and Octet® Analysis Studio software linked? How is the audit trail saved after the user logs out from the GxP software?

Yes, the audit trails are all stored on a single database that the GxP server manages (Figure 1). Therefore, the server location must be chosen when logging into either the Octet® BLI Discovery or Octet® Analysis Studio software. During login, you can use the Project setting (when logging in) to link experiments in the audit trail, and you can also sort/filter by experiment ID when reviewing the audit trail.
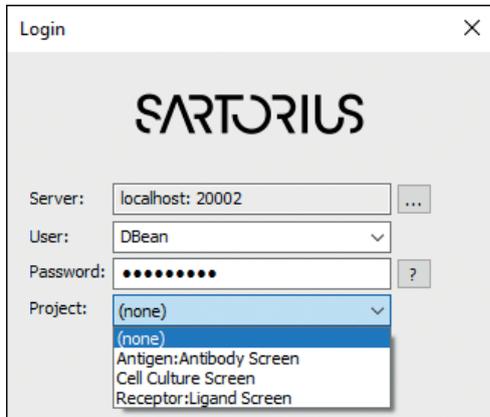
Figure 1. Project selection is possible when starting a user session.

13. We currently have an older version of the Octet® CFR software in our development group and have released assays using the older version; When we purchase the new version of the software (version 13), do we need to re-qualify released assays? What is different between our old version and version 13?

You would need to re-validate the assay using the new software to ensure that the method under the new software is still fit for purpose. Please refer to version 13 software release notes for "what has changed".

It is important to note that after upgrading to GxP server v13.0, do not downgrade to a previous version of GxP server as there is a risk of data loss. Always make a backup of the database files before performing an update to the GxP server software.

14. What happens if the customer (an administrator or any other group member) forgets the password to access the software?

Users and administrators cannot see an existing password. If a user forgets their password, the administrator cannot recover the lost password. The only solution is for the administrator to set a new password for the user.
A potential problem occurs when as administrator forgets their password as an administrator cannot reset their own password without first entering the old password. If the

administrator loses their own password, then resetting the password is not possible. For this reason, we recommend storing a written copy of the password in a secure location and/or assigning a second person with administrator privileges so that if one administrator password is forgotten, the other administrator can reset the password.

15. Are the server and server administration pre-installed in the computer when purchasing the instrument with the CFR software? If not, who is responsible for doing this?

The Octet® CFR software and GxP server software are not pre-installed. Sartorius FAS/FSE will install the software upon installation. If the customer purchased GxP packages (Octet® R8, RH16, and RH96 systems), these packages would also include IQ/OQ services that direct and document the software's installation. Since GxP server setup and configuration will require customer IT and QA support, the installation of the software should be coordinated with the respective customer teams beforehand. IT usually advises on server configurations (GxP server locations), and QA/IT will inform of company password and administrator policies established at the customer site.

16. How are the changes registered when the Octet® 21 CFR part 11 software is not connected to the server?

If a computer cannot connect to the GxP server, user activity is recorded and stored locally. When the computer re-establishes a connection with the GxP server, the local stored events are uploaded to the GxP server audit log database. In addition, if a user tries to log in to the Octet® software on a computer that cannot connect to the GxP server, the software will use a temporary local token to authenticate their identity. This token is created during the first successful login to Octet® Analysis Studio or BLI Discovery. The token is good for 5 days and can be refreshed by reconnecting with the GxP server. If a user is traveling and would like to use the Analysis Studio to work on their data, for example, it is possible to set up a VPN so they can periodically connect to the GxP server. Administrator can change this setting (e.g., number of days to "0") to prevent offline use (Figure 2).
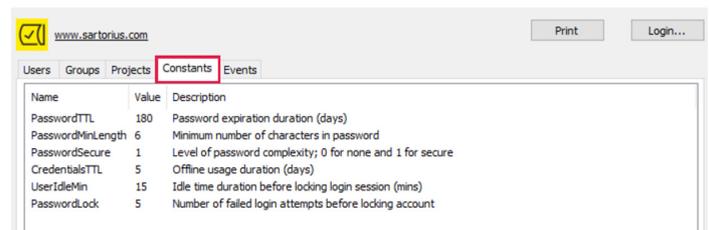
Figure 2. Offline usage can be allowed or prevented in the Constants tab.

17. Can only administrators have access to the server and grant privileges?

Any user can log into the GxP server administration tool. Non-administrators can see the various settings, but they can only edit their name and change their password. All other settings are locked (see Q5 on user privileges).

