PHARMACOVIGILANCE SYSTEM MASTER FILE (PSMF)

Biocon Biologics
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Version 2.0

PHARMACOVIGILANCE SYSTEM MASTER FILE

For

Biosimilar Collaboration Ireland Limited-BCIL, Ireland

PSMF XEVMPD Number	MFL20789
UK PSMF Number	UKPSMF01802
Marketing Authorization Holder (MAH)	Biosimilar Collaboration Ireland Limited-BCIL, Ireland Unit 35/36, Grange Parade, Baldoyle Industrial Estate, Dublin 13, Dublin, Ireland, D13 R20R
There are no other MAH(s) covered by this Pharmacovigilance System Master File (PSMF). There are no other PSMFs in use by Biocon.	
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This Pharmacovigilance System Master File (PSMF) describes an overview of the key elements of the Pharmacovigilance (PV) system of Biosimilar Collaboration Ireland Limited-BCIL, Ireland (hereinafter referred to as Biocon Biologics) to comply with Directive 2010/84/EU, Regulations (EU) No. 1235/2010 and (EU) No. 520/2012, and the latest version of the Guideline on good pharmacovigilance practices (GVP) Module II –Pharmacovigilance system master file (PSMF).

Biocon Biologics has its primary business location in Ireland (Biosimilar Collaborations Ireland Limited-BCIL, Ireland). BCIL act as Marketing Authorization Holder (MAH) BCIL is the step-down wholly owned subsidiary of BBL. The Pharmacovigilance department of Biocon Biologics is located in the Biocon House, Tower 3, Semicon Park, Plot No 29-P1 & 31-P, KIADB Industrial Area, Electronic City Phase-2, Bangalore, Karnataka, India – 560100. This is the site principal Pharmacovigilance activities are undertaken for products marketed by BCIL or its affiliates. This PSMF is applicable to Biocon Biologics and all its affiliates of Biocon Biologics.

As the Marketing Authorization Holder, Biocon Biologics ensures that all information relevant to the risk-benefit balance of a medicinal product is reported to the Competent Authorities fully and promptly in accordance with the legislation.

To meet pharmacovigilance obligations globally Biocon Biologics use a single integrated pharmacovigilance system. Biocon Biologics performs the pharmacovigilance activities in-house and outsourced to 1) global Pharmacovigilance Service Provider Eversana and 2) EU/UK QPPV/NCP Services to Primevigilance. The relationships between Biocon Biologics and service providers are furthermore described by the detailed contracts on delegation of the PV activities.

Eversana has been delegated the following Pharmacovigilance activities on behalf of Biocon Biologics

- Individual Case Safety Report (ICSR) assessment and processing including reporting to Health Authorities.
- Global literature search and medical literature monitoring through EMA MLM service
- Local literature monitoring

- Periodic Safety Update Reports (PSUR) preparation, review and approval
- Argus Implementation, Data Migration, Managed services to support and maintain Argus database.
- Safety Data Exchange Agreement Compliance
- Regulatory Intelligence
- Biocon Biologics Pharmacovigilance E-mail Inbox Management
- Handling Medical information Call Centre (MICC)

PrimeVigilance has been delegated the following Pharmacovigilance activities on behalf of Biocon Biologics

- EU/UK QPPV,
- NCP/Local QPPV Services
- Audits and inspections support
- Support for PV contact person at the National level

Biocon Biologics in house Pharmacovigilance activities are

- PV training
- Signal Management
- Risk Management Plan Management (RMP) review and approval
- Regulatory Authority Queries
- Audits and Inspections
- Clinical Trial Safety Support
- Safety Support (Hazard Analysis, QA Trend Analysis, Label Review)
- Safety Data Exchange Agreements

The Biocon Biologics commits to keep the PSMF up to date at all times. Whenever required by changes in the EU legislation, regulatory requirements, or internal PV processes, the PSMF will be updated. Any potential changes to the PSMF will be submitted to the Competent Authorities (CAs) in accordance with applicable regulatory procedures, or on request.

Contents

ABBREVIATIONS 7

1 QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE (QPPV) 10

1.1 EU/UK QPPV 12

1.1.1 Delegation of activities by the EU/UK QPPV 14

1.1.2 Proof of Registration with EudraVigilance Database 14

1.2 Qualified Person for Pharmacovigilance in UK (UK QPPV) 14

1.3 Information on the PV contact person at national level in EU and UK 15

2. ORGANIZATIONAL STRUCTURE OF THE MARKETING AUTHORIZATION HOLDER (MAH) 16

2.1 Location of Pharmacovigilance Activities 16

2.1.1 Pharmacovigilance Activities undertaken by Global PV Service Provider Eversana 17

2.1.2 Pharmacovigilance Activities undertaken by Primevigilance 18

2.1.3 Pharmacovigilance Activities undertaken by Biocon Biologics 18

2.1.4 Overview of Pharmacovigilance Activities. **19**

3 SOURCES OF SAFETY DATA 20

4 COMPUTERIZED SYSTEMS AND DATABASE 25

5 PHARMACOVIGILANCE PROCESSES 28

5.1 Continuous Monitoring of Product Risk-Benefit Profile(s) 29

5.2 Risk Management System(s) and Monitoring of the Outcome of Risk Minimisation Measures 34

5.3 Individual Case Safety Report (ICSR) collection, collation, follow-up, assessment and reporting 36

5.4 Periodic Safety Update Reports (PSUR) and Addendum to Clinical Overview (ACO) Scheduling, Production and Submission] 39

5.5 Communication of Safety Concerns to Consumers, Healthcare Professionals and the Competent Authorities 40

5.6 Implementation of Safety Variations to the Summary of Product Characteristics (SmPC) and Patient Information Leaflets 42

5.7. Literature management.....44

5.7.1 Medical Literature Monitoring By EMA 45

5.7.2 Medical Literature Monitoring.....45

5.7.3 Local Literature Search 45

5.8 Data Retained and Data Repository 46

5.9 Global Safety Regulatory Intelligence 46

6 PHARMACOVIGILANCE SYSTEM PERFORMANCES 46

6.1 ICSR Reporting to Competent Authorities 47

6.2 PSUR Submission 47

6.3 Submission of Safety Variation 47

6.4 Risk Management Plan Commitments.....47

7 QUALITY SYSTEM.....47

7.1 Documentation and Record Control.....48

7.2 Procedural documents 49

7.3 Training 52

7.4 Auditing of the PV system 55

7.4.1 Management of deviations and CAPAs 57

7.4.2 Biocon Deviation management 58

7.4.3 Biocon CAPA management 58

ABBREVIATIONS

ADR	Adverse Drug Reaction
BBL	Biocon Biologics Limited
BCIL	Biosimilar Collaboration Ireland Limited
CA	Competent Authority
CAPA	Corrective Action Preventive Action
GMP	Good Manufacturing Practice
CIOMS	Council for International Organizations of Medical Sciences
CV	Curriculum Vitae
DHPC	Direct Healthcare Professional Communication
DME	Designated Medical Event
DSC	Drug Safety Committee
DSRT	Drug Safety Review team
EEA	European Economic Area
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
ESI	Emerging Safety Issue
ESM	Electronic Submission Module
EU	European Union
EURD	European Union Reference Dates
EVDAS	EudraVigilance Data Analysis System
EVWEB	EudraVigilance Web
FAERS	FDA Adverse Event Reporting System
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
HMR	Human Medicines Regulations
ICSR	Individual Case Safety Report
IRD	Initial Receipt Date

IQ	Installation Qualification
IT	Information Technology
JD	Job Description
LCPPV	Local Contact Person for Pharmacovigilance
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medical and Healthcare Products Regulatory Agency
MLM	Medical Literature Monitoring
NCA	National Competent Authority
NCP	National contact person
OQ	Operation Qualification
PASS	Post Authorization Safety Studies
PIL	Patient Information Leaflet
PQ	Performance Qualification
PRAC	Pharmacovigilance Risk Assessment Committee
PRLS	Person Responsible for Local Screening
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV/PVG	Pharmacovigilance
PVD	Pharmacovigilance Department
QA	Quality Assurance
QC	Quality Check/Control
QMS	Quality Management System
QPPV	Qualified Person for Pharmacovigilance
QNCR	Quality Non-Conformance Report
RA	Regulatory Affairs
RFI	Request For Further Information
RMP	Risk Management Plan

RQA	Research Quality Assurance
RMMs	Risk Minimization Measures
SDEA	Safety Data Exchange Agreement
SER	Signal Evaluation Report
SmPC/SPC	Summary of Product Characteristics.
SOP	Standard Operating Procedure
SPS	Pharmacovigilance System Summary
UK	United Kingdom
USR	Urgent Safety Restriction

1 QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE (QPPV)

As per the dated and signed statement, it has been declared that the EU QPPV is appointed and that the necessary means for collection and notification of any Adverse Drug Reaction (ADR) occurring either in the EU or in a third country are in place.

The PV system is operational, and all items of the system are in place. Biocon Biologics also declared in the Summary of the applicant's Pharmacovigilance System (SPS) that it has the necessary means to fulfill the tasks and responsibilities listed in Title IX of the Directive 2001/83/EC, as amended and Regulation 182 of the Human Medicines Regulations 2012 (as amended) (HMR) Article 10 of the Commission Implementing Regulation (EU) No 520/2012 (CIR).

The EU QPPV has sufficient authority over the PV system in order to promote, maintain and improve compliance. The EU QPPV is an individual residing in the EEA, who acts as a single point of contact for EEA CAs on a 24-hour basis.

A dedicated Standard Operating Procedure, PVL-PVSOP-012 Qualified Person for Pharmacovigilance in the EU and UK, PVL-PVSOP-031 EU QPPV Governance and PVL-PVFORM-162 QPPV Job Description (JD) represent documents describing EU QPPV functions and responsibilities in line with requirements of the EU legislation, and include but are not limited to the following:

- establish and maintain the PV System and have an oversight over the functioning of the system in all relevant aspects.
- supervise the PV system, including review and revision of documented procedures (e.g. SOPs), and identification of a need for development or revision of existing documented procedures;
- be continuously available to MAH and Regulators and ensure adequate back-up procedures are in place.
- verify that the PSMF is up to date and accurate.

In relation to the medicinal products covered by the PV System, specific responsibilities of the EU QPPV should include:

- having an overview of medicinal product safety profiles and any emerging safety concerns.
- having awareness of any conditions or obligations adopted as part of the Marketing Authorization (MA) and other commitments relating to safety or the safe use of the product.
- having awareness of risk minimization measures (RMMs).
- being involved in the review, approval and sign-off of protocols of post-authorization safety studies.
- having awareness of Post-Authorization Safety Studies (PASSs) requested by a CA including the results of such studies.
- providing input into Risk Management Plans (RMPs).
- ensuring conduct and maintenance of PV system related activities and submission of all PV-related documents in accordance with the legal requirements and GVP.
- ensuring the necessary quality, including the correctness and completeness, of PV data submitted to the CAs in Members States and the Agency/Licensing Authority.
- ensuring a full and prompt response to any request from the CAs in Members States and from the Agency/Licensing Authority for the provision of additional information necessary for the evaluation of the benefits and risks of a medicinal product.
- providing any other information relevant to the benefit-risk evaluation to the CAs in Members States and the Agency/Licensing Authority.
- providing input into the preparation of regulatory action in response to emerging safety concerns (e.g., variations, urgent safety restrictions, and communication to patients and Healthcare Professionals (HCPs)).
- acting as a single PV contact point for the CAs and the Agency on a 24-hour basis and also as a contact point for PV inspections.
- ensure Deputy EU and UK QPPV is appointed and available in case of EU QPPVs absence.

The specificities are also further detailed in all SOPs pertinent to PV and risk management, delegation letters, handover meeting minutes and other documents governing and guiding the daily operational activities.

