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:	Herceptin [1]
Manufacturers of Prequalified Product:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 USA and /or Genentech, Inc. 4625 NE Brookwood Parkway Hillsboro, OR, 97124 9332 USA
Active Pharmaceutical Ingredient (API):	Trastuzumab
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agent, monoclonal antibody (L01XC03)
WHO recommended therapeutic indications:	early stage HER2 positive breast cancer or metastatic HER2 positive breast cancer

1. Introduction

Herceptin (trastuzumab) is a recombinant humanized monoclonal IgG1 antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced in mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, 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 "Health Canada 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

[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/

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 different active and passive shipping containers are exposed at extreme environmental conditions. Furthermore, the Applicant provided evidence that the shipment set up can be successfully performed for all shipments and will meet the required criteria. The data are considered in compliance with WHO requirements.

The Applicant confirmed the performance of 100% temperature monitoring for all shipments. Calibrated monitoring devices are used to assess the incoming material. Potential temperature excursions during the transport are revealed and the product quality impact is assessed against the stability data of the affected product.

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.

In case of delays in transportation the first priority is to ensure the proper storage and handling of the material. Established and documented procedures are in place to limit the time of exposure of pharmaceuticals to uncontrolled temperatures as much as possible

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, root cause investigation process and impact assessment on other batches and/or products, established timelines for effective recall system, definition of quality issues/recalls that implies notification to Authorities and timelines for 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 also provided the quality agreement provisions for complaints notified to a 3rd party customer that has to recall the prequalified product.

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)

Risk Management Plan Addendum for WHO Prequalification Pilot

Herceptin (trastuzumab) 150mg and 440mg

Based on EU RMP Version 21.0

Approval Date: See latest date in date stamps below.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
EBC	Early Breast Cancer
EEA	European Economic Area
EMA	European Medicines Agency
HER2	human epidermal growth factor receptor 2
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRRs	Infusion-Related Reactions
IV	intravenous
LMIC	Low and Middle Income Countries
MBC	Metastatic Breast Cancer
MGC	Metastatic Gastric Cancer
NAPs	Nationally Approved Product
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
SRA	Stringent Regulatory Authority

1. INTRODUCTION

1.1 INDICATION(S) AND DOSAGE(S) IN THE EUROPEAN ECONOMIC AREA (EEA)

Herceptin is indicated for the treatment of metastatic breast cancer, early breast cancer and metastatic gastric cancer in the EU. Only the breast cancer (metastatic breast cancer and early breast cancer) indications are invited for the WHO prequalification programme. Herceptin is administered intravenously at a dose of 6 mg/kg trastuzumab once every 3 weeks after a loading dose of 8 mg/kg or 2 mg/kg weekly after a loading dose of 4 mg/kg

Detailed information on the above indications and dosages in the European Economic Area (EEA) are provided in the EU RMP version 21.0 and in the Summary of Product Characteristics.

1.2 SUMMARY OF SAFETY CONCERNS

Table 1 Summary table of the Safety Concerns, Pharmacovigilance Activities and Risk Minimization Measures as per EU RMP v21.0

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cardiac dysfunction	**Routine risk communication:** EU SmPC Section 4.4 Warnings and Precautions for Use EU SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Table 1 Summary table of the Safety Concerns, Pharmacovigilance Activities and Risk Minimization Measures as per EU RMP v21.0 (cont.)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion-Related Reactions (IRRs)	**Routine risk communication:** EU SmPC Section 4.2 Posology and Method of Administration EU SmPC Section 4.4 Warnings and Precautions for Use EU SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Guidance on observation period after administration has been adequately captured in Section 4.2 of EU SmPC. **Other risk minimization measures beyond the Product Information:** Pack Size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Table 1 Summary table of the Safety Concerns, Pharmacovigilance Activities and Risk Minimization Measures as per EU RMP v21.0 (cont.)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Oligohydramnios	**Routine risk communication:** EU SmPC Section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** **(Guided questionnaire for pregnancy related adverse events)** Please see Annex 4 of the EU RMP v21 for details Global enhanced PV pregnancy program is effective and being implemented globally for the identified risk of oligohydramnios **Additional pharmacovigilance activities:** None

1.3 ACKNOWLEDGEMENT FROM APPLICANT

The Applicant 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. The Applicant will implement sufficient pharmacovigilance, risk minimization measures, and product traceability following product prequalification even if differences, compared to Stringent Regulatory Authorities (SRAs), in health care settings and/or infrastructure, are found at a national level.