18. How is the transition from non-CFR software to CFR software? Can customers do their own installation using a downloadable link?

Octet® CFR software can be installed on an Octet® BLI system that does not currently use Octet® CFR software. Sartorius FAS/FSE will need to guide you through the validation process. We strongly recommend that non-CFR software should be uninstalled as an Octet® system validated for CFR compliance should not use software that does not check the permissions set in the GxP server software.

19. Can customers access the software if they do not have the privileges to run experiments or analyse data?

Yes, depending on their assigned privileges, they can use Octet® BLI Discovery and Analysis Studio Software. A user with no explicit privileges is a Guest and can only open, view, and print data and method files.

20. What happens if an experimental file is modified?

Modification of files outside the Octet® BLI software environment will cause the data integrity checks to fail. There is no recovery process.

21. Regarding the software installation, which option is recommended?

There are two options available to users:

Option 1: Recommended Configuration

Install the Octet® GxP server onto a dedicated administrator computer (Figure 3). This can be a dedicated physical server workstation, or a virtual machine. Typically, the Octet® GxP server computer will be under local IT control. Ensure that the server is always on and available for client connections. The Octet® hardware controller PC must have network connectivity to the Octet® GxP server. Other optional workstations with the Octet® Analysis Studio software, will also need network connectivity to the Octet® GxP server.

It is important that users ensure compliance. The Octet® GxP server is a key part of keeping records compliance. Strictly control the access to the computer hosting the Octet® GxP server software. Any Windows accounts that are Administrators on the server can directly access the user and audit trail databases to backup work. Place the server under the control of a department separate from the day-to-day users of the Octet® system, for example local IT,

or the Quality department. Control the Octet® GxP server installation media to prevent the setup of "rogue" GxP server instances.
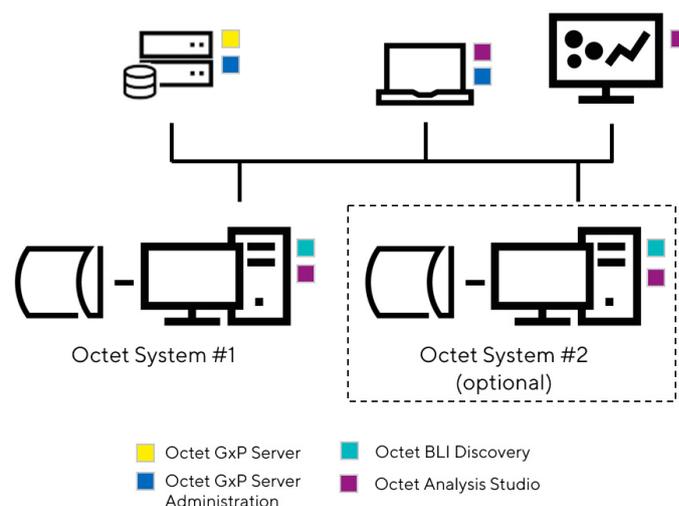
Figure 3: Network layout.

Option 2: Single Computer Configuration

If you cannot use the recommended network configuration, install the Octet® GxP server software on a single computer along with the Octet® BLI Discovery software (Figure 4). This is a last resort.
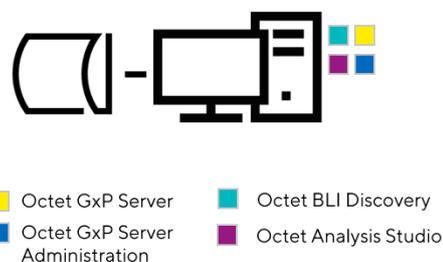
Figure 4: Layout of a single computer with the Octet® system.

IMPORTANT: If you are using the Single Computer Configuration, configure the Windows user accounts for Octet® system users as Windows standard accounts. Any Windows user with Administrative privileges on the computer will have access to the Octet® GxP server database files.

Systems and Services – Frequently Asked Questions

22. Are the Octet® R2, R4, RH16, and RH96 also GxP compliant and if so what IQ/OQ products do we use with them?

Yes, all Octet® BLI systems are GxP compliant (Figure 5). They are all compatible with Octet® 21 CFR Part 11 software. Each system has its own separate IQ/OQ guideline.

All Octet® R-Series BLI systems can use the Octet® 21 CFR Part 11 software package with basic Installation qualification and Operational Qualification (IQ/OQ) and Performance Qualification (PQ), but the Octet® R8 and Octet® RH16 (beginning SN 20325+) are better suited for a GxP environment due to the availability of extended IQ/OQ, and PQ packages that add more tests and documentation to verify the functioning of the systems and QC assays kits that generate automatic reports in the Octet® Analysis Studio Software.

