WHO-PQTm SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Inmazeb [1]
Manufacturer of Prequalified Product:	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707 U.S.A.
Active Pharmaceutical Ingredient (API):	Atoltivimab, maftivimab, and odesivimab
Pharmaco-therapeutic group (ATC Codes):	J05A-X (Other antivirals)
WHO recommended therapeutic indication:	Treatment of infection caused by *Zaire ebolavirus*

1 Introduction

Inmazeb (atoltivimab, maftivimab, odesivimab-ebgn) is a combination of 3 recombinant human IgG1, κ monoclonal antibodies (mAb) directed against the Ebola Virus surface glycoprotein (EBOV GP). Each individual mAb drug substance (DS) is produced by recombinant DNA technology using Chinese Hamster Ovary (CHO) cells.

The prequalification of this product by the WHO Prequalification Team Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely "U.S. FDA" (https://www.fda.gov) in line with the "WHO Procedure for Prequalification of BTPs or their corresponding SBPs"[2].

Hence, no assessment of the data underlying this approval has been undertaken within PQTm. However, according to the above-mentioned guidelines, WHO requested additional data for the safe use of the product in regions relevant for prequalified products and this information is included in this section of the WHOPAR.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

[2] https://extranet.who.int/prequal/sites/default/files/document_files/01_Prequalification_procedure_General.pdf

2 Assessment of Quality

Product packaging and shipping

The assessment of the packaging and shipping of the product has been done according to the principles laid down in the WHO guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23), partially applicable also to biotherapeutics.

The Applicant performed qualification studies providing evidence that the shipment boxes are able to maintain temperatures of 2 – 8 °C when challenged to an ambient maximum temperature range between 46.5 – 51.5 °C for 30 hours and at 23.4 °C for 96 hours. The applicant also provided the performance qualification data demonstrating that the active container can maintain the required temperature when exposed to fluctuating real-world temperature for 166 hours. Real-world transport validation studies have been performed by the applicant for multiple commercial programs successfully qualifying the use of the shipment containers across multiple climate zones. Confirmatory real-world transport validation was completed using the labeled drug product to demonstrate that there is no impact to product quality (including chemical, physical, and microbiological product specifications) under real-world shipping conditions and to confirm that cold chain and pallet/packing integrity is maintained.

The shipments are continuously monitored by a minimum of two calibrated temperature logging devices from the moment the pallets are dispatched until they are received at their final storage destination.

Finally, the applicant provided the stability studies supporting short term temperature excursions.

Arrangements for handling complaints and product recalls

The applicant provided information on the procedure for the identification, handling and management of product complaint, identification, handling of critical product complaints including decisions, requirement and process for information to authorities and handling of product recalls.

The procedure for handling product quality complaints and product recalls submitted by the applicant provides details, among others, on the complaint triage performed to establish whether an investigation is required, risk classification, investigation timelines and complaints trend analysis. The description of the applicant procedures details also the established timelines for potential market actions, recall notification to National Medicines Regulatory Authorities, description of the recall arrangements and actions to put in place at the distribution level, as well as description of the periodical mock-recall.

The applicant confirmed that the handling of complaints and recalls are also clearly defined in the agreements or contracts between the manufacturer and relevant third parties.

Stability of the product

Shelf-life of 54 months at 5 °C

Store Inmazeb vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake. If diluted:

- 0.9% Sodium Chloride Injection, USP - Store at room temperature up to 25°C (77°F) for no more than 8 hours or refrigerated at 2°C to 8°C (36°F to 46°F) for no more than 24 hours.

- 5% Dextrose Injection, USP - Store at room temperature up to 25°C (77°F) for no more than 4 hours or refrigerated at 2°C to 8°C (36°F to 46°F) for no more than 24 hours.

- Lactated Ringer's Injection, USP - Store at room temperature up to 25°C (77°F) for no more than 4 hours or refrigerated at 2°C to 8°C (36°F to 46°F) for no more than 4 hours

Conclusion: The quality part of the dossier is accepted.