2. SUMMARY OF THE METHODOLOGICAL CONCEPTS THAT WILL BE EMPLOYED AT A NATIONAL LEVEL FOR COUNTRY SPECIFIC RMPS

2.1 SAFETY CONCERNS

Based on assessment of data collected for more than 20 years since market authorization, and with an overall post-marketing exposure of 2,890,113 patients, the safety profile of Herceptin IV is well characterized and a favorable benefit-risk profile is well established in the approved oncology indications.

Before a product enters into a new market in a country, on the basis of either the Core RMP or the EU RMP (depending on the country specific requirements), the Local Safety Responsible at the Roche Affiliate for the new market country, is responsible for the preparation and implementation of a local RMP. This could be performed, as applicable, in collaboration with other Affiliate functions (e.g. Medical; Local Drug Regulatory Affairs) in order to get a full understanding of the local settings. Based on this, it will be determined whether the information included in the core or EU RMP (e.g. description of safety concerns; PV activities) is applicable to the local market, and whether there are any potential different or new safety concerns for the country in scope.. This step includes the assessment of several specific country factors that are variable across countries that could include the current practices where the product is intended for use, such as local healthcare settings, local medical practice and infrastructures, epidemiology, local label. Ultimately, this could result in a local adaptation of the RMP (e.g. including revision and/or description of local specific safety concerns) depending on specific national needs, feasibility and local regulations.

In case there is no Roche Affiliate in a certain country, the tasks/steps described above are conducted by a designated representative in the respective country or by a Roche affiliate in another country with in depth knowledge of the country of intended new launch.

Roche 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 Roche products' risk profiles are continuously monitored. Signal detection activities are performed at local levels by Local Safety Responsibles based on safety data collected at local level (e.g., ICSR), as well as by the global drug safety staff in the context of the globally collected data. For each product, a Signal Detection Plan is in place which outlines the Events to Monitor, Adverse Events of Special Interest, 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 in place, a potential further revision and local adaptation (which is primarily managed at local level by the Local Safety Responsibles). In addition, the safety profile of medicines approved locally

is also monitored by local Health Authorities, which can request the local affiliates to modify the local RMP and the PV measures in place to address any new identified safety concerns or situations.

2.2 PHARMACOVIGILANCE ACTIVITIES

Roche's global PV system employs a robust and comprehensive process to ensure signal detection, validation, prioritization, and assessment. The process ensures appropriate escalation to the company 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.

Roche proactively identifies and evaluates potential safety issues from reported adverse events (AEs) and other available safety data and assesses the potential impact of these data on the risk profile of Roche medicinal products. Established routine pharmacovigilance and signal generation activities are used to capture and review safety information, including cases entered onto the Roche Global Safety Database and information retrieved from other sources, including from regulatory authorities.

Signal generation strategies are employed to systematically review safety data, including: Customized Periodic Listings; Standardized periodic case review; Systematic, regular literature searches of internationally recognized biomedical databases; Signal Detection, Assessment and Management Using Disproportionality Analysis; Trending analysis for potential product defects.

Safety data (e.g. AE reports) collected at a national level from the use of Herceptin will also be integrated in the global PV system described above to monitor its safe use and to ensure a positive benefit-risk profile based on local practices or specificities of the areas where the product is intended for use. This is also achieved via Affiliates drug safety units in local territories that ensure that safety data relating to the use of Roche drugs are systematically collected to high standards of medical quality, enabling the evaluation of causal relationship, identification of changes of frequency, or a modification of the treated population, as well as managed in accordance with medical ethics, current local regulations and industrial requirements. This also includes assessment of any additional PV activities required to address local specificities that may change the benefit/risk profile defined within local settings. Local specificities considered could include epidemiology (e.g. infection), healthcare infrastructure, clinical practice, social, economic and other.

Roche 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 focal PV point is not present, Roche Affiliate or representative responsible for that particular country will

confirm who the appropriate contact is to establish contact for PV questions between company and National Regulatory Authority or other National Health Agency/Organization.