The current fully signed and dated JD and other relevant supporting documentation can be found in PSMF ANNEX A.

1.1 EU/UK QPPV

Sanja Prpic, expert with over 15 years of experience in all areas of PV working in a regulatory agency and for different types of pharmaceutical companies including the role of EU and UK QPPV. Sanja Prpic Curriculum Vitae (CV) and the high-level training records are provided in PSMF ANNEX A01. The Proof of Registration with the EV Database is presented in PSMF ANNEX A06.

The EU/UK QPPV for Biocon Biologics Sanja Prpic resides and carries out her tasks in the Croatia , European Union, in the place where PSMF is located:

Contact details of the EU QPPV:

Name: Sanja Prpic

Office address: Oreškovićeva 20A, 10010 Zagreb, Croatia

Mobile: +385 912188002

Email: sanja.prpic@primevigilance.com

To ensure the 24-hour coverage in PV, the following mechanisms are in place:

- The Deputy EU QPPV will support the EU QPPV in keeping a general oversight of PV related activities and the safety profile of drugs.
- The Deputy EU QPPV ensures the back-up procedure in case of the EU QPPV absence/unavailability and takes over all the EU QPPV PV responsibilities.
- The Deputy EU QPPV resides and operates in Czech Republic, European Union;
- The Deputy EU QPPV has an equivalent JD to the EU QPPV. The Deputy EU QPPV assumes these functions only when the EU QPPV is absent or unable to take up her duty for any reason.

- The out-of-office e-mail message has to be set to indicate a period of EU QPPV absence and a contact for urgent matters.
- Both EU QPPV and Deputy EU QPPV carry mobile phones all the time.
- EU QPPV informs Deputy EU QPPV about planned unavailability sufficiently in advance. In case of unforeseen absence, EU QPPV informs Deputy EU QPPV as soon as possible. Deputy EU QPPV confirms overtaking of EU QPPV role immediately after receiving the information on EU QPPV absence/unavailability in writing. Before EU QPPV QPPV ´s unavailability, there is a hand over meeting, where the EU QPPV informs the Deputy EU QPPV about all pending tasks that need to be solved during the EU QPPV ´s absence. Meeting minutes are recorded preferably using PVL-PVFORM-163 Hand Over Meeting – Template. All hand-over information, such as any outstanding or planned activities will be added to the hand-over form. An out-of-office message has to be set to indicate a period of the EU QPPV absence and a contact for urgent matters. When the EU QPPV is available again, she takes back the responsibilities, discusses with the Deputy EU QPPV all topics, which were solved during the absence, and all pending and new tasks. Meeting minutes are recorded preferably using PVL-PVFORM-163 Hand Over Meeting – Template. The confirmation/Hand Over Meeting is archived in client-specific files by the project manager.

Both the EU QPPV and Deputy EU QPPV, when needed, can be contacted 24 hours a day, 7 days a week on their mobile phone numbers or via e-mail (see contact details of the EU QPPV and Deputy EU QPPV).

The EU QPPV also has access to Medically qualified person as described in ANNEX A07

The Deputy EU/UK QPPV for Biocon Biologics, Jana Tomkova, resides and carries out her tasks in Czech Republic, EU:

Contact details of the Deputy EU QPPV:

Name: Jana Tomkova, MD

Office address: Vaclavske namesti 2132/47 (Flow building) 110 00 Prague 1, Czech Republic

Mobile: +420 773 955 274

Fax number: +420 227 204 763

Email: jana.tomkova@primevigilance.com

1.1.1 Delegation of activities by the EU/UK QPPV

The description of activities and responsibilities that are delegated by the QPPV to appropriately qualified and trained personnel of Primevigilance is included in the list of delegated tasks as per Annex A 05.

1.1.2 Proof of Registration with EudraVigilance Database

Annex A06 contains proof of QPPV and Biocon Biologics registration with EudraVigilance.

1.2 Qualified Person for Pharmacovigilance in UK (UK QPPV)

As per the dated and signed statement, it has been declared that the QPPV is appointed and that the necessary means for collection and notification of any Adverse Drug Reaction (ADR) occurring either in the UK or in a third country are in place. The PV system is operational, and all items of the system are in place.

In accordance with Regulation 182 of the Human Medicines Regulations (HMR) 2012 (as amended). , the UK QPPV's roles and responsibilities are equivalent to that of the EU QPPV. The QPPV for UK authorised products is also the EU QPPV. The EU/UK QPPV for Biocon Biologics, Sanja Prpić, resides and carries out her tasks in Croatia, European Union. Please refer to section 1.1 above regarding the summary curriculum vitae and contact details of UK QPPV. Deputy EU/UK QPPV for UK authorized products is also Deputy EU QPPV. Deputy EU/UK QPPV for Biocon Biologics, Jana Tomková, resides and carries out her tasks in the Czech Republic, European Union. Please refer to section 1.1 above regarding the contact details of Deputy UK QPPV.

A copy of the UK-QPPV and the deputy UK-QPPV's CVs are enclosed in Annex 01 and Annex 02 respectively.
Job descriptions of the UK QPPV and the deputy UK-QPPV are enclosed in Annex 03 and Annex 04 respectively.

PrimeVigilance provides the local UK PV services for Biocon Biologics according to the latest legal, business, and procedural needs in alignment with local legislation and regulatory requirements.
The UK NCP resides, operates within the UK, reports to the UK QPPV and has permanent access to the EU/UK PSMF. The UK NCP has access to adverse event reports for UK authorised products and has knowledge of UK pharmacovigilance requirements, facilitate responses to MHRA pharmacovigilance queries and inspections.

Contact details of the UK NCP:
Name: Emma Jones
Office address: 1, Occam Court, Occam Road, Surrey Research Park, Guildford, GU2 7HJ, UK
Telephone number: +44 1483 961 945
E-mail: emma.jones@primevigilance.com

1.3 Information on the PV contact person at national level in EU and UK

In order to meet relevant national pharmacovigilance regulations, Biocon Biologics established the PV contact person at national level. Primevigilance is the Pharmacovigilance service provider for Biocon Biologics NCP/LCPPV functions and responsible for providing the service of the local national contact person responsible for pharmacovigilance (NCP/LCPPV) activities as per the local requirements in EU and UK.
All PV contact person at national level and their contact information are listed in Annex A08.

2. ORGANIZATIONAL STRUCTURE OF THE MARKETING AUTHORIZATION HOLDER (MAH)

Biocon Biologics, headquartered in Bengaluru, India, is a leading global biosimilars company with several in-market and in-development biosimilars including monoclonal antibodies for cancer and autoimmune diseases, insulin, and insulin analogs for diabetes, and conjugated recombinant proteins. It has a strong research pipeline of biosimilar molecules across diabetes, oncology, immunology, and other non-communicable diseases.
BCIL is newly established entity in Ireland to commercialize and distribute the biosmilar products in Europe and UK territory.

An organizational chart detailing Biocon Biologics structure is included in Annex B01. The organizational chart details the position of EU/UK QPPV within the company. The EU/UK QPPV oversees the safety of authorized products in EU/UK and the performance of the PV system, in collaboration with Biocon Biologics.

The QPPV has sufficient authority over the PV system in order to promote, maintain and improve compliance with pharmacovigilance activities and responsibilities.

All outsourced PV activities are overseen by the EU/UK QPPV. The EU/UK QPPV reports to the Head of Pharmacovigilance in Biocon Biologics, which is in India.

2.1 Location of Pharmacovigilance Activities

This Pharmacovigilance System Master File (PSMF) describes an overview of the key elements of the Pharmacovigilance (PV) system of Biosimilar Collaboration Ireland Limited-BCIL, Ireland to comply with Directive 2010/84/EU, Regulations (EU) No. 1235/2010 and (EU) No. 520/2012, and the latest version of the Guideline on good pharmacovigilance practices (GVP) Module II –Pharmacovigilance system master file (PSMF).

Biocon Biologics has its primary business location in Ireland (Biosimilar Collaborations Ireland Limited-BCIL, Ireland). BCIL act as Marketing Authorization Holder (MAH).

Biocon Biologics uses a single integrated pharmacovigilance system and maintains responsibility for the Global Pharmacovigilance System. Biocon Biologics performs the pharmacovigilance activities in-house and outsourced to 1) global Pharmacovigilance Service Provider Eversana and 2) EU/UK QPPV/NCP Services to PrimeVigilance.

According to Article 57(2) of Regulation (EC) No. 726/2004, BCIL PSMF has been registered in XEVMPD and the reference number is MFL20789 and is located at the below address:

PrimeVigilance Zagreb d.o.o.,
Oreškovićeva 20A, 10010 Zagreb, Croatia

For UK regions, Biocon's PSMF has been registered with MHRA and the reference number is UKPSMF01802 and is located at the below address:

PrimeVigilance Limited
1, Occam Court, Occam Road, Surrey Research Park,
Guildford, GU2 7HJ, United Kingdom

2.1.1 Pharmacovigilance Activities undertaken by Global PV Service Provider Eversana

Responsibilities for pharmacovigilance activities outsourced to Eversana are listed in the table below

Global PV Service Provider Eversana	Pharmacovigilance Activities
EVERSANA Ireland Limited, 70 Sir John Rogersons' Quay Dublin 1, Ireland https://www.eversana.com/solutions/integrated-commercial-services/integrated-compliance/pharmacovigilance/	• Global and Local Individual Case Safety Report (ICSR) management, • Global & Local Literature Management • Aggregate Reports • Argus Implementation, Data Migration, Managed services to support and maintain Argus database • Regulatory Intelligence

	• Biocon Biologics Pharmacovigilance E-mail Inbox Management

The Eversana PV organogram is provided in Annex B01. This PV organizational chart includes the sites where PV activities are undertaken, mainly ICSRs collection, evaluation, and reporting, PSURs production and submission, Global and local literature management.

2.1.2 Pharmacovigilance Activities undertaken by Primevigilance

Responsibilities for pharmacovigilance activities outsourced to Primevigilance are listed in the table below:

PV Service Provider- Primevigilance	Pharmacovigilance Activities
The PrimeVigilance Limited, Occam court, Occam Road, The Surrey research park, Guildford, Surrey, GU2 7HJ, United Kingdom. https://primevigilance.com/	• EU/UK QPPV • Other EU member states NCP/Local QPPV as per the EMA requirements/UK NCP.