Pharmacovigilance - WHO PREQUALIFICATION-SPECIFIC ADDENDUM to the RMP

WHO assessed the latest SRA-approved Risk-Management Plan (RMP) and post-marketing safety reports together with a WHO PQ-specific addendum to the RMP according to the structure detailed on the WHO-PQT website[3]

The WHO-prequalification-specific addendum to the RMP is reported below.

Conclusion: The pharmacovigilance part of the dossier is accepted.

[3] https://extranet.who.int/pqweb/sites/default/files/documents/RMP_AddStructureDec2019-2.pdf

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Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASR	Annual Safety Report
EBOV	Zaire Ebola Virus
EEA	European Economic Area
EMA	European Medicines Agency
ETU	Ebola Treatment Unit
EVDAS	EudraVigilance Data Analysis System
FAERS	FDA Adverse Event Reporting System
GP	Glycoprotein
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
IECs	Independent Ethics Committees
IRBs	Institutional Review Boards
IRRs	Infusion-related reactions
LMIC	Lower Middle-Income Countries
NAPs	Nationally Approved Products
PV	Pharmacovigilance
QAA	Quality Assurance Agreement
RMM	Risk Management Measure
RMP	Risk Management Plan
sGP	Zaire Ebola Virus Glycoprotein
SAR	Suspected Adverse Reaction
SHR	Systemic Hypersensitivity Reaction
SMT	Safety Monitoring Team
SRA	Stringent Regulatory Authority
USPI	United States Prescribing Information
WHO	World Health Organization

1. INTRODUCTION

Inmazeb (combination of atoltivimab, odesivimab, and maftivimab, also referred to as REGN-EB3) for the treatment of infection caused by Zaire ebolavirus was invited for the World Health Organization (WHO) prequalification programme. Detailed information relevant to the indication are provided in the REGN-EB3 Core Risk Management Plan (RMP) version 1.0 and in the Inmazeb United States Prescribing Information (USPI).

1.1. Product overview

Trade name (INN name)	INMAZEB® (combination of atoltivimab, odesivimab, and maftivimab)
Brief description of the product	**Summary of mode of action:** INMAZEB, also known as REGN-EB3, is a combination of 3 recombinant human IgG1κ monoclonal antibodies (atoltivimab, odesivimab, and maftivimab), each targeting a different epitope on the Zaire Ebola virus (EBOV) glycoprotein (GP). Atoltivimab combines neutralization and Fc gamma receptor 3A (FcyRIIIa) signaling activities. Odesivimab is a non-neutralizing antibody that induces antibody-dependent effector function through FcyRIIIa signaling when bound to its target. Odesivimab also binds to the soluble form of Zaire ebolavirus glycoprotein (sGP). Maftivimab is a potent neutralizing antibody that blocks entry of the virus into susceptible cell lines. Importantly, the 3 antibodies that make up the combination bind to 3 non-overlapping epitopes on GP and all 3 antibodies can bind the GP simultaneously.
Invited indication for WHO pre-qualification:	Treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients, including neonates born to mothers who are RT-PCR positive for *Zaire ebolavirus* infection.
Invited drug product(s)	A combination of atoltivimab, 241.7 mg, maftivimab 241.7 mg, and odesivimab 241.7 mg per 14.5 mL (16.67 mg/16.67 mg/16.67 mg per mL) in a single-dose vial. A combination of 483.3 mg of atoltivimab, 483.3 mg of maftivimab, and 483.3 mg of odesivimab per 14.5 mL (33.33 mg/33.33 mg/33.33 mg per mL) in a single-dose vial.
Posology	Proposed (in accordance with US approved label): The recommended dosage of REGN-EB3 is 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg diluted and administered as a single IV infusion.
Current Marketing Authorisation(s)	United States of America (Approval: 14-October-2020)

1.2. Summary of Safety Concerns

There are no important identified or important potential risks associated with Inmazeb.