Overall, Herceptin is expected to be used in oncology centers, where other oncology products (e.g., biologics) are also handled, which are expected to follow PV standards.

Additional PV and risk minimization activities, once approved by the European Medicines Agency (EMA) or other national competent authority, are considered PV commitments. The overview of adherence to Risk Management Plan (RMP) commitments is monitored by two components as outlined below.

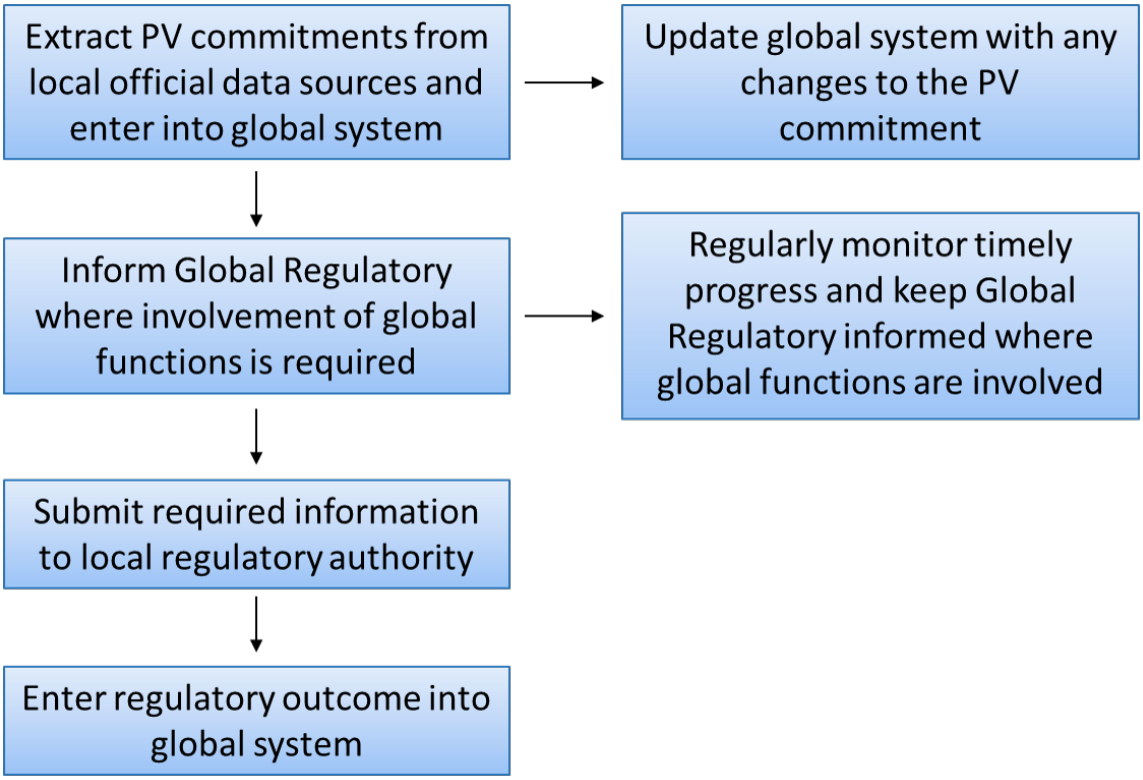
The RMP Implementation Coordinator monitors the local implementation of additional PV and/or risk minimization activities for their assigned countries (or territories) and tracks these in the relevant specific company system. This provides oversight of adherence to Roche defined submission timelines for additional risk minimization activities. This data is integrated with the product approval and marketing status and a compliance assessment is performed and documented, providing the basis for compliance metrics generated on a monthly timeframe.

All PV commitments are tracked using the relevant system which provides oversight of adherence to Regulatory Authority agreed submission timelines. 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.

Depending on requirements, which differ from country to country, Roche Affiliates establish contacts with National Regulatory Authorities, and the RMPs are submitted to the National Regulatory Authorities responsible for their assessment and approval as applicable. In countries without a National Regulatory Authority, the local Affiliates determine the local adaptation and implementation of the core or EU RMP based on local needs, following the assessment described in Section 2.1. In some situations, a “reference” National Regulatory Authority (e.g. of a neighbouring country), can assess and approve the RMP for a country where no National Regulatory Authority is present.