2.1.3 Pharmacovigilance Activities undertaken by Biocon Biologics

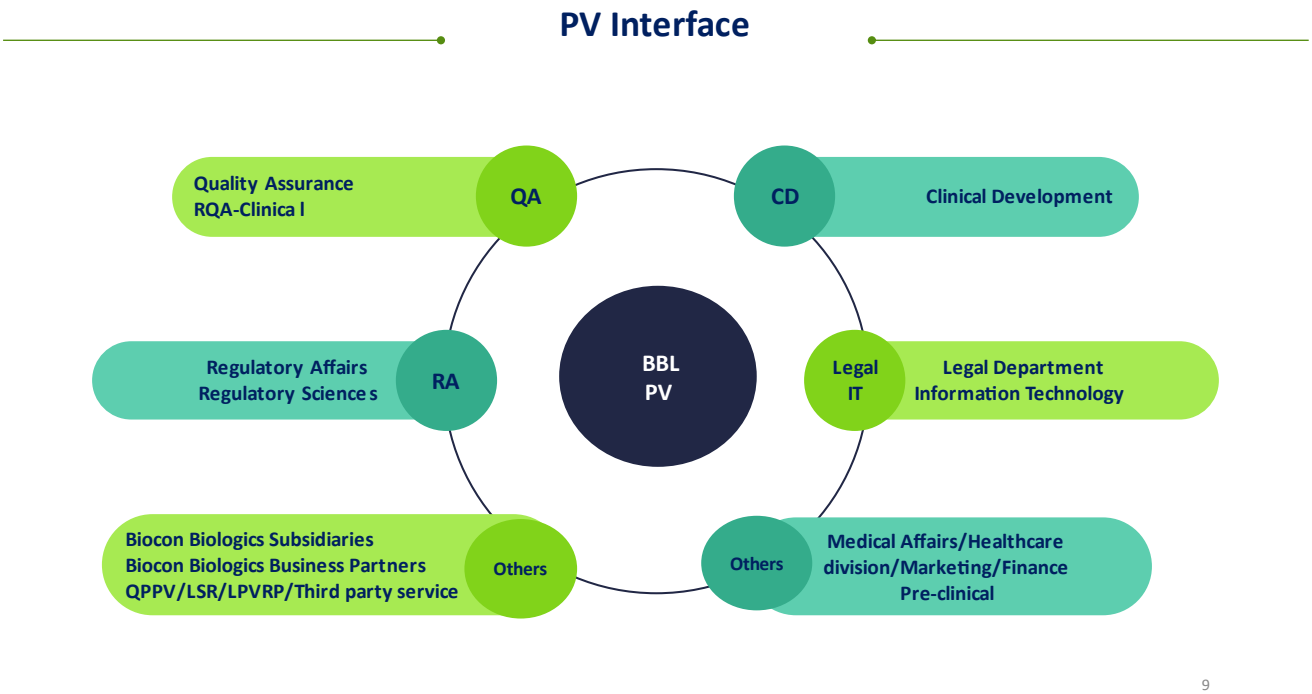
Biocon Biologics pharmacovigilance activities are conducted at the following locations.

Biocon Biologics in-house PV	Biocon Biologics in House Pharmacovigilance Activities
Biocon Biologics Pharmacovigilance Biocon House, Semicon Park Electronic City Phase 2	• Safety Database (Argus) BBL owned cloud base • Signal Management • Risk Management Plan • Safety Data Exchange Agreements

Bengaluru-560100 India	• Regulatory Authority Queries • Audits and Inspections • Clinical Trial Safety Support • Safety Support (Hazard Analysis, QA Trend Analysis, Label Review)

The Biocon Biologics Organizational structure is provided in Annex B01

2.1.4 Overview of Pharmacovigilance Activities.



Department	Activity
Quality Assurance	Product Complaints
Clinical Development	Clinical Trials
Regulatory Affairs	Marketing Authorization Approvals
Legal Department	Safety Data Exchange Agreements
Information Technology	General network, system maintenance, internal IT support
Medical Affairs	Post Approval Studies

3 SOURCES OF SAFETY DATA

Biocon Biologics receives safety data mainly from the following sources:

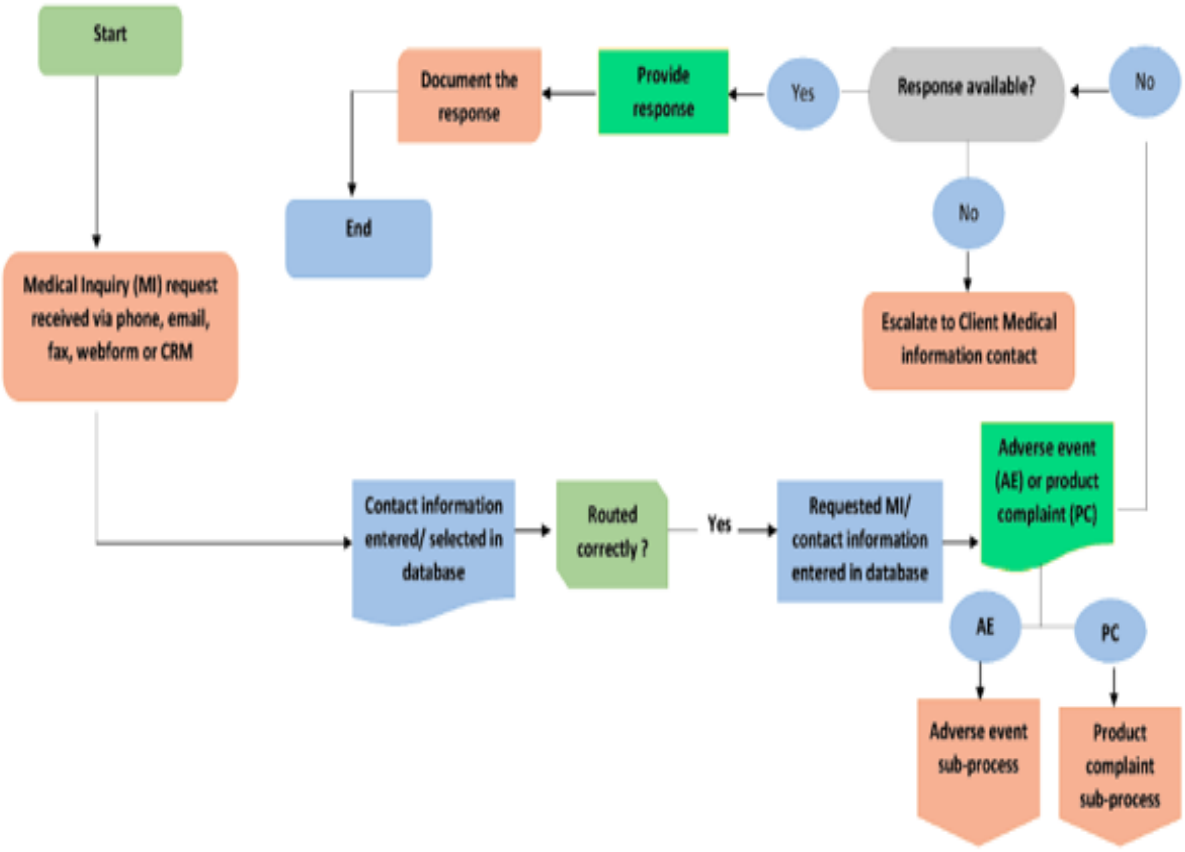
- Spontaneous reports from healthcare professionals, patients, consumers as well as other sources clinical trials, PQCs , Medical information inquiries, digital media, Patient Support program.
- Global literature searching (including MLM) and local literature search.
- ICSR downloaded from Regulatory Authorities
- Other sources such as business partners or distributors (If applicable)

Flow of Safety Data to BBL PV

AE Receiving Modalities


BBL PV
Regulatory Downloads
Literature Reports
Internet and Digital Media
Medical Information Call Centre
Competent Authority
National Contact Persons, QPPV
SDEA/ Business Partners
Interventional and Non-interventional Clinical Trials
Registries/Patient Support Program
Spontaneous Reports HCP/Consumer

Process Flow Diagram for Medical Information Case Inquiry



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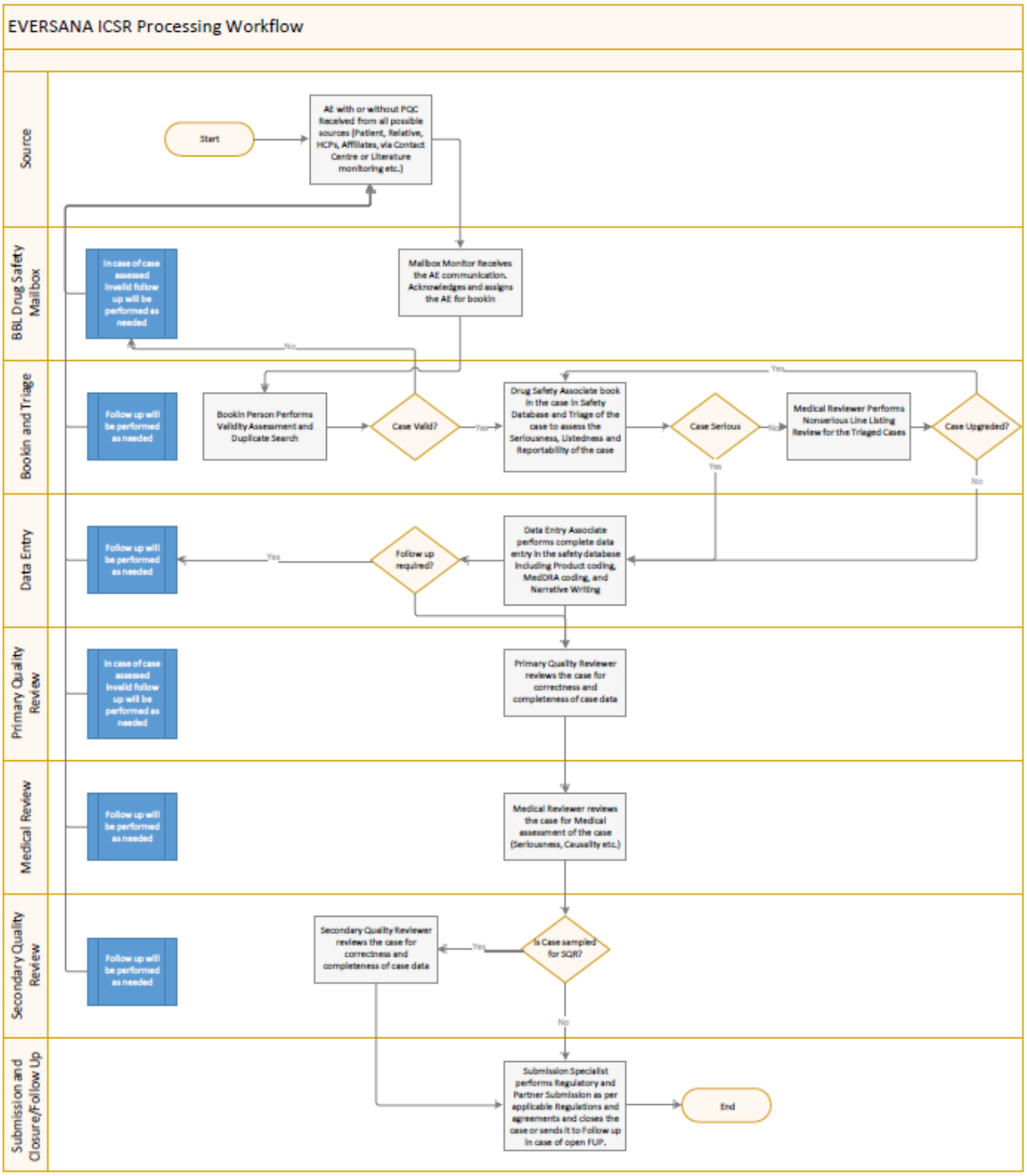


All cases that are received are evaluated and triaged as per applicable List of SOPs at Eversana as listed in Annex E01.

Whenever required/applicable follow-up is performed by Eversana for missing information or for information on progress and outcome for all types of spontaneous reports (including pregnancy reports, occupational exposure, overdose, misuse, abuse, medication errors, lack of efficacy reports and other miscellaneous reports)

Individual assessment for every case is done by Eversana's PV personnel. Eversana also creates new cases, processes them and establishes if follow-up is required.

All literature searches are being conducted by Eversana to identify any cases reported based on active substance(s) and also by its brand name(s). Literature cases from MLM service originating from EU and non-EU countries where Biocon Biologics has a Marketing Authorization and also cases from national competent authorities (NCA cases) from EU member states are downloaded from EudraVigilance database via EVWEB tool and imported into Biocon Biologics Safety Database.

The local literature publications are monitored in the EU countries where product is authorised.

Biocon Biologics regularly screens the internet and digital media, for potential reports of suspected adverse reactions, and potential valid ICSRs are submitted to the competent authorities within the appropriate regulatory submission time frames based on the date the information was posted on the internet site/digital medium.

A list of sources of safety data (including affiliates and third-party contacts) is included in Annex C 03.

4 COMPUTERIZED SYSTEMS AND DATABASE

The location, functionality, and operational responsibility for computerized systems and databases used to receive, collate, record, and report safety information and an assessment of their suitability for purpose is described in this chapter.