Important identified risks	None
Important potential risks	None
Missing information	None

1.3. Pharmacovigilance activities and risk minimisation measures for the safety concerns

Routine Pharmacovigilance Activities	Beyond Adverse Reactions Reporting and Signal Detection: Specific adverse reaction follow-up questionnaires for use during pregnancy
Additional pharmacovigilance activities	None
Routine Risk Minimization Measures	Not applicable - No safety concerns.
Additional Risk Minimization Measures	Not applicable – No safety concerns.

1.4. Acknowledgement from the Applicant

Regeneron acknowledges that the healthcare settings and infrastructure may vary between countries and that following prequalification, the adequacy of safety concerns, PV activities, risk minimization measures and traceability of the product at a national level, will be evaluated. Furthermore, should any new safety concerns be identified, Regeneron will implement any necessary Pharmacovigilance (PV) activities and risk minimization measures at a national level. Furthermore, Regeneron asserts it will implement sufficient PV activities, risk minimization measures and product traceability following product prequalification.

2. SAFETY CONCERNS AND PV ACTIVITIES

2.1. Safety Concerns

As mentioned in Section 1.2, there are no important identified or important potential risks associated with REGN-EB3. Identified risks (not considered important) include Systemic hypersensitivity reactions (SHRs), including acute infusion-related reactions (IRRs). Aside from IRRs and Hypersensitivity (including anaphylaxis),there are no other ADRs expected for REGN-EB3 at this time. Risk minimisation measures are included in the REGN-EB3 product information (e.g., USPI) which provides clear instructions on management of IRRs and SHRs. In terms of applicability in Lower Middle-Income Countries (LMICs), physicians working in hospitalized or local clinic settings, where Inmazeb will likely be used, have experience in recognizing and managing effects resulting from IRRs and systemic hypersensitivity (anaphylaxis). In addition, REGN-EB3 is expected to be used for the treatment of infection caused by Zaire Ebola virus in the Ebola Treatment Unit (ETU). This set-up allows for appropriate administration of REGN-EB3 and management of adverse events through close observation of patients by medical staff and availability of appropriate emergency care in case of severe hypersensitivity/anaphylaxis, if necessary.

Regeneron global PV system includes Signal Detection and Management processes which identify, assess and address any potential safety issue in a timely and effective manner to ensure that Regeneron products' risk profiles are continuously monitored. Signal detection activities are performed on safety data collected locally (e.g., Individual Case Safety Report (ICSR)), and globally (e.g. medical literature, Eudravigilance). For each product, a Signal Detection Plan is in place which outlines the Events to Monitor, Adverse Events of Special Interest (AESIs), standard routine signal detection activities, and product specific signal detection activities. The outcome of the PV activities performed globally and locally could lead to a re-evaluation of the adequacy of the safety information described in the local RMP, a potential further revision and local adaptation. In addition, the safety profile of medicines approved in individual countries is also monitored by national Health Authorities, which can request the local affiliates to modify the local RMP and the PV measures in place in order to address any new identified safety concerns or situations.

The product label is available on public websites such as FDA's Drug Database, Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/) and Regeneron's website (https://www.inmazeb.com/) and can also be provided on local authority's websites.

When required, non-promotional product education material can be provided by Regeneron to ensure health-care professionals (HCPs) are adequately informed and trained about the product. In addition, HCPs have the opportunity to directly contact a Regeneron representative responsible for inquiries through a dedicated medical information hotline.

The effectiveness of routine risk minimization activities at the local level is generally monitored by the frequency (spontaneous reporting rates) and/or severity of an adverse reaction at local level in relation to patients' exposure via signal detection activities, which provides an overall measure of the level of risk control that has been achieved with any risk minimization activity in place.

In case of additional PV and/or risk minimization activities, effectiveness measures are also typically monitored by "Process indicators", i.e., measures of the extent of implementation (e.g., distribution records of risk minimization material), which are tracked and recorded via

specific Regeneron processes. The actual success rate is calculated based on the success assessment criteria and determined in advance for the methods of distribution. In case the actual success rate is lower than the predefined target success rate, appropriate actions are taken as defined in the local implementation strategy or could be discussed directly with the local health authority if applicable.

