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:	Herzuma [1]
Manufacturer of Prequalified Product:	Name and address of the manufacturer of the biological active substance CELLTRION Inc., 20 Academy–ro 51 beon-gil Yeonsu-gu, Incheon, 22014, Republic of Korea
Active Pharmaceutical Ingredient (API):	Trastuzumab
Pharmaco-therapeutic group (ATC Codes):	Antineoplastic agent, monoclonal antibody (L01XC03)
WHO recommended therapeutic indication:	early stage HER2 positive breast cancer or metastatic HER2 positive breast cancer

1. Introduction

Herzuma (trastuzumab) is a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures.

The prequalification of this product by the WHO Prequalification Team: Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely the "European Medicines Agency" (EMA http://www.ema.europa.eu/ema/) in line with the "WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities"[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

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 provided data to demonstrate the maintenance of the required 2°C - 8°C temperature conditions during shipment when the shipping container is exposed at extreme environmental conditions. Furthermore, the Applicant provided evidence that the shipment set up can be successfully

[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://www.who.int/medicines/regulation/biotherapeutic_products/en/

performed for all shipments and will meet the required criteria. The data are considered in compliance with WHO requirements.

The Applicant confirmed also that the products are shipped through a direct route and are managed to arrive at the airport of final destination within 48 hours unless unavoidable.

The Applicant provided evidence that temperature data loggers will be used for every shipment and that they will be programmed to show an alert on the device when exposed to temperatures outside the required range (2°C - 8°C).

The Applicant confirmed also that information and training required for handling the temperature monitoring device at the packing/sending and receiving sites will be provided.

Arrangements for handling complaints and product recalls

The procedure for handling product quality complaints and product recalls submitted by the Applicant provides details, among others, on the criteria to define the complaint criticality to assign the risk classification, the investigation process, established timelines for effective recall system, definition of the risk of the quality issues, corrective and preventive actions, established timelines for recall notification to National Medicines Regulatory Authorities and WHO, 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 will also be clearly defined in the agreements or contracts between the manufacturer and relevant third parties.

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://www.who.int/medicines/regulation/RMP_AddStructureDec2019-2.pdf?ua=1)

WORLD HEALTH ORGANISATION PREQUALIFICATION SPECIFIC ADDENDUM TO THE EU-RMP FOR CT-P6 (Herzuma®)

1. Product information

Marketing Authorisation Holder	Celltrion Healthcare Co., Ltd.
Product Name:	Herzuma®
Active Ingredient(s):	Trastuzumab
Pharmaco-therapeutic Group (ATC Code):	Antineoplastic agents, monoclonal antibodies (L01X C03)
Indications for WHO PQ	*Metastatic Breast Cancer (MBC)* - As monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone-receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments. - In combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable. - In combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. - In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab. *Early Breast Cancer (EBC)* - Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). - Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. - In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin. - In combination with neoadjuvant chemotherapy followed by adjuvant Herzuma therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter. Herzuma should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Posology for WHO PQ	*Metastatic breast cancer* *Three-weekly schedule* The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. *Weekly schedule* The recommended initial loading dose of Herzuma is 4 mg/kg body weight. The recommended weekly maintenance dose of Herzuma is 2 mg/kg body weight, beginning one week after the loading dose. *Administration in combination with paclitaxel or docetaxel* In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of trastuzumab (for dose, see the Summary of Product Characteristics (SmPC) for paclitaxel or docetaxel) and immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated. *Administration in combination with an aromatase inhibitor* In the pivotal trial (BO16216), trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration (for dose, see the SmPC for anastrozole or other aromatase inhibitors). *Early breast cancer* *Three-weekly and weekly schedule* As a three-weekly regimen the recommended initial loading dose of Herzuma is 8 mg/kg body weight. The recommended maintenance dose of Herzuma at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. *Breast cancer* *Duration of treatment* Patients with MBC should be treated with Herzuma until progression of disease. Patients with EBC should be treated with Herzuma for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended. *Dose reduction* No reductions in the dose of Herzuma were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

	If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Herzuma should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up. *Missed doses* If the patient has missed a dose of Herzuma by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. The patient who missed the dose should not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively. If the patient has missed a dose of Herzuma by more than one week, a re-loading dose of Herzuma should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent Herzuma maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively. *Special populations* Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition. *Paediatric population* There is no relevant use of Herzuma in the paediatric population.