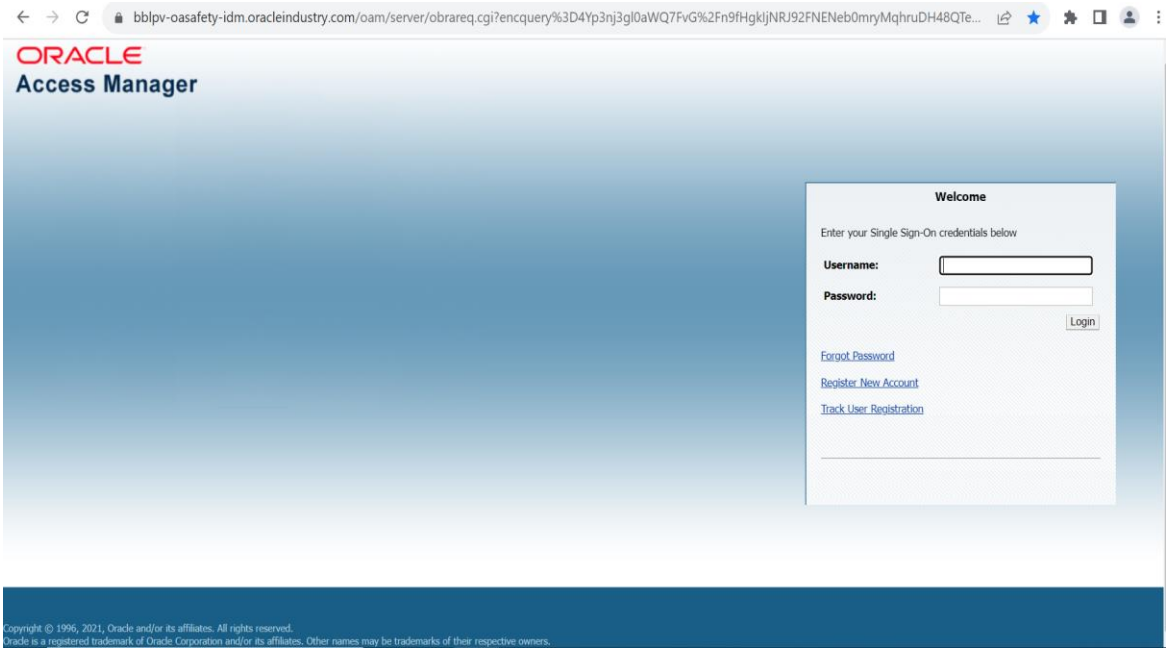
Further information about these computerized systems and databases is presented in Annex D.

Global Safety Database

The Global safety database is held at Biocon Biologics.
The Oracle Argus Safety is developed by Oracle, and is implemented at Biocon Biologics Limited for capturing, processing and storage of all individual case safety reports. It is fully validated and is compliant with Internationally agreed standards for electronic submission of adverse reaction reports for medicinal products for human use. The system is operated and maintained by BBL PV, the database is used to compile safety reports, delivering full E2B R2/R3 compliance, for expedited reporting to competent authorities, sharing and access safety information. The database provides all the tools for efficient case processing of clinical and post-marketing safety cases, including case entry, quality control, medical assessment and expedited reporting. Oracle Argus Safety allows for the generation of variety of safety reports including expedited reports, line listing, summary tabulation, CIOMS, MedWatch report, and XML reports. The application has access-controlled role-based security systems implemented. It is a web-based application with access restricted to trained PVD personnel of BBL/PV service providers. The database is stored on the cloud-based server by Oracle the responsibility of the maintenance of the database lies with Oracle. Database administrator Oracle is responsible for maintaining the database in a validated state and controlling access to the system. The safety database is validated by the PV service provider Eversana (PV service provider).

Name and Version

Database name	Version number
Argus Safety	8.4



URL of the Validation Environment: https://bblpv-test-oasafety-as.oracleindustry.com/

URL of the Production Environment: https://bblpv-oasafety-as.oracleindustry.com/

Learning Management System

Document Management System

PrimeVigilance

Validation status and fitness for purpose

Computerized systems which are used by PrimeVigilance are validated to comply with PrimeVigilance procedure IT-POL-002 Computerized Systems Validation Lifecycle, as well as applicable health

authority regulations. PrimeVigilance IT Quality team oversees validation activities. Validation includes documentation of user requirements and associated testing to demonstrate the system capability to meet specific requirements and ensure fitness for purpose.

PrimeVigilance performs testing manually according to predefined test scripts. All changes to the system are governed by a change control process as described in IT-SOP-006 IT Quality Risk Management. Documentation pertaining to the validation is maintained by the IT Quality team.

SharePoint Online

A secure common shared area called the SharePoint is accessible to Vendors/Contractual Partners employees in order to file, share, manage and maintain all documentation generated in the process of performing PV Network activities. Access to the shared drive by PrimeVigilance is restricted and is granted by the project manager only upon the approval of the System Owner (or designee) as a part of the PrimeVigilance change control process.

Master Control (QMCS)

PrimeVigilance uses an electronic Quality Management System to manage training records and track the completion of employees' trainings, controlled procedures, validation documentation, electronically sign documentation, change request, access requests to controlled systems and CAPAs.

Cornerstone

PrimeVigilance uses Cornerstone Learning Management System, a part of the Cornerstone OnDemand (CSOD) computerized system, which is a cloud-based application, for training of third parties such as LCPPVs. The system supports training-management and documentation within PrimeVigilance Network. The system supports the training process from creation of the training demand until production of training records and the contained electronic records provides sufficient evidence of trainings acceptable during audits and inspections.

Eversana

Scimax MI

Medical information management system for managing medical inquiries and initial intake of adverse events and product complaints.

Intelex

Quality Management System used internally at Eversana for document control, nonconformance investigations, CAPAs, and audits.

ComplianceWire

Learning Management System used internally at Eversana for managing training assignments and training records.

GxpManager

Electronic validation management system used internally at Eversana for paperless validation records and script execution.

5 PHARMACOVIGILANCE PROCESSES

Eversana, Primevigilance and Biocon Biologics have written procedures in place to cover all aspects of Pharmacovigilance. Additionally, General, IT, QA and Regulatory SOPs are also in place.

All Eversana, Primevigilance and Biocon Biologics PV employees receive training on relevant SOPs upon joining the company and on an ongoing basis where new processes are implemented.

The list of documented procedures for Eversana, Primevigilance and Biocon Biologics is included in Annex E.

5.1 Continuous Monitoring of Product Risk-Benefit Profile(s)

The Biocon Biologics SOPs on signal management cover procedures for the continuous monitoring of the safety profile of authorized medicinal products, risk-benefit assessment, reporting and communication with Competent Authorities and healthcare professionals about any changes into the risk-benefit balance of authorized medicinal products.

Signal Management

Signal management is performed for all Biocon Biologics authorized medicinal products. The signal management processes are followed as per PVD-SOP-0005 (Signal detection, Signal management and continuous monitoring of product risk-benefit profile). Biocon Biologics signal management process consists of signal detection, signal validation and prioritization, signal assessment, Recommendation for action and exchange of information. The signal management activities are initiated from the time of marketing authorization approval till the authorization is active.

Safety Governance structure

Biocon Biologics follows a 2-tiered safety governance structure.
The first tier involves in-function review of safety information by Drug Safety Review team (DSRT) which includes members from pharmacovigilance team: Drug Safety Specialist Safety Surveillance, Drug Safety Physician Safety Surveillance, Lead Safety Surveillance & Risk Management, PV Operations Lead & PV Head Drug Safety and Operations. DSRT provides inputs during Signal detection activities, Signal Validation & Signal Assessment.

The second tier involves Drug Safety Committee (DSC) which is a senior level Global Cross-functional Committee led by the Pharmacovigilance team that holds decision-making authority for endorsement of signal assessment and corresponding recommendation of action presented. DSC includes members from cross function team. Core members of DSC includes Chief Medical Officer, Qualified person for Pharmacovigilance (QPPV) or Designee, PV Head Drug Safety & Operations, and Head of Regulatory Affairs or designee. Adhoc members include other members from pharmacovigilance and regulatory affairs, Head of Medical Sciences or designee, Head of Clinical Development or Designee, Drug/Device

Quality team members (as applicable) and applicable team members from other relevant cross functional team (eg: pre-clinical, Pharmacokinetics, Biostats, Legal, Medical Affairs etc) based on the safety topic under review.

Signal Detection

Potential signals are identified during routine Pharmacovigilance activity such as review of ICSRs, review of aggregate reports, and literature review, through responses to queries from regulatory authorities or other sources. Applicable invalid cases (containing details of at least an adverse reaction and a suspect product), safety information from the product quality complaints/device complaints and special situation reports are also included in signal detection activity. Special situation report includes medication errors, off-label use, overdose/misuse/abuse, pregnancy/breastfeeding/lactation, the suspected transmission of infectious agents, pediatric use, elderly etc.

Sources of data and information for signal detection

Sources of data and information for signal detection include ICSRs, aggregate/periodic safety reports, from invalid reports of safety information, from the literature review and other sources like clinical trials or pharmaco-epidemiological studies or registries or post-authorization safety study (PASS), Reports from drugs of the same class or indication or reference product, Reports from regulatory websites or through regulatory requests and signal information from the licensing partner as per safety data exchange agreement (SDEA).

Analysis of EudraVigilance data/EVDAS monitoring/published literatures is also performed, as per regulatory authority requirements. Pharmacovigilance Risk Assessment Committee (PRAC) monthly meeting minutes/FAERS reports are monitored to identify any recommendations made by PRAC/regulatory authority for Biocon-authorized Products.

Methods of Signal Detection

The signal detection methodology applied at BBL is primarily qualitative in nature. It also includes the monitoring of health authority databases (e.g., EudraVigilance data analysis system or EVDAS) that support quantitative analysis. Particular attention paid to events for further monitoring and Designated Medical Events (DMEs).

Frequency of Signal detection

The signal detection of individual products is based on the signaling strategy as described in the corresponding Signaling Strategy Form (SSF). The data sources as well as frequency of review is risk-proportionate and account for the time since first authorization, the extent of patient exposure, whether product is under additional monitoring, the periodic safety update report (PSUR) submission frequency, the number of individual case safety reports (ICSRs) received over a given period, the important identified risks, the important potential risks and the need for additional information on the biosimilar or its reference medicinal product/reference product.

The SSF is reviewed at least annually or on an ad-hoc basis (example: initiating of a new clinical study, addition or removal of new safety concerns in the RMP, addition or removal of a new event in the list of events for further monitoring etc.).

Signal Validation and Prioritization

Safety signals that have been detected following the qualitative and quantitative review of safety data are validated in order to determine the need for further assessment, according to clinical relevance and context, Previous awareness and strength of evidence. Validation step constitutes the decision that the signal detected is judged to be of sufficient likelihood to justify verificatory action and moves into full evaluation.

Signal prioritization is evaluated at the same time as the validation step. A key element of the signal management process is to promptly identify validated signals with important public health impact, or

that may significantly affect the benefit-risk profile of the medicinal product in treated patients. These signals require urgent attention and are prioritized for further management without delay.

Signal Assessment

The signal assessment step consists of thorough pharmacologic, medical and epidemiological assessment of safety signal using all available relevant information.

Signal assessments are documented in the Signal assessment Report (SAR). The result of the assessment is discussed with DSRT, and proposed recommendations and proposed recommendation will be documented in SAR.

After a signal is validated, further action is taken at Drug Safety Committee (DSC) meetings. The drug safety committee review SAR report and recommends further action. The signal assessment step may result in signal confirmed as a risk (weight of evidence is sufficient to support a conclusion of a relationship between a product and an event) or signal refuted (the weight of evidence is insufficient to support conclusion of a relationship between a product and the event at the point of time it was evaluated). For the signals confirmed as a risk, DSC determines appropriate measures to be taken.