2.2. PV activities

Regeneron has an established pharmacovigilance system to collect and collate adverse event and special situation reports, associated with Regeneron medicinal products originating from unsolicited (spontaneous sources, literature, lay-press/media, internet etc.) and solicited sources (clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs etc.). The system is designed to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for clinical assessment. All notifications that contain pharmacovigilance data are recorded and archived in compliance with the applicable data protection requirements. The system is structured in a way that allows for reports of suspected adverse reactions to be validated in a timely manner and exchanged with competent authorities within the legal submission time frame.

Safety signals can arise from a wide variety of data sources. This potentially includes all scientific information concerning the use of medicinal products and the outcome of the use, i.e., scientific literature, product quality, non-clinical and clinical data (including pharmacovigilance and pharmacoepidemiologic data). Regeneron proactively identifies and evaluates potential safety signals from these sources and continuously monitors the risk-benefit profile of its medicinal products. The Regeneron signal detection process includes the periodic monitoring of the Regeneron Global Safety database and FDA Adverse Event Reporting System (FAERS).

In addition, depending on the product, a ‘review of national databases, the EudraVigilance Data Analysis System (EVDAS) and the database of the World Health Organization (WHO) Programme for International Drug Monitoring (VigiBase) may also be conducted. Regeneron’s global PV system employs a robust and comprehensive process for signal detection, validation, prioritization, and assessment. The process ensures appropriate escalation to the company's governance body, in addition to the prompt communication of safety concerns to regulatory authorities, Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), investigators, treating physicians, and the public throughout the product lifecycle.

Signal detection strategies are employed to systematically review safety data and may involve a review of Individual Case Safety Reports (ICSRs), statistical analyses, or a combination of both; trend analysis; and/or an aggregate assessment, depending on the size of the data. Safety data (e.g. AE reports) collected at a national level from the use of REGN-EB3 will also be integrated into the global PV system described above and undergo signal detection activities, to monitor its safe use and to ensure a positive benefit-risk profile. This will be achieved via an online Regeneron AE collection form that can be accessed in local territories ensuring safety data relating to the use of REGN-EB3 are systematically collected, enabling evaluation of causality and identification of new safety signals or changes to the safety profile of the product. Additionally, Suspected Adverse Reactions (SARs) may be reported by phone. Adverse event reporting details for both methods are included in the labelling document. This

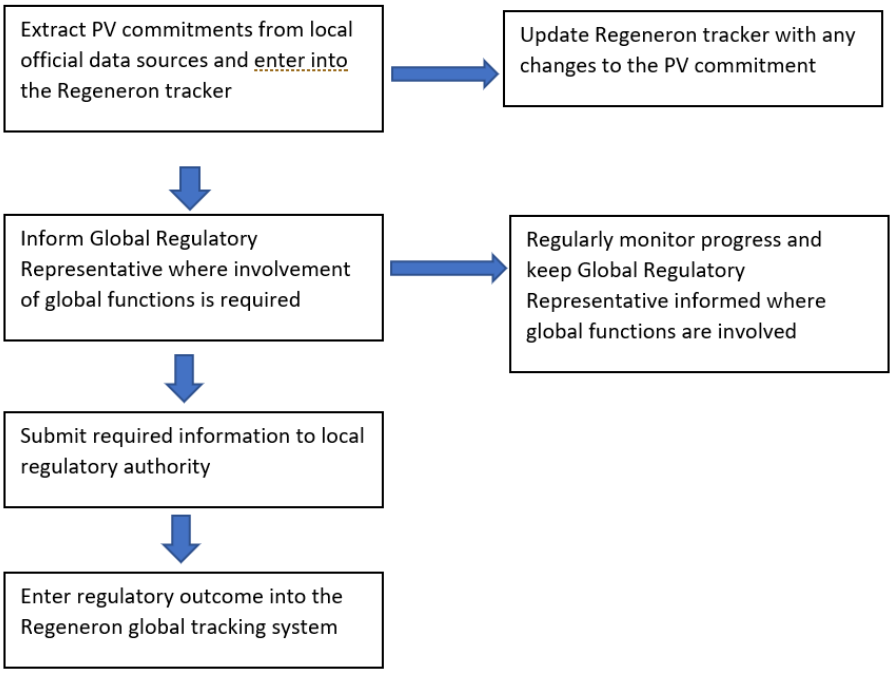
process also allows for assessment of any additional PV activities required to address local specificities, in terms of epidemiology (e.g. infection), healthcare infrastructure, clinical practice, socioeconomic and other factors, that may change the benefit/risk profile defined within local settings.