A Periodic Safety Update Report (PSUR) including an evaluation of all safety data collected globally during the reporting period is prepared annually (for Herceptin the data-lock point is 24 September). PSURs are submitted in the EU in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. PSURs will be prepared and submitted in accordance with the national requirements.

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



Note: The actions described in Figure 1 are all fulfilled by the appropriate local regulatory manager who has responsibility for the product in question.

2.3 RISK MINIMIZATION MEASURES

The EU RMP for Herceptin describes only routine risk minimization activities. Currently there are no ongoing additional risk minimization activities (e.g. patient or physician education programs) or additional pharmacovigilance activities (e.g. post-authorization safety studies). A description of the important identified and potential risks and associated routine risk minimization activities are provided below.

Table 2 Risk Minimization Measures

Important Identified Risks	Routine Risk Minimization Activities	Applicability in LMICS
Cardiac dysfunction **Description:** Patients treated with Herceptin are at increased risk of developing CHF (New York Heart Association [NYHA] class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Herceptin therapy alone or in combination with taxane following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin.	**Routine risk communication:** **SmPC Section 4.4 Warnings and Precautions for Use** **SmPC Section 4.8 Undesirable effects** **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC. **Other risk minimization measures beyond the Product Information:** **Pack size: Each carton contains one vial** **Legal Status: Herceptin is a prescription only medicine.**	Product information provides clear instructions on prevention, recognition and management of Cardiac Dysfunction. Applicability in LMICs All candidates for treatment with Herceptin in LMICs, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination in a center with suitable facilities by electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Patients receiving Herceptin in LMICs should receive regular cardiac monitoring, as described above in a centre with facilities suitable for LVEF assessment by ECHO or MUGA. If neither ECG, MUGA or MRI scanning is available, to monitor for cardiac dysfunction, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age.

Table 3 Risk Minimization Measures (contd..)

Important Identified Risks	Routine Risk Minimization Activities	Applicability in LMICS
Infusion-related reactions (IRRs) **Description:** The majority of acute reactions to Herceptin infusion occurr typically during the patient's first infusion, mediated by release of cytokines from immune effector cells. Incidence estimates vary depending on the definition (e.g. 5%-20% or greater).	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Guidance on observation period after administration has been adequately captured in Section 4.2 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack Size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.	Product information provides clear instructions on prevention, recognition and management of IRRs ***Applicability in LMICs*** Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms Severe reactions occasionally may require administration of vasopressors, volume expansion, and in some rare instances intubation and mechanical ventilation, which are available in LMICs If available in LMICs, drugs used to treat IRRs i.e. antipyretics, antihistamines, steroids, adrenaline, intravenous fluids should be administered. Pre-medication may be used to reduce the risk of these events. The product information states clearly that patients must receive their infusions in an oncology center where resuscitation facilities are available.

Table 4 Risk Minimization Measures (contd..)

Important Identified Risks	Routine Risk Minimization Activities	Applicability in LMICS
Oligohydramnios **Description:** Oligohydramnios is associated with risks to fetal development and therefore may have a significant impact on an individual patient. In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. The percentage of pregnancies complicated by oligohydramnios in patients exposed to Herceptin is higher than that seen in the population unexposed to Herceptin. However, this does not take into account previous or concurrent chemotherapy or radiotherapy and given the small number of pregnancies reported in the Herceptin exposed population, there is only a very limited, if at all, potential public health impact.	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.	Product information provides clear instructions on prevention, recognition and management of Oligohydramnios. ***Applicability in LMICs*** Given the risks associated with fetal development, women of childbearing potential in LMICs should be advised to use effective contraception during treatment with Herceptin and for 7 months after treatment has concluded. If a pregnant woman is treated with Herceptin in LMICs or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable.
LVEF=left ventricular ejection fraction; SmPC=summary of product characteristics		

In general, access to the diagnostic and treatment facilities needed to diagnose and manage patients with breast cancer in low and middle income countries (LMICs) would imply access to the basic diagnostic and treatment facilities that are needed to manage the key risks associated with Herceptin therapy. Herceptin is expected to be used in oncology centers with certain standards. Availability of resuscitation facilities is also required for other oncology products (e.g., biologics).