Recommendation For Action and Exchange of Information

DSC makes the final decision on any safety issue and is responsible for discussion, approve, refute any new safety signal and identify the need for additional data collection or investigations or an update to the product information through a regulatory procedure or recommend further actions.

- Each signal originating from internal signal management process, which is confirmed by DSC shall be communicated to relevant key stakeholders for example- EU/UK QPPV, all Responsible Person for Pharmacovigilance (RPP) of Biocon Biologics, Other applicable departments of BBL e.g. GMP QA, and RA, BBL partners as per the SDEA and Licensing authorities of all regions where BBL holds marketing authorization

Signals detected through EudraVigilance monitoring

The DSC may request to send standalone notification to EMA and EEA competent authorities when further analysis by competent authorities is required, based on Biocon's assessment of signal detected through Eudravigilance monitoring. This should be done as soon as possible and no later than 30 days after Biocon has completed their assessment and concluded that further analysis by the competent authorities is required.

The standalone notification is not required when:

- The new or changed risk lead to a labelling variation
- A PSUR is due to be submitted to the EEA within 6 months after signal assessment completion.
- It qualifies as an emerging safety issue.

The standalone signal notification is send using the stand-alone signal notification form available on the European medicines web-portal and send it to the Agency using the mailbox "MAH-EV-signals@ema.europa.eu" and signalmanagement@mhra.gov.uk and to the competent authorities in Member States where the medicinal product is authorized (Reference section IX.C.4.3. Standalone signal notification; Module IX – Signal management)

Emerging safety issues

Any safety issues identified by BBL that require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals falls under emerging safety issues. Emerging Safety Issue (ESI)s can be identified at any stage during signal management process regardless of the source and are prioritized accordingly.

Emerging Safety Issue (ESI) i.e Signals or issues that may have implications for public health, and/or significant impact on the benefit-risk balance of the product are promptly identified to allow immediate notification to the local regulatory authorities where the medicine is authorized.

In EMA region, ESI are notified in writing to the competent authority(ies) of Member State(s) where the medicinal product is authorized and to the Agency to the mailbox P-PV-emerging-safety-issue@ema.europa.eu as soon as possible and no later than 3 working days after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue. For UK MAH will notify the MHRA at signalmanagement@mhra.gov.uk within 3 working days after establishing that a signal or a safety issue from any source which meets the definition of an emerging safety issue.

5.2 Risk Management System(s) and Monitoring of the Outcome of Risk Minimisation Measures

Risk management plans are in place for the products authorized for Biocon Biologics
Biocon Biologics PV prepares, reviews and approves any required RMP in accordance with regulatory obligations. Any routine PV activities or additional risk minimization measures as described in the approved RMP are implemented by BBL or by business partner. The outcome of risk minimization measures are assessed and submitted to the concerned authorities, whenever applicable. Biocon Biologics has a documented procedure for preparation, review and approval of risk management plan (RMP) for the medicinal products, PVD-SOP-0023 Preparation, Review, Approval of Risk Management Plan. The structure and format of the RMP as described in GVP Module V are followed for any new/updated EU-RMP.
RMP New/updates are required:

-All new marketing applications

-For renewal of Marketing authorization

- At the request of EMA or an NCA

- Whenever the risk-management system is modified, especially as a result of new information being received that may lead to a significant change to the benefit-risk profile or as a result of an important pharmacovigilance or risk-minimization milestone being reached.

-When there is a significant change in MA such as a new indication, dosage form, route of administration, new manufacturing process of a biotechnology product, pediatric indication, other significant change in indication

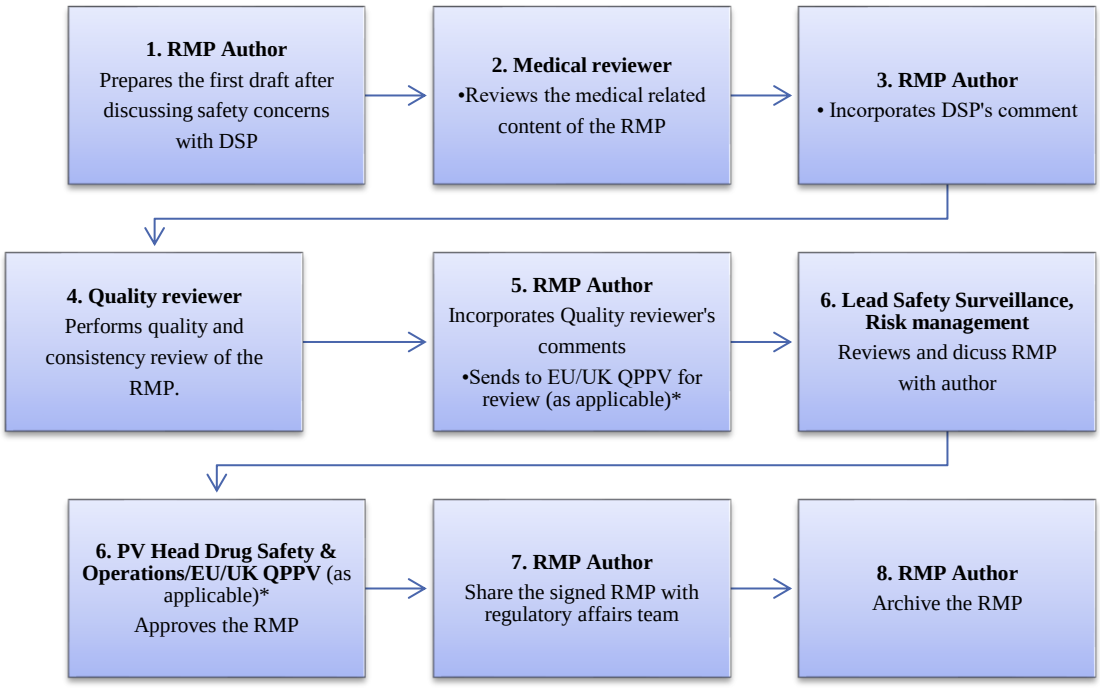
-with a PSUR for single centrally authorized medicinal product, when the changes to the RMP are a direct result of data presented in the PSUR.

EU/UK-RMPs are shared with EU/UK QPPV for review and sign off. The final signed RMPs are submitted to competent authorities by Biocon Regulatory affairs Team.

The EU/UK QPPV and Biocon Biologics will identify all relevant functions/roles to be trained on the content of the RMP.

Any routine PV activities or additional risk minimization activities measures as described in the approved RMP will be implemented by Biocon Biologics. The outcome of risk minimization measures will be assessed periodically and submitted to the concerned authorities, whenever applicable.

RMP Process-Preparation, Review, Approval of Risk Management Plan



*EU/UK QPPV review and approve the RMP (as applicable as per country-specific regulations)

Distribution Of Educational Material

Education materials are distributed as a "stand-alone" communication by Biocon Biologics in co-ordination with the regulatory affairs and commercial team. The method of distribution of educational material and target group followed as per the national competent authority's recommendation.

Local implementation of RMP commitments

Biocon Biologics implements post-approval risk minimization activities described within approved RMPs under the supervision of the EU-QPPV and NCPs/LQPPVs. The outcome of risk minimization measures are assessed periodically and submitted to the concerned authorities, whenever applicable

Notification on safety concerns

Requirements to submit the list of safety concerns of initial approved RMP or updates/revisions of RMPs to competent authority notifications, received by RA department as part of the new product approval, renewal process or update of RMP. The notifications are then forwarded to PV department for further analysis.

Requirements In UK

The EU RMP along with a specific UK annex are submitted to the MHRA for the Biocon Biologics UK MA. Where the MHRA has made a specific request for information to be included, or where the risk management system in the UK differs from that in the EU, this information are provided to the MHRA in UK specific annexes.

5.3 Individual Case Safety Report (ICSR) collection, collation, follow-up, assessment and reporting

The sources of the safety data are described in section 3, Sources of safety data. Cases received by Biocon Biologics and/or its affiliates/subsidiaries from non-EU territories concerning product

authorized/registers also in EU are sent to Eversana PV personnel via dedicated e-mail address DrugSafety@biocon.com.

All cases received by Eversana are evaluated and triaged to identify a Biocon Biologics suspect product(s) and minimum information required for a valid ICSR.

The ICSRs are collected into Biocon Biologics safety database. Case reports are processed through workflow steps of: Duplicate check, Data Entry and Quality Check and Medical review. The case processing timelines for each workflow step are defined in the applicable Eversana's SOP. Routine case follow-up is performed in order to obtain the minimum information required for expedited reporting or for further case assessment. For specific safety concerns as described in the approved RMP, a specific targeted follow-up questionnaire are used to collect additional data for events of interest. Any follow-up attempts are documented and performed with due diligence as per the process described in Eversana's SOPs.

Expedited reporting of valid ICSRs to EMA are performed by Eversana as per defined timeline (15 days for serious and 90 days for non-serious ICSRs).

In addition, valid as well as non-valid case reports received by Eversana are exchanged with Biocon affiliates/subsidiaries from non-EU territories or with contractual partners according to the agreed format (XML, CIOMS etc.) within the timelines specified in the SDEA.

An ICSR tracker is maintained by Eversana for reconciliation purposes and exchanged between parties on a regular basis.

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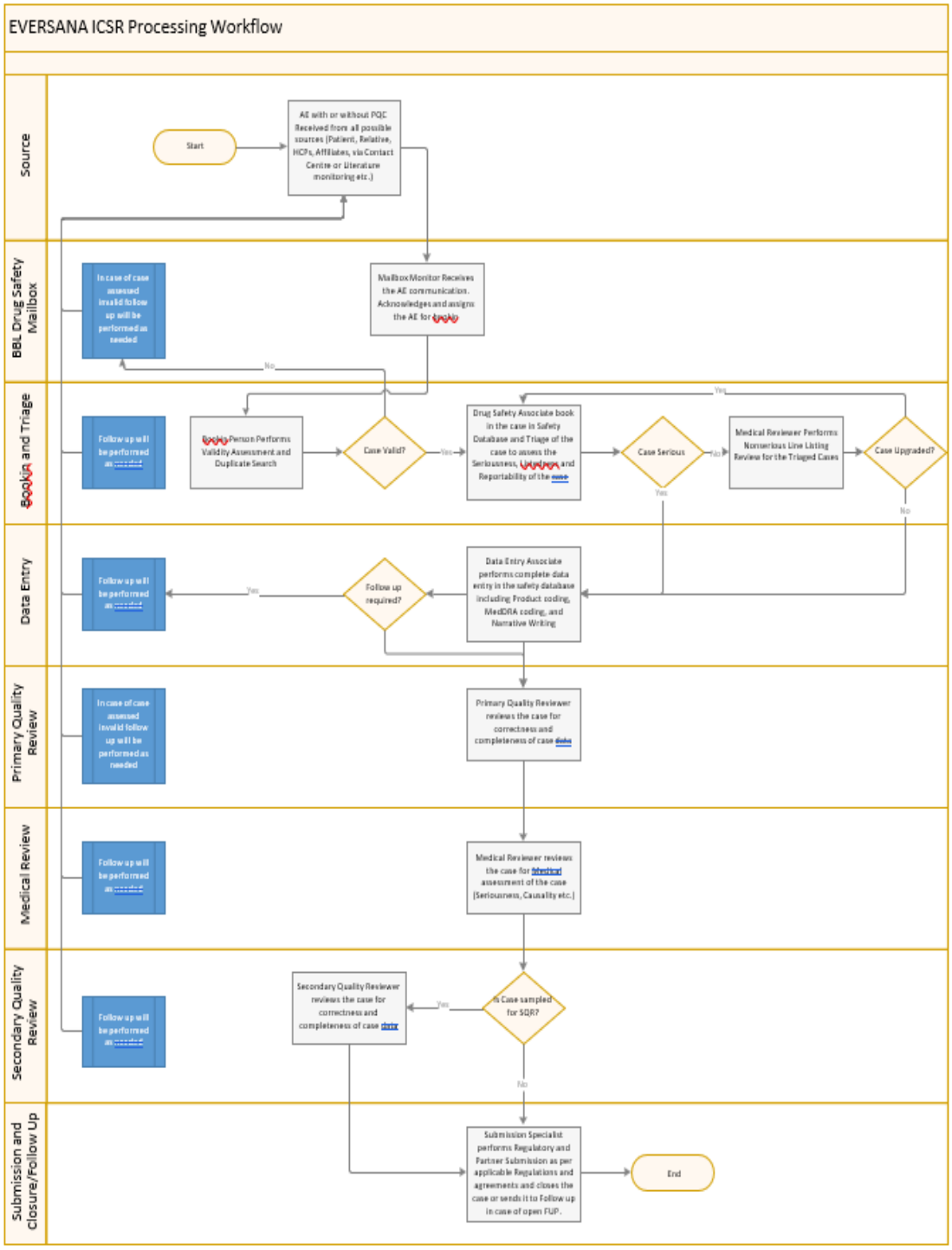