Furthermore, Regeneron confirms that the company affiliate or company representative will establish contact with the appropriate PV contact/function within the national PV centre (e.g. Ministry of Health) or National Regulatory Authority. In countries where a local PV point is not present, a Regeneron Affiliate or representative responsible for that particular country will confirm who the appropriate contact is to establish contact for PV questions between the company and the National Regulatory Authority or other National Health Agency/Organization.

As stated earlier, REGN-EB3 has no safety concerns and therefore no additional PV or risk minimisation measures are required. However, should any additional PV and risk minimization activities be required once approved by a competent authority, these are considered PV commitments. The overview of adherence to Risk Management Plan (RMP) commitments is monitored by the Regeneron RMP Implementation Coordinator.

Following confirmation or approval of a new/updated RMP, the RMP Coordinator utilizes the RMP Implementation Tracker to document the implementation status of RMP activities (i.e., those noted in PV Plan and additional risk minimization measures (RMM)). This provides oversight of adherence to Regeneron defined submission timelines for additional risk minimization activities. The RMP Coordinator also obtains progress updates, via Safety Monitoring Team (SMT) meetings, from the stakeholders, vendor(s) and Alliance Partner(s) responsible for implementing the PV plan and/or RMMs. The RMP Coordinator maintains the RMP Implementation Tracker and files it within the departmental secure site and shares progress updates with the Head of Global Patient Safety. The process for tracking PV commitments for Nationally Approved Products (NAPs) in EEA countries and all non-EU country specific requirements is shown in Figure 1.

Figure 1: Tracking PV Commitments for Nationally Approved Products within the EEA Countries and All Non-EU Country Specific Commitments



Core RMPs are generally adopted at local level as the main reference for risk minimization activities, which can be further adapted depending on several variables across countries (and approved by local regulatory authorities if applicable) as well as revised to add additional risk minimization activity, if required.

Following WHO pre-qualification, Regeneron confirms Periodic Safety Reports, will be prepared and submitted in accordance with national requirements.

2.3. Product traceability

Regeneron ensures traceability of bulk inventory using an electronic system which covers the entire Regeneron supply chain for our finished products up to shipment to the first-tier customers (i.e. first party outside of Regeneron control). Traceability beyond this point is under the responsibility of the customer. Regeneron acknowledges the healthcare settings and infrastructure within each country will vary. If a decision is made to pursue licensing within a country, Regeneron would engage with wholesale / distribution partners with expertise within the country. The selection process would include a review of the product traceability systems for the product.

AE reports will be collected electronically through the Regeneron website and via a dedicated medical information hotline, details of which will be provided in the country-specific product label. If either the name or batch number is missing, follow-up requests will be initiated to request this information from the reporter. These follow-up attempts are documented, and if the reporter is unwilling or unable to provide the missing information, this is also documented within the case.

Where product traceability concerns may be highlighted, Regeneron would propose an additional control within that country to provide a Dear Healthcare Provider Letter (DHPL) to accompany the product. The DHPL would state the batch number and expiry date of product being delivered and include guidance to report the batch number of the administered product along with the adverse event report, in order to improve traceability of REGN-EB3. The responsibility of the DHPL would reside with the first-tier customer. This responsibility would be documented in a Quality Assurance Agreement (QAA), or equivalent agreement.