2. Summary of Safety Concerns

For global harmonisation, safety concerns about Herzuma for WHO PQ are aligned with those included in the latest approved version of the EU RMP for Herzuma. In addition, local specific condition can be considerable and the local specific RMP could address to those at national level to ensure upon request of regulatory authorities. The applicant will assess the local healthcare settings and practice, infrastructure, epidemiology in the area where the product will be newly marketed, in comparison to the EU setting. It will contribute to identify any potential safety concerns which are newly arisen depending on the local specific condition.

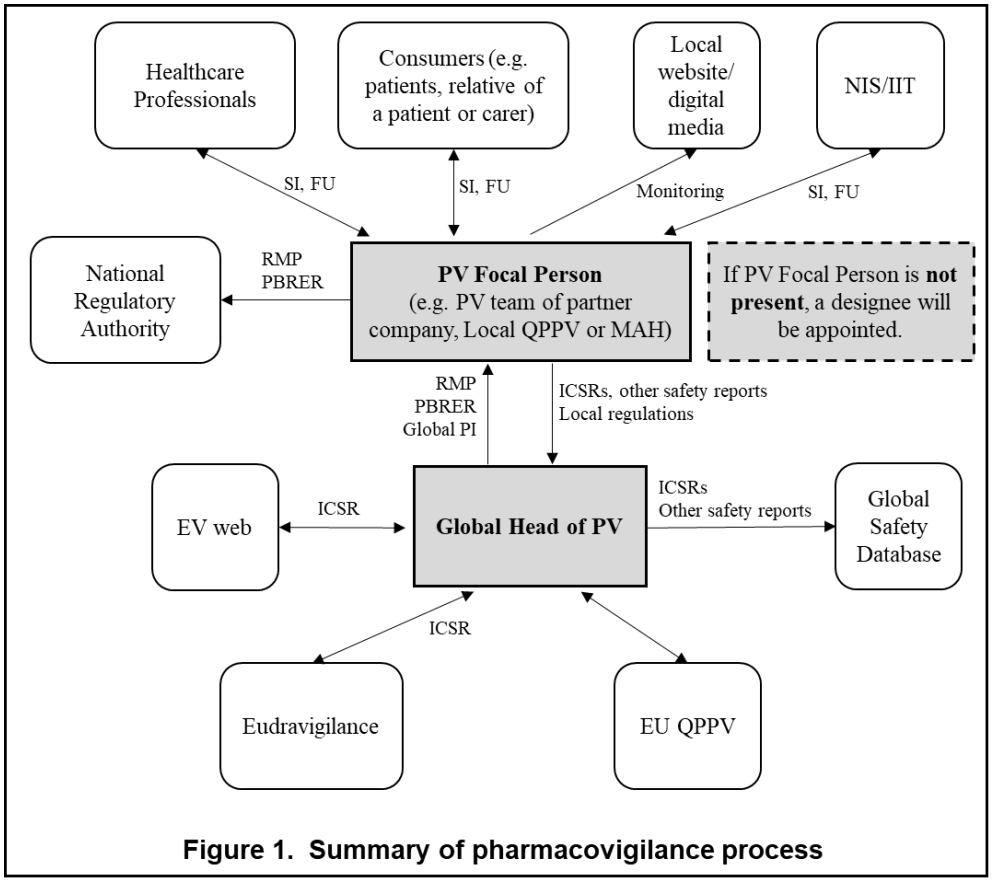
List of safety concerns	
Important identified risks	Cardiac dysfunction Administration-Related Reactions (ARRs) Haematotoxicity Oligohydramnios Pulmonary disorders
Important potential risks	Infections Medication errors (e.g. reduced efficacy due to SC administration of IV formulation, incorrect dosing leading to adverse events)
Missing information	Treatment in male patients Safety of 75mg/m^2 v 100mg/m^2 docetaxel dose

3. Pharmacovigilance Activities Specified for WHO PQ

The applicant will establish contact with a PV responsible person at the national PV centre or national regulatory authority (NRA) of the country for all safety issues in order to ensure the systematic and effective functioning of PV activities through regular reporting of ADRs. The applicant will appoint a designee/designees in countries where a PV responsible person is not present according to the local regulation. It is expected that designees to perform the majority of their functions within the bounds of that area of responsibility.