5.4 Periodic Safety Update Reports (PSUR) and Addendum to Clinical Overview (ACO) Scheduling, Production and Submission]

Whenever applicable, Periodic Safety Update reports (PSURs) and Addendum to Clinical Overview (ACOs) are prepared for Biocon Biologics products in accordance with the relevant Eversana's SOP (QMS-4-PV-09 Aggregate Safety Reporting, WI-4-PV-09a, Aggregate Data Reports). Eversana maintains schedules for all approved Biocon Biologics products which require PSUR submission based on current European Union reference dates (EURD) list available on EMA website.

Based on the registration dates provided by Biocon Biologics for the medicinal product, Eversana Aggregate Reporting team publishes the aggregate report schedule. Eversana uses an inhouse tool for Aggregate report scheduling and tracking.

Biocon Biologics provides the source data for preparation of PSUR/ACO in response to Eversana request. The PSUR/ACO is prepared, and quality and medical reviewed by Eversana personnel in accordance with current regulations and sent to Biocon Biologics for a further review. After review by Biocon Biologics/EU/UK QPPV, further incorporation of necessary changes performed by Eversana, and final PSUR/ACO is signed off.

Submissions of PSURs to the regulatory authorities is ensured by Biocon Biologics regulatory affairs in accordance with timeline specified in EURD list published by the EMA. PSURs are submitted to the EMA repository after conversion of PSUR submission packages to Electronic Common Technical Document (eCTD) format.

With respect to Addendum to Clinical Overviews (ACO), these are prepared and quality check by Eversana's team and sent to Biocon for submission as per renewal application timeline.

5.5 Communication of Safety Concerns to Consumers, Healthcare Professionals and the Competent Authorities

Communicating safety information to patients and HCPs is a public health responsibility and is essential to achieve the objectives of PV in terms of promoting the safe and rational use of medicines, preventing harm from ADRs and contributing to the protection of patients' and public health.

Urgent information of HCPs and the public may be necessary in cases of suspension, withdrawal or revocation of the MA or changes to the Summary of Product Characteristics (SmPC) that have impact on the conditions of appropriate use of a medicinal product. The communication to HCPs or to public is performed in close coordination and agreement with concerned competent authorities.

Procedure for communication of safety concerns to consumers, healthcare professionals and the competent authorities is in place for Biocon Biologics.

In consultation with EU/UK QPPV, Biocon Biologics is responsible for communication of safety concerns and will ensure that any changes in the benefit-risk balance of medicinal products are notified to competent authorities.

Depending on the potential medical significance of the safety concern, the appropriate action will be determined.

Biocon Biologics in consultation with QPPV communicates signals that may have implications for public health and the benefit-risk profile of a product immediately to the CA as a new or Emerging Safety Issue.
Biocon Biologics sends an e-mail about the main aspects of the safety information at P-PV-emerging-safety-issue@ema.europa.eu.

Biocon Biologics will notify the MHRA at signalmanagement@mhra.gov.uk of emerging safety issues within 3 working days after establishing that a signal or a safety issue from any source meets the definition of an emerging safety issue.

When appropriate this will include proposals for action with timescale implementation.

Any product related safety issues which result in a recommendation to amend the Summary of Product Characteristics (SmPC) and/or Patient Information Leaflet (PIL) are implemented by Biocon Biologics in all EU Member States where its products are authorized by submission of safety variations.

Whenever new or emerging safety information needs to be communicated to healthcare professionals, patients or general public, the QPPV/deputy QPPV and Biocon Biologics will discuss and agree on the content and nature of the safety communication. If safety communication includes distribution of Direct Healthcare Professional Communication (DHPC), the QPPV and Biocon Biologics Regulatory Affairs will liaise with the CA as necessary to finalize the wording of the DHPC. Final DHPC will be distributed once the content and format of the information, recipients, and distribution timetable was agreed and after the corresponding regulatory procedure has been completed.

In addition, when Biocon Biologics or QPPV receives a safety communication/request for further information (RFI) from the European Agency (EMA) or other CAs within EU, they will collaborate to ensure that a full and prompt response to any request for provision of additional information to EMA or other CAs in Members States is provided in a timely manner.

Biocon Biologics maintains a Safety Communication Tracker to capture any RFIs, timelines for responses and other safety communications.

5.6 Implementation of Safety Variations to the Summary of Product Characteristics (SmPC) and Patient Information Leaflets

The necessity of safety variations may derive from a variety of sources, such as clinical data, quality related deficiencies of the product as well as from signals emerging in the scope of ongoing monitoring and signal detection activities. The update to SmPCs/PILs may be required upon a request from Competent Authority or identified internally through PSURs or signal evaluations.

Biocon Biologics is responsible SmPC/PIL management during the life cycle of each product, based on the accumulated safety information.

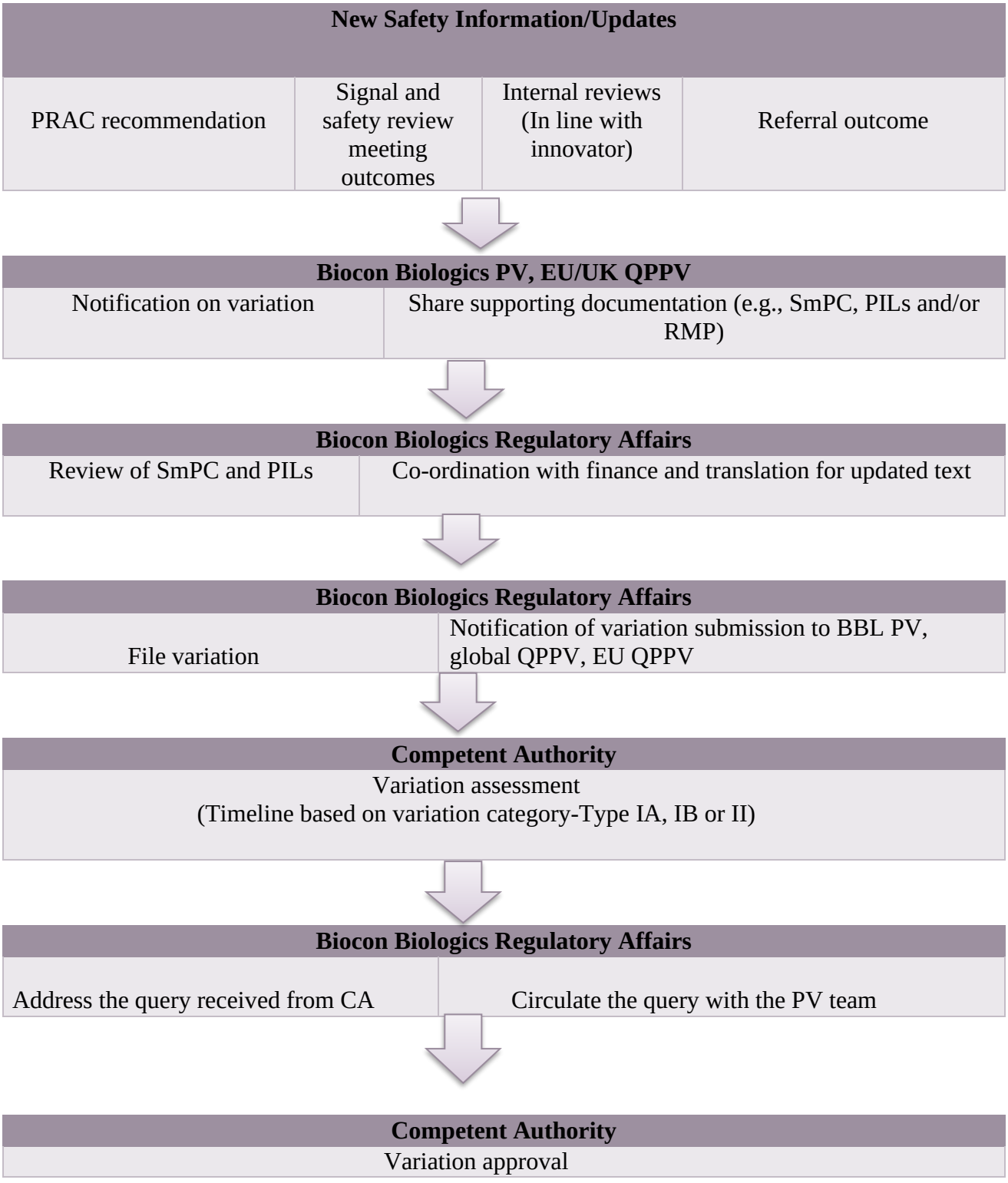
Biocon Biologics is responsible for management of safety variations to SmPC /PIL.

Once a request is received from the competent authority or from any internal source such as notification from PV personnel and/or QPPV, the update SmPC/PIL is prepared and submitted by the regulatory team at Biocon Biologics

After the safety variation approval has been received from the competent authority, Biocon Biologics will communicate the approval date and send the updated SmPC/ PIL to Eversana PV personnel and EU/UK QPPV.

EU/UK QPPV will undertake a review of the safety variations status on a quarterly basis to ensure compliance with timescales and deadlines wherever applicable.

Flow Chart: Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets (PILs)



Biocon Biologics Regulatory Affairs

Circulate the approval with the stakeholders
(PV, QA etc.,)

Implementation of updated SmPC/PILs by MAH

5.7. Literature management

Eversana performs global and local literature activities. Ovid platforms are utilized for literature screening for Biocon Biologics products. The literature articles indexed in Embase database are fetched through Ovid platform.

The literature search strategy is defined as per the Eversana's SOP.

Sample review (5%) of rejected articles (assessed as invalid) are performed on a monthly volume. This will be documented and shared with Biocon Biologics in case any inconsistency is observed during this review will be addressed immediately and appropriate action will be taken and documented by Eversana team.

Full Text Article (FTA) procurement

If a valid case is identified from an abstract or it is unclear if all the elements of a valid cases are present, or there is insufficient information for an appropriate assessment, the full text article will be sought for further review.

This is documented and tracked from an action item created in the safety database and in Full Text

Article (FTA) Procurement tracker as applicable.

Upon receipt of the FTA, the case would be triaged/ processed. Initial Receipt Date (IRD, Day 0) will be the day, when the case was validated based on the four minimum criteria and causality in an abstract or FTA that was received.

Translation

Literature abstracts and articles that are not received in English and not accompanied by an English translation upon initial receipt require translation by Eversana.

As required, the translation is requested, and this is documented and tracked from an action item created in the safety database and in Literature Translation Tracker as applicable.