Core or EU RMPs are generally adopted at local level as main reference for risk minimization activities, which can further be 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.

Before a new market entry, the Local Safety Responsibles and/or RMP Implementation Coordinators at Affiliates assess the adequacy of the safety concerns, PV activities and risk minimization activities described in the core or EU RMP, approved by SRAs, or whether a revision is required depending on local settings in order to address potential specific national needs (see also Section 2.1). This evaluation for local adaptation, can be performed with the involvement from different functions, as applicable, at Affiliates (e.g. Medical; Local Drug Regulatory Affairs) to get a comprehensive understanding of the country settings.

For this purpose, several key elements of the country settings are taken into account such as the local medical practice, including how familiar the healthcare professionals are with the product, local regulations, local technical language, target audience in the country, local healthcare system and infrastructure including the local healthcare delivery system of the product, and local label.

In the perspective of ensuring the risk minimization activities fit the local healthcare system and adherence to treatment behavior guideline, the RMP Implementation Coordinator verifies the adherence to the local requirements, and a Compliance officer ensures the adherence to additional monitoring requirements and non-promotional content. If needed, each risk minimization activity is then expected to be adapted to local needs to ensure it is tailored for the local market. This could include for instance addition to the local label of specific guidance for the HCPs or specific requirements to be in place as routine or additional risk minimization activities.

Herceptin product information (e.g., Summary of Product Characteristics/package leaflet) provides healthcare professionals (HCPs) and patients with the essential information on how Herceptin should be used, including routine risk minimization activities. Product label is available on public websites such as EMA and FDA websites, and could also be available on local authority websites.

The Herceptin label also includes instructions for it to be used under close supervision by an experienced HCP. Local company representatives in contact with local HCPs ensure this is appropriately communicated. If deemed necessary, additional locally developed documents, e.g. checklists, can be used to inform and train HCPs about the correct use of Herceptin and the risk minimization requirements.

Additional information, e.g. on the safe use of Herceptin is also provided on the Roche website, accessible in all countries. When required, non-promotional product education material can be provided by Roche local staff on field to ensure HCPs are adequately informed and trained about the product. In addition, HCPs have the opportunity to directly contact responsible local affiliate for their country for inquiries.

Information on how Roche monitors whether the risk minimization activities are being implemented has been included within Section 2. The effectiveness of routine risk minimization activities at 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.

For 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 by local affiliates via specific Roche internal systems. The actual success rate is calculated based on the success assessment criteria customized by each affiliate 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 HA if applicable. In rare instances, a local HA can request a local study to be conducted locally to assess the effectiveness of risk minimization activities. In general, it is expected that these studies are multi-country studies and are operated by the global functions.

2.4 PRODUCT TRACEABILITY

Roche ensures traceability using an electronic system which covers the entire Roche supply chain for our finished products up to delivery to the first tier customers (i.e. first party outside of Roche). Traceability beyond this point is under the responsibility of the customer. This responsibility is emphasized under the Roche Quality Exhibit, which is an integral part of the purchasing agreement with the customer. Roche applies the same standardized procedure to all external customer deliveries globally and acknowledges the varying levels of infrastructure among them. In order to manage this we are supporting our first tier customers globally, e.g. with

- additional written guidance, for instance in performing Mock Recalls
- Roche-organized face to face trainings targeted to our customers as well as part of industry peer group initiatives (e.g. Rx360 educational stream)
- an established, focused global supply chain and affiliate quality organization. This includes sub-regional quality managers within the regions, who work closely with the local customers, e.g. by cutting out language barriers and being available for face to face interactions

Further Roche is driving initiatives to simplify the distribution chain in order to reach the patient faster by reducing the number of intermediaries.

For AE reports, if either the trade name or batch number is missing from the initial reports, follow-up requests are 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. For any case reported with generic drug trastuzumab, the case processors are therefore trained to raise follow up queries to obtain from the reporter the trade name and batch number. Once received, this information is captured in the AE report.

In addition, to ensure recording by the healthcare professionals of the trade name and batch number, the Herceptin product information/label includes a warning that the tradename and batch number of the administered product should be clearly recorded in order to improve traceability of biological medicinal products.