23. After IQ/OQ, what services are recommended by sartorius on an annual basis to maintain the system?

After installation and initial Operational Qualification (OQ), Instrument Preventive Maintenance (PM), and Performance Qualification (PQ), currently available only on the Octet® R8 and Octet® RH16 BLI systems are recommended on a planned/scheduled service interval as it removes the risk of the system and software being out of specification (OOS).

24. Does Sartorius offer an extended service for the GxP environment and what is handed over to the customer to verify that the service was performed according to GxP rules?

GxP customers can request a Performance Certification (PC) service or PMOQ service. A PMOQ service includes a Preventive Maintenance (PM) service with operational qualification (OQ) tests for a specific instrument type. In the case of the Octet® R8 and Octet® RH16 BLI systems, it also includes the Performance Qualification – Quantitation (PQ-Q) assay in addition to the two Performance Qualification – Kinetics (OQ-K) assays (see Figure 5).

25. How is the temperature of the plate determined for the systems other than Octet® R8 and Octet® RH16 BLI Systems? Is there an internal measurement of temperature?

During the assembly process, the heater plate temperature is verified to be within a window of 32.8 – 33. 2°C. The plate's temperature is controlled using closed loop temperature controllers. The temperature is verified at manufacturing and during system preventative maintenance (PM) and Performance Certification (PC) described in question 24. A record of the value is created during PC.

26. How is the RPM of the shaker determined?

Shaker speed is controlled using a closed control loop that ensures that the shaker is operating within range. The shaker speed and % error is stipulated by the shaker manufacturer and is verified through a diagnostic software tool available on the system. Verification is done at Preventive Maintenance (PM) and during Performance Certification (PC). A record of the value is created.

Model	Octet® R2	Octet® R4	Octet® R8	Octet® RH16*	Octet® RH96
GxP option	Yes	Yes	Yes	Yes	Yes
IQ/OQ Kit	41-0327	41-0326	41-0325	41-0285	41-0217
IQ/OQ Service	84QAFR2	84QAFR4	84QAFR8	84QAF16	84QAF96
PQ Service	N.A.	N.A.	84QFFR8	84QBF16	N.A.
2x PMOQ Service	84MCFR2	84MCFR4	84MCFR8	84MBF16	84MBF96
Performance Qualification Bundle Kit	N.A.	N.A.	18-1178	18-5140	N.A.

*beginning SN 20325+

Assays and Method Development – Frequently Asked Questions

27. What key parameters need to be demonstrated in a GxP assay during method qualification?
These parameters are assay dependent and should follow regulatory requirements for the assay type. The determination of such parameters is the responsibility of the sponsor. Users interested in assay validation guidelines that can be used to develop well-qualified assays should see the Application Note Harmonizing Regulatory Guidelines for Assay Validation: A Focus on Kinetics-Based Assays Using Octet® BLI Systems.

28. What type of assays is Octet® BLI currently utilized for in QC?
The Octet® BLI platform is used mainly for lot release and in-process testing assays. These are typically quantitation, potency assays, impurities testing or ligand binding assays.

29. Is BLI technology used in a current GxP compliant release process approved by the FDA?
There are several groups using the Octet® BLI platform for lot release assays. Organizations tend to keep certain information confidential and as a result, it may be difficult to point out specific accounts without their permission. The "Octet® BLI Characterization Data Used for Approved Drugs" table on the next page gives examples of cases in the public domain where Octet® BLI has been used to generate supporting data for regulatory submission of various products (Table 2).

30. How do we measure potency using the Octet® BLI? What are the reportable parameters?
Please see the Application Note Octet® Potency Assay: Development and Validation Strategies.

Reportable parameters should be established by the sponsor but generally include % recovery and % CVs. K_D (Affinity) values can also be reported depending on the type of the method.

31. What is the accepted % CVs for a kinetics assay?
% CVs and other acceptance criteria are product dependent and should be set by the sponsor. Users interested in assay validation guidelines that can be used to develop well-qualified assays should see the Application Note Harmonizing Regulatory Guidelines for Assay Validation: A Focus on Kinetics-Based Assays Using Octet® BLI Systems.

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

Table 2. Examples of approved drugs utilizing Octet® BLI data in their applications. This table includes examples of drugs where the Octet® BLI system has been used to generate data submitted as part of the supporting information for the drug's approval with regulatory bodies.