5.7.1 Medical Literature Monitoring By EMA

EMA provides MLM service for medicinal products for which a high number of Marketing Authorisations (MAs) were granted to various MAHs in the EEA. The Eversana personnel is responsible for monitoring and downloading published confirmed ICSR literature information as per SOP QMS-4-PV-08

5.7.2 Medical Literature Monitoring

A global weekly literature search and review is performed to monitor safety information for BBL products in the worldwide scientific and medical literature. This process is described in SOP QMS-4-PV-08

5.7.3 Local Literature Search

Local literature search is performed by Eversana as per Local Literature Monitoring Matrix for applicable BBL products.

Local Literature searches

- Identification of Local Journals
- Setting up the frequency
- Perform periodic search.
- Abstract assessment for Valid and Aggregate Literature cases
- Full Text Article (FTA) procurement for applicable abstracts
- Translations of non-English FTA
- FTA review
- ICSR creation for Valid and Aggregate literature cases

5.8 Data Retained and Data Repository

All documentation with regards to Pharmacovigilance are maintained as per the SOP on Documentation Practices at Pharmacovigilance Department (SOP: PVD-SOP-0012). The PV documents are maintained electronically in the pharmacovigilance share point. The ICSR source documents are maintained in BBL safety database.

5.9 Global Safety Regulatory Intelligence

Eversana provides global regulatory intelligence updates to BBL Any new updates from Global Safety Regulatory Intelligence is provided to BBL through email.

6 PHARMACOVIGILANCE SYSTEM PERFORMANCES

The performance of Biocon Biologics Pharmacovigilance system is described through presentation of compliance figures for ICSRs, PSURs, safety variation submissions and adherence to RMP commitments and other MA obligations/conditions. This includes compliance monitoring for submission of RMPs, ICSRs, and PSURs to CAs or EMA in a timely manner. An overview of the reporting statistics of the timeliness of expedited reports, PSUR reporting to competent authorities,

targets for the performance of the pharmacovigilance system with a list of performance indicators are provided in Annex F01.

6.1 ICSR Reporting to Competent Authorities

Timeliness of 15-day and 90-day reporting over the past year:
Rate (%) of submitted serious ICSR within 15 days
Rate (%) of submitted non-serious ICSR within 90 days

6.2 PSUR Submission

Timelines of PSUR reporting to competent authorities in the EU:
Rate (%) of submitted PSURs

6.3 Submission of Safety Variation

All identified safety variations along with their due date and actual submission dates are performed by Biocon Biologics regulatory affairs.

6.4 Risk Management Plan Commitments

Adherence to RMP commitments and other obligations or conditions of MA will be assessed whenever applicable for each approved product based on the type of PV activities and RMMs described in product's approved EU-RMP. Any additional risk minimisation measure shall be monitored on a quarterly basis.

Any non-compliance identified is investigated and corrective and preventive action is implemented for avoiding it in future.

7 QUALITY SYSTEM

Biocon Biologics is committed to ensure that every product it manufactures and distributes consistently meets with standards of quality, purity, efficacy, and safety.

Implementation of quality is achieved by Biocon Biologics through quality systems based on current Good Practice Standards (e.g. GMP, GDP and GVP) as required, in conformity with national and international standards.

Pharmacovigilance is regarded as an important function in Biocon Biologics. Biocon Biologics has established a comprehensive quality system. The Research quality assurance team of Biocon Biologics Ltd. is responsible for the implementation of the quality system at BBL PV. The RQA-Clinical is independent in its function and reports to the Head, Research Quality Assurance The RQA-Clinical, Head PV, Chief Medical Officer, and Chief Development Officer ensure that the BBL Pharmacovigilance department follows systems and processes laid down in various procedural documents in order to comply with the regulatory authority requirements. The RQA-Clinical also evaluates the Biocon Biologics Pharmacovigilance periodically and in coordination with the Head PV ensures timely completion of corrective and preventative measures as required.

There is a continuous quality improvement process in place supported by organizational learning through individual and group learning activities in addition to quality audits conducted by RQA-Clinical enabling and supporting corrective processes that enables the company to maintain global standards in Pharmacovigilance.

7.1 Documentation and Record Control

Biocon Biologics, and Eversana's procedures on archiving cover the policy of archival at Biocon Biologics, PrimeVigilance and Eversana, respectively.

PrimeVigilance follows their respective quality procedures for filing and archiving all documents and records relating to the Biocon Biologics.

All documentation supporting Biocon Biologics PV and Network activities is archived in SharePoint as the main document management system as per PVL-GENOG-031, Filing and Archiving. PrimeVigilance uses common Microsoft software to support its document management system. Access to Biocon Biologics specific area of the SharePoint is restricted to PVL employees assigned to the Biocon Biologics project.

Currently all source documents are archived at respective Eversana PV sites. The ICSR source documents are maintained in Biocon Biologics safety database.

All documentation with regards to Pharmacovigilance is held and maintained as per the SOP on Documentation Practices at Pharmacovigilance Department (SOP: PVD-SOP-0012). The PV documents are maintained electronically in the pharmacovigilance drive/share point. The changes to the PSMF are recorded in the PSMF log (Annex I01).

PrimeVigilance will also keep each version of the final PSMF and SPS in specific area of the SharePoint dedicated to the Biocon Biologics project.

7.2 Procedural documents

The list of documented procedures of Eversana, PrimeVigilance and Biocon Biologics PV are included in Annex E01.

PrimeVigilance

PrimeVigilance have procedures in place to conduct all tasks and activities delegated to them by Biocon Biologics. Arrangements are in place for periodic review, update, implementation, training, and version control, as necessary.

Information about the documentation systems applied to relevant procedural documents under the control of third parties – PrimeVigilance

The PrimeVigilance procedure hierarchy is as follows:

- Policy Documents (POLs)
- Standard Operating Procedures (SOPs)
- Operating Guidelines (OGs), equivalent to a working instruction (WI)
- Reference Documents (REFs)
- Forms

All PrimeVigilance procedures are developed and maintained electronically through PrimeVigilance's QMCS.

All PrimeVigilance procedures:

- Follow a standard format and are written in English;
- Are reviewed and approved by at least one Subject Matter Expert in a Director-level or management-level position and by a Director / Manager of the Quality team;
- Are reviewed every three years following their effective date, and as required by, for example, changes in legislation or in PrimeVigilance procedures, or following CAPAs and findings resulting from audits or inspections.

This process is described in PVL-GENSOP-004 PrimeVigilance Controlled Procedures.
PrimeVigilance procedures are available to its employees via the QMCS. This system ensures that only current versions of procedures are accessible.

Eversana

Eversana have procedures in place to conduct all tasks and activities delegated to them by Biocon Biologics. Arrangements are in place for periodic review, update, implementation, training, and version control, as necessary.

The Eversana Procedures are as follows

- Standard Operating Procedures

- Reference Documents
- Work Instructions

Biocon Biologics

Biocon Biologics have procedures in place to conduct all tasks and activities performed in house by Biocon Biologics. Arrangements are in place for periodic review, update, implementation, training, and version control, as necessary.

The Biocon Biologics Procedures are as follows

- Standard Operating Procedures
- Working Guidance Documents

-We have standard operating procedures (SOPs) and working guidance documents (WGDs). The forms/format are available as annexures (ANNs) and templates as attachments (ATTs) in SOPs. Also, templates are available as working attachments (WATs) in WGDs.

-The change control, deviation and CAPA are managed using TrackWise. However, audits are managed using manual system.

Change management

A procedure for management of change (change control) is in place. This ensures proposed changes undergo appropriate assessment and approval prior to implementation, and provides an assurance that there are no unintended consequences of change. Any change (e.g., for new introduction) is routed through a change proposal, review and approval process. The review is achieved through a change review team discussion consisting of the originator function, RQA-Clinical, CQC (if needed) and other cross functional affected teams (if any). The change control also includes a post-change assessment of notification (e.g., to affected groups within or research partners or training needs) and implementation.

This change management covers changes to the following.

- Documents (SOPs, WGDs, and associated documents)
- Systems and facility (e.g. software)

- The SOP on management of procedures, describe the procedure for preparation, review, approval, revision and control of procedures, working guidance documents and associated documents (annexures and attachments) and the SOP on good documentation practices is

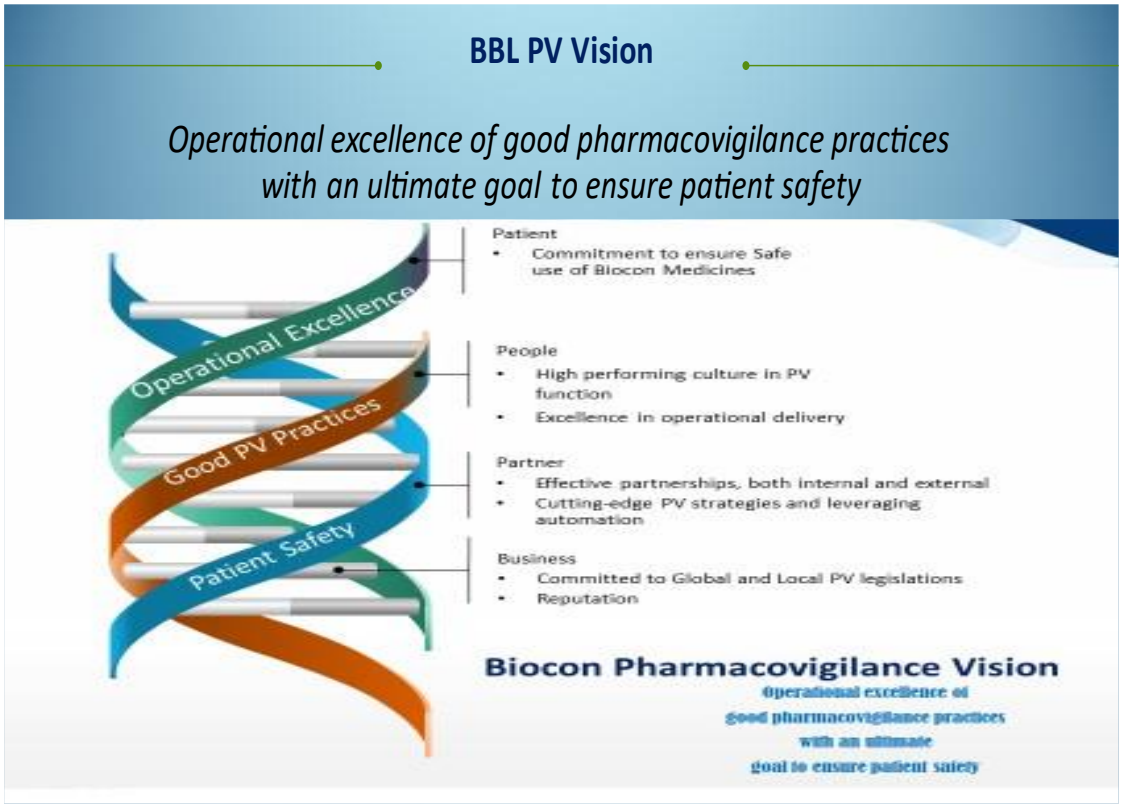
applicable for recording, processing, transcribing, reviewing, and maintaining raw /source data and handwritten (paper) documents / records and electronic systems /computerized systems.

- The SOPs, WGDs and their associated documents (i.e., ANNs, ATTs and WATs) are prepared/created, reviewed, finalized/signed off, approved, made effective, revised and stored in eDMS (electronic document management system). The frequency of updating the SOPs/WGDs and their associated documents is 2 years from the effective date. Note: For management of SOPs, FileNet was used in past and the eDMS comes into effect from August 04, 2024 which will be used henceforth.
- Training for the SOPs/WGDs is provided using learning management system (LMS).