A flow chart summarising how the applicant currently communicates with NRAs is presented in Figure 1 and it will apply to the same for applicable countries. These communication flow can be modified in accordance with local regulations in NDA or procurement units after prequalification.

Figure 1. Flow chart summary



(SI = Safety Information; AEs, ADRs, quality complaints, events of special interest (e.g. Reports of overdose, abuse/misuse, off-label use, medication error or occupational exposure), FU= Follow-up, PI = Product Information, NIS/IIT=Non-Interventional Study/Investigator-Initiated Trial)

3.1 Routine Pharmacovigilance Activities

All newly acquired safety information will continue to be actively monitored in accordance with Good Pharmacovigilance Practices, including regular review and evaluation of cumulative data. Communication with regulatory agencies will occur through submission of individual expedited reports, and periodic pharmacovigilance reports, as needed for newly detected adverse reactions that might materially influence the benefit-risk assessment of Herzuma.The purpose of routine pharmacovigilance activities is to monitor outcomes and trends in incidence and to implement appropriate risk minimisation activities, if required.

Collection of Individual Case Safety Reports (ICSRs)

The MAH has been collecting ICSRs via solicited and unsolicited reporting such as spontaneouse cases, literature. In accordance with the regulations of each Regulatory Authority, expedited reports are submitted to the Regulatory Authority in a given timeline.

Signal Detection

The MAH has been using a validated signal detection system. The MAH also updates on safety-related regulatory actions taken by other regulatory authorities, i.e. EMA, US FDA.

Periodic Benefit-Risk Evaluation Report (PBRER)

Safety information about CT-P6 will be generated periodically in scheduled PBRERs. In the PBRER, all spontaneous and clinical cases reported during the review period are discussed in detail under the

relevant SOC. Periodic safety update reports (PSURs) will be available and submitted in accordance with the each national requirements. In addition, the applicant will discuss with the NRA on harmonisation of PSUR frequency agreed with the Stringent Regulatory Authority (SRA) in order to comply with the ICH E2C guideline.

Specific adverse reaction follow-up questionnaires

In order to obtain structured information on reported suspected adverse reactions, specific adverse reaction follow-up questionnaires has been used for following risks:

Important identified risk

- Oligohydramnios

Important potential risk

- Medication errors (e.g. reduced efficacy due to SC administration of IV formulation)

The proposed routine pharmacovigilance activities are adequate to be implemented in not only EU countries but also low-and middle-income countries (LMIC).

Current clinical practices, the healthcare settings and infrastructures may vary between EU countries and LMIC. However, no matter where patients receive Herzuma, it should be administered by healthcare professionals who are experienced in the use of this treatment (see the EU SmPC section *4.2 Posology and method of administration*). They should monitor the patients closely while giving the medicine and check if the patients get any adverse reaction. They are asked to report any suspected adverse reaction, if noticed. The package leaflet of Herzuma includes this message for the safe use of Herzuma.

In addition, the package leaflet provides information about how to report adverse reactions. Based on collected reports of adverse reactions, the MAH conducts the proposed routine pharmacovigilance activities.

Since adverse reactions are reported by healthcare professionals, the information collected in LMIC is as reliable as that of EU countries. Also, the MAH will make follow-up attempts to identify omitted information if necessary

3.2 Additional Pharmacovigilance Activities

Additional pharmacovigilance activities are not proposed for WHO PQ at the moment of application proposal. It is aligned the fact that there is no additional pharmacovigilance activities in the EU RMP.

The applicant will undertake an assessment at national level whether any additional pharmacovigilance activities are required to address local specificities that may change the benefit/risk profile defined within the SRA settings upon discussion with the NRA, in the local specific RMP. Local specificities could include epidemiology (e.g. infection), healthcare infrastructure, clinical practice, social, economic and other.

4. Risk Minimisation Activities Specified for WHO PQ

4.1 Routine and Additional Risk Minimisation Activities

Following routine risk minimisation measures are proposed based on the EU Summary of Product Characteristics (SmPC) which is company core data sheet.

