Individual Case Study Report

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# Guidelines (remove in final version)

The Individual Case Study Report (ICSR) should be based on the case study description linked above and written using the provided template.

Requirements:

• 4 pages in length

• double-spaced (not including references)

• minimum two obligatory EU Health Authority requirements (following, among other references, the EU and ICH guidelines, as referenced in the required readings) for the each of the following five sections

• and write a short executive summary and a conclusion by himself or herself.

Required sections for ICSR-Track on Drugs:

1. Preclinical Plan

2. Clinical Plan

3. Chemistry, Manufacturing and Controls (CMC)

4. Pre-IND Meeting / Scientific Advice

5. Inspection Readiness

~~For the track on Devices: The ICSR should contain the general requirements of identifying EU and US regulatory requirements for your Insulin Infusion Pump.~~

* Each team member will include a minimum of two obligatory Health Authority requirements (EU and US) and
* two points of comparison (EU versus US), as mentioned in the template provided.

Each should write the executive summary and conclusion by himself or herself and submit their report (maximum 4 pages).

# Overview

**Due date**: 2022/10/15

**Name**:Dylan Lawless

**Track**: Drugs

**Product Profile**: Our product is a monoclonal antibody to be used in a phase 1 clinical trial in oncology. The company is named VaudBioTech with headquarters located in Switzerland. This company is the discoverer of the product in question. The planned phase 1 clinical trial will be conducted in Germany.

**Group:** C

**Group members:** Priya Bhutada, Mouna Hadiji, Raluca Ganea, Dylan Lawless, Olivia-Augustina Colbea.

**Company:** VaudBioTech

**Product name**: Hertumig.

**Treatment**: Treatment of HER2 receptor positive breast cancer.

**Delivery**: Subcutaneous administration.

**Mechanism/target**: Similar to the mode of action from Pertuzumab and Herceptin (as illustrated in **Figure 1**), Hertumig targets a newly defined antigen of HER2 which inhibits the [dimerization](https://en.wikipedia.org/wiki/Protein_dimer) with other HER receptors, thereby preventing [signaling](https://en.wikipedia.org/wiki/HER2/neu#Signal_transduction) in ways that promote cell growth and proliferation. HER2 positive breast cancer is caused by *ERBB2* gene amplification that results in overexpression of HER2 in approximately 15-30% of breast cancer tumors. Stimulates cell proliferation and cell growth. It is a bispecific monoclonal antibody (BsMAb) which targets two epitopes.

**Discussion**: This drug is reminiscent of the classical mAb anticancer treatments; (i) similar to [Pertuzumab](https://en.wikipedia.org/wiki/Pertuzumab) (RG6264, Perjeta) from [Genentech](https://en.wikipedia.org/wiki/Genentech) which was first approved in 2012, Europe in 2013, etc. (ii) similar to [Trastuzumab](https://en.wikipedia.org/wiki/Trastuzumab), Herceptin from Genentech very well known, approval US 1998, EU 2000, WHO essential medicine.

Map

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**Figure 1**. Cryo-EM structure of HER2 (cyan) extracellular domain, Trastuzumab Fab (Herceptin - red and pink), and Pertuzumab Fab complex (Perjeta - yellow and orange). Derived from PDB 6OGE <https://doi.org/10.1371/journal.pone.0216095>.

## Part A: Preclinical Plan

A preclinical plan will be completed summarizing the work that needs to be done and included in the application for the above mentioned Investigational Medicinal Product. This consists of a short description of the preclinical studies to cover the clinical trial, namely the animal studies, the duration of treatment, pharmacology and toxicology studies in the appropriate animal model.

Guidance documents used in this plan include:

* [An introduction to little-known aspects of nonclinical regulatory writing](https://journal.emwa.org/preclinical-studies/an-introduction-to-little-known-aspects-of-nonclinical-regulatory-writing/); Nürnberg and Pierre [1].
* European Comission: ***EudraLex Volume 10 clinical trials guidelines*** (<https://ec.europa.eu/health/documents/eudralex/vol-10_en>) [2].
* European Comission: ***EudraLex Volume 10 clinical trials guidelines***: ***Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states; To guidance for the conduct of good clinical practice inspections 2008***. (see chapter 4 <https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en>) [2].
* EMA committee for medicinal products for human use (chmp): ***Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials*** (<https://health.ec.europa.eu/system/files/2016-11/18540104en_en_0.pdf>).
* ICH harmonised tripartite guideline*:* ***Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2) version step 4 2009*** (<https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf>) [3].
* ICH harmonised tripartite guideline: (<https://www.ich.org/page/safety-guidelines>), specifically section ***S9 Nonclinical evaluation for anticancer pharmaceuticals version step 4 2009*** (<https://database.ich.org/sites/default/files/S9_Guideline.pdf>) [4].
* ICH harmonised guideline: ***Integrated addendum to ICH e6(r1): guideline for good clinical practice*** ***E6(r2)step 4 version 2016*** (<https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf>) [5].
* EMA Committee for medicinal products for human use (chmp): ***Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials 2022***
* (<https://www.ema.europa.eu/en/requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational-medicinal>) [6].