7.3 Training

Training of the Eversana and Primevigilance staff are governed by their internal processes.

Biocon Biologics Pharmacovigilance vision “Operational excellence of good pharmacovigilance practices with an ultimate goal to ensure patient safety”.



The pharmacovigilance training is a mandatory training for Biocon Biologics employee. The PV training are imparted at the time of joining during the induction program and annually through either face-to-face, Tele Communication tools or through LMS to the Biocon Biologics employees. The PV training to Biocon Biologics employees aims to provide the importance of Pharmacovigilance, Biocon Biologics PV system, definitions, and reporting of adverse event reports/product complaints to whom, why, what, and where to Biocon Biologics.

All personnel involved in Pharmacovigilance activities are appropriately trained for performing the PV activities. A training and development program is in place so that personnel involved are aware of Pharmacovigilance principles and current regulatory requirements in Pharmacovigilance. Training and development are conducted by appropriately qualified individuals and the detail of training and evaluation through Learning Management Suite. The written procedure followed is PVD-SOP-0017 Management of Training of Personnel for Pharmacovigilance. An ongoing training and development program for Biocon Biologics PV is prepared as per this SOP to ensure continuous learning, identify areas of improvement and to keep the employee updated on evolving regulatory

requirements in Pharmacovigilance across the globe. Pharmacovigilance-specific training includes Initial Training, Continuous training, and Refresher training.

The QPPV is responsible for maintaining an oversight of the requirements for training. All members of the PV department have the following:

- Curriculum Vitae
- Job Description
- Training record

The CVs and Job descriptions of all Pharmacovigilance staff are held at Biocon Biologics PV, and for local affiliates locally at respective sites, and a copy is obtained from the respective office.

PrimeVigilance

There are procedures in place detailing the processes related to training in PV for each of the parties involved in PV activities. PrimeVigilance training process is detailed in their procedure PV-GENSOP-005 PrimeVigilance training.

Summary description of the training concept – PrimeVigilance

All PrimeVigilance employees are required to attend an initial training program. The training program is dependent on the employee's role but all employees receive a core training program covering general company-specific subjects including but not limited to:

- PV training.
- Quality management system (QMS).
- Company procedures.

Time to complete the initial training plan will vary from role to role but an employee is not permitted to start "live" work unless their training records indicate they have completed all required training and, where needed, passed all competency tests.

Existing employees who are changing roles or being promoted are assigned a training program relevant to their new role (covering procedures and instructor-led training sessions).

Relevant employees receive refresher training on key PV activities. All training for an employee is recorded and managed electronically through the PrimeVigilance QMCS, and training is assigned according to a Training Matrix. In addition to their training records, each PrimeVigilance employee maintains an up-to-date CV and JD in QMCS.

7.4 Auditing of the PV system

Audits are periodically conducted in order to monitor the implementation and compliance with GVP, to monitor the compliance with internal procedures and to propose necessary actions. The aim is to continuously improve the internal process and compliance with Biocon Biologics PV Processes. Internal audits are conducted as per the SOP (CQA-SOP-0011: Management of Audits).

Internal QA audit for Biocon Biologics PV system occurs on a regular period and findings are recorded. A corrective and preventative action plan will be implemented for any identified issues requiring action, and the progress of all actions will be closely monitored by the Head PV and EU/UK QPPV.

The PV and quality systems of other business /marketing partners/vendors are also audited by Biocon Biologics Research Quality Assurance (RQA)-Clinical in the form of on-site or off-site audits (remote) as per audit plan or need basis.

Audits assure adherence to quality systems and identify areas for continual improvement. Audits are performed based on risk and defined frequency. Internal quality system audits are performed as per audit plan. Audits are also performed for the studies done at CROs or trial sites, and for assessment of quality systems at vendor locations per audit plan. Audits are performed on-site or remotely, based on the feasibility and mutual agreement between the auditors and auditees. Auditors are selected based on qualification and experience and are independent of the activity performed. Audit findings are categorized as critical, major, minor, or recommendation for remediation or improvement. A final audit report and observations are summarized by the auditing team and provided to the auditee for resolution of observations. It is the responsibility of the auditee to develop corrective and / or preventive actions. Implementation of CAPA compliance is verified by RQA-Clinical.

A list of audit schedules and audits conducted and completed in the last 5 years is included in Annex G01.

Auditing – PrimeVigilance

PrimeVigilance has established an internal audit program, which ensures that key functional areas (including GxP Systems/processes) and vendors are audited. A risk-based approach is used to develop audit schedules for internal systems and vendors. Audit scheduling is managed via a tactical audit plan. The relevant processes are described in PVL-GENSOP-012 Conducting Internal Audits and PVL-GENSOP-010 Conducting Quality Risk Assessments.

For all internal and vendor audits, reports are prepared and sent to the relevant parties. CAPAs are proposed and completed (as needed).

As a service provider PrimeVigilance is regularly audited by or on behalf of clients (both as part of due diligence and periodic review activities).

The relevant processes are described in PVL-GENSOP-014 Audits of PrimeVigilance by clients.

Post receipt of the audit report and findings (if any), the audit responses are completed and returned within the timeline assigned by the auditor(s) or 30 calendar days (as per PVL procedures), should no timelines be specified.

Auditing – Eversana

Internal Audit – EVERSANA Medical Communications and Pharmacovigilance are subject to internal audits that are identified and scheduled in accordance with a risk-based approach, organized at both a strategic and tactical level.

1. External Audit Program - Supplier Audits - External supplier audits will be planned and performed in accordance with the steps and procedures outlined in QMS-3-09, Supplier Management, including the process of audit planning, audit conduct, audit outcomes and reporting, audit communication, audit follow-up, and supplier disposition (approval).

1. **Audit Schedule:**

- Annual strategic audit risk assessment by Quality and Compliance with Management Team.
- Assessment will be completed by the end of Q1 and documented using RD-5-04g.
- Audit frequency is finalized based on risk level:
    - High: Every 1-2 years
    - Medium: Every 2-3 years
    - Low: Every 3-5 years
    - After finalization of the strategic risk assessment and audit plan, Annual audit schedule documented using RD-5-04a and approved by Quality System Management Team.

The relevant processes are described in QMS-5-04 Internal and External Audits.

7.4.1 Management of deviations and CAPAs

This chapter provides the system of management of findings identified via audits performed by the MAH or by vendors (PrimeVigilance and Eversana). In case the system was in addition inspected by regulatory bodies then the findings will also be presented here as well.

Biocon Biologics

All deviations and CAPA are documented and continuously monitored to ensure the compliance with European Union (EU)/UK PV legislations. Management of deviations are described in CQA-SOP-0009 and CAPAs are described in CQA-SOP-0013.

The objective of a CAPA system is to continuously improve the Biocon Biologics PV quality system to make it compliant, effective, and efficient.

7.4.2 Biocon Deviation management

A procedure for deviation handling is in place. This involves systematic identification, evaluation, and investigation of deviations (root cause and impact analysis) to ensure appropriate corrective and / or preventive action (CAPA) is taken to avoid recurrences. Any deviation is routed through a deviation review and approval process. The review is done in a deviation review team comprising of the originator function, RQA-Clinical, CQC (if needed) and other cross functional affected teams (if any). A deviation is classified either as a critical, major or minor, with immediate notification of critical deviations to the management. Deviation management also includes post-CAPA implementation assessment for effectiveness and closure.

Deviation management covers deviations to the following:

- Approved procedures (internal and external), established standards and regulatory requirements
- At sponsor (internal), and at study sites and vendors (external)

The deviations along with appropriate CAPAs if applicable are approved by BBL RQA-Clinical.

List of deviations are included as Annex G03.

7.4.3 Biocon CAPA management

Upon identification of the root cause in the deviation necessary corrective and preventive measures are initiated. Proposed CAPA will be compliant, effective, and efficient. The suggested measures are approved by BBL RQA-Clinical.

All tasks/action plans in the approved CAPA will be initiated, completed, and documented within agreed timelines by respective owner of CAPA.

Corrective actions and preventive actions (CAPAs) are managed through a procedure. The CAPAs originating from deviations, audits (performed by RQA-Clinical), inspections (formal audits by

regulatory agencies), and audits by research partners, internal depts., external consultants are logged and tracked for appropriate closure.

PrimeVigilance CAPA management

Audit reports will be reviewed on receipt by the QA team. A CAPA plan will be developed for all critical and major findings, to determine the root cause of the findings and why they occurred, as well as how they can be corrected and further prevented. The need for effectiveness assessment will also be determined based on the root cause and actions proposed. All Audit CAPAs will be tracked and managed in QMCS.

All Audit CAPAs will be reviewed and approved by QA Management as well as the SME/Department Head. The CAPA plan will be shared with the auditor, within the assigned timelines for approval. A CAPA plan will be considered closed once all actions are completed and effectiveness is assessed (as required). Significant CAPAs (Critical and Major) from audits will be shared with Biocon Biologics and included in the PSMF Core and ANNEX G until the closure of the CAPA.

PrimeVigilance Deviation management

This process for the Management of Deviations and CAPAs is governed by PVL-GENSOP-008. Any deviation identified during day-to-day activities against a:

Regulatory requirement.

PrimeVigilance controlled procedure.

PrimeVigilance Quality Standard.

must be reported via an electronic form to the Quality team and notified to the Project Manager by the PrimeVigilance employee who identified the deviation or received feedback from Biocon within one business day of the deviation being identified.

The Quality team will review the deviation and:

Enter the details of the deviation into the Deviation Tracking tool and/or QMCS, as applicable; Assess the grading of the deviation.

Determine if a CAPA plan is required.

Notify the Global Quality Council and the Head of PV Operations/MI of any potentially critical deviations.

Deviations where no further action is required are closed.

For Deviations where a CAPA plan is required:

The Quality team completes the CAPA form with information already received for the deviation and sends to the Deviation Owner.

The Deviation Owner proposes any corrective or preventive actions based on the identified root cause and specifies how and when effectiveness assessment will be performed.

The Quality team reviews the proposed CAPA plan and, once agreed, ensures further review and approval of the CAPA plan by the:

Relevant Department/Unit Head for Major and Minor graded deviations

Head of PV Operations/Head of MI and Head of Quality for Critical graded deviations

Eversana CAPA and Deviation management

Quality Nonconformance Reports

General reporting mechanism for any instances of non-compliance, deviations, quality issues, client service-related complaints, as well as tracking audit findings

Nonconformance – An internally identified instance of Eversana not adhering to a procedure, policy, regulation, contract, etc. Also includes internally identified quality issues or system outages (e.g. Eversana did not follow SOP on holding quarterly management review meetings)

Client/Customer Complaint – A complaint from a client or customer regarding the quality of services being provided to the client. Also includes instances of noncompliance brought to Eversana attention externally through a client. (e.g. client complaining that Eversana has been routinely sending cases late)

Entire process is managed using QNCR/CAPA Module in the Intelex system, along with a specialized form for collecting and structuring the information in an easily exportable format.

Treated as individual action items to remediate issues and trends.

CAPAs are child records of a parent QNCR.

In other words, a QNCR can have one or many CAPAs attached to it, or a QNCR may have no CAPAs at all.

CAPAs contain the following information:

Action Required - A description of what steps need to be taken.

CAPA Assigned To - A person the action is assigned to.

CAPA Target Date - A target date for implementation or completion of the action

Once completed, CAPA record is updated with the Date of Completion, a summary of what was completed, and evidence of completion is attached.

Effectiveness Checks / Verification:

All CAPAs must undergo CAPA effectiveness verification, which is scheduled for 60 or more days after the latest CAPA is completed.

Investigator or CAPA owner is assigned the task of assessing whether or not the CAPA(s) was/were effective in resolving the root cause and preventing recurrence.

The relevant processes are described in QMS-5-05, Quality Nonconformance & CAPA.