Proposed routine and additional risk minimistation measures are harmonised with the EU RMP.

Safety concern	Proposed routine risk minimisation activities	Proposed additional risk minimisation activities
Important identified risk – Cardiac dysfunction	EU SmPC section: 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Important identified risk – Administration-Related Reactions (ARRs)	EU SmPC section: 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Important identified risk – Haematotoxicity	EU SmPC section: 4.8 Undesirable effects	None
Important identified risk – Oligohydramnios	EU SmPC section: 4.6 Fertility, pregnancy and lactation	None
Important identified risk – Pulmonary disorders	EU SmPC section: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Important potential risk – Infections	EU SmPC section: 4.8 Undesirable effects	None
Important potential risk – Medication errors (e.g. reduced efficacy due to SC administration of IV formulation, incorrect dosing leading to adverse events)	EU SmPC section: 4.2 Posology and method of administration 6.6 Special precautions for disposal and other handling	None
Missing information – Treatment in Male Patients	EU SmPC section: 5.3 Preclinical safety data	None
Missing information – Safety of 75 mg/m^2 v 100 mg/m^2 docetaxel dose	EU SmPC section: 4.2 Posology and method of administration	None

The proposed routine risk minimisation measure is adequate to be implemented in not only EU countries but also low-and middle-income countries (LMIC).

Upon assessment, taking into consideration how familiar healthcare professionals are with the product, local clinical practice and healthcare setting/infrastructure, the applicant will implement additional risk

minimization measures at a national level if considered necessary for example non-promotional educational material.

The applicant will ensure accessibility of SmPC where relevant, and non-promotional purpose educational materials to HCPs considering healthcare setting/infrastructure in that country. The education materials will cover that the product is only used where there are adequate facilities to implement the risk management measures (RMMs), e.g. for the important identified risk 'administration related reactions' with trastuzumab, close supervision by an experienced HCP is required in an environment where full resuscitation facilities are immediately available. This could take the form of a checklist for each of the safety concerns and the proposed actions that may be required. Implementation in national level will subsequently discussed with the NRAs.

4.2 Risk Minimisation Activities Monitoring

The applicant will monitor whether the risk minimisation measures are being implemented and whether they are effective via methodology introduced in the EU RMP, signal detection.

5. Product traceability

The essential information presented in the packaging material are provided in Annex III of EU SmPC as well as 2D barcode and serial number. Also the tertiary packaging material contains information, such as Product Name, Lot No. Quantity, Storage condition, Manufacturer and Expiry date of drug product. The applicant keeps tracking the history of drug product lot release, generating a document including a lot number, the destination of shipments, etc. This allows the applicant to track the drug product lot from manufacturing to distribution.

As EU SmPC of Herzuma® is provided for WHO PQ as product information, Product traceability can be improved by recording the tradename and the batch number of the administered product and it is stated in the EU SmPC section *4.4 Special warnings and precautions for use* as follows:

> **4.4 Special warnings and precautions for use**
>
> In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Any healthcare professional can access the information which are written on the secondary packaging of the product, so that healthcare professionals easily record relevant information in the patient file or the individual case safety reports. In addition, the applicant is collecting batch number via ICSR reporting to monitor product traceability. The applicant will try to emphasize the importance of providing the tradename and batch number when reporting adverse events in order to ensure recording of this information in the patient's file.

In addition, the applicant is collecting the tradename and batch number via ICSR reporting to monitor product traceability. If any initial ICSRs received does not include either the tradename or batch number, follow-up will be performed to procure this information.

Product traceability system for Herzuma® can be amended in accordance with local regulation by NRA or procurement unit after prequalification.

6. Conclusion

A commitment from the Applicant that they acknowledge healthcare settings and infrastructure may vary between countries, and following prequalification, they will evaluate the adequacy of the safety

concerns, Pharmacovigilance (PV) activities, risk minimization measures (RMMs) and traceability of the product at a national level. Furthermore, that the Applicant will implement sufficient PV activities, RMMs and product traceability following product prequalification even if differences, compared to Stringent Regulatory Authority (SRA)s, in healthcare settings and/or infrastructure are found at a national level.