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Chemical Name: Immunoglobulin G1 (human-mouse monoclonal rhuMAb HER2γ1- chain anti-human P185c-erB2 receptor) disulphided with human-mouse monoclonal rhuMAb HER2 light chain, dimer.

Molecular Formula/Molecular Weight: C6460H9972N1724O2014S44 / 148 kDa (without the N- glycan moiety).

Structure or Biochemical Description:

SB3 (trastuzumab) contains human framework regions with the complementarity- determining regions of a murine antibody (4D5) that binds to HER2. SB3 consists of 1,328 amino acids. The amino acid sequences for the heavy and light chains of SB3 are listed in the following fasta format:

>Hertumig\_Heavy\_Chain

EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR IYPTNGYTRY

ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG GDGFYAMDYW GQGTLVTVSS

ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS

GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG

PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN

STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE

MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW

QQGNVFSCSV MHEALHNHYT QKSLSLSPG

>Hertumig\_Light\_Chain:

DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS

RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ GTKVEIKRTV AAPSVFIFPP

SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT

LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

Production

Alternative method: <https://www.nature.com/articles/s41598-020-59818-2#Sec11>

Hertumig was generated by immunization of Balb/c mice

*Production and control of active substance.*

Hertumig was generated by the immunisation of Balb/c mice with cells expressing HER-2 on their surface and partially purified membranes containing p185 HER-2 according to standard hybridoma techniques.

Hybridomas were either screened by an ELISA utilising immobilised p185-HER-2 protein, an assay detecting HER-2 mediated growth inhibition of SK-BR-3 cells or a nude mice breast cancer xenograph model, resulting in muMAb 4D5.

The humanisation of muMAb4D5 was performed according to standard procedures after the determination of the primary sequence of the VH+L chain regions of muMAb 4D5.The resulting constructs were designed to express the human Fc γ1 isotype to maximally support CDC and ADCC. The resulting antibody of the humanisation huMAb 4D5-8, which expressed maximal amount of the humanised antibody, is reported to bind to ECD of HER-2 about 3-fold more tightly than muMAb 4D5.

The active substance trastuzumab is produced in recombinant Chinese Hamster Ovary cells using a serum free medium. The MCB, WCB and End of Production Cells were characterised sufficiently. MCB andWCB were adapted to growth in serum free medium.

Manufacturing process of the active ingredient starts with thawing and expansion of cells from the MCB or the WCB derived from the MCB. Cells are expanded using a seed train and fermenters from 80 liters up to 12 000 liters.

After harvesting different chromatographic steps are used for purification. With affinity chromatography (Protein A) unwanted protein and potential endotoxin contaminants can be removed. Cation ion exchange chromatography removes antibody aggregates and fragments and CHO impurities. Anion ion exchange chromatography is intended to separate DNA, endotoxin, and retrovirus, if present. With hydrophobic interaction chromatography antibody aggregates, fragments and CHO proteins can be removed. After formulation and filtration into freeze/thaw stainless steel tanks the formulated bulk can be stored at 2-80C and/or frozen and stored at –200C or lower until further processing to finished product takes place.

Process validation (active substance and finished product)

The critical steps of the manufacture of the finished product have been validated using pilot scale and full-scale batches: influence of the mixing parameters during pooling, protein yield, homogeneity during filling, simulation of an interruption during filling, homogeneity during filling tested after lyophilization, homogeneity of drying, evaluation of the lyophilization cycle. In addition, adequate in- process controls have been established and analysis of three full-scale finished product batches shows consistency of the manufacturing process. As a follow-up measure, the data on in-process and release controls for two further batches will be provided

For active substance, process validation studies were presented to demonstrate the removal of host- related DNA, Chinese Hamster ovary cell proteins (CHOP) and non-host-related impurities. Lifetime of purification columns and hold points during the purification process were validated.

Data from the validated release assays for five lots of bulk active ingredient produced at Vacaville were presented and compared to the ranges of these assays specified for trastuzumab.

Consistency of the drug substance was assessed using test methods and specifications as described in the MAA in section II.C.1.1

All results were within the specification limits and within the range of the lots produced at the previous site, South San Francisco.

Comparing the cell culture process of Vacaville and the previous manufacturing site assessed production culture performance.

All results were within the ranges of the results of the previous production. Recovery performance was assessed by comparing recovery yields of the Vacaville lots with the lots produced at the previous site and the yields of every production step were within the range of the known results. In-process controls for the Vacaville lots showed results within the specified limits.

Impurity profiles were obtained by testing for host cell proteins, host cell DNA, and residual Protein A at various intermediate stages in the process

All results were within the ranges of the lots produced at the previous site. Stability studies were performed after storage for 1 month at 37°C.

Changes observed were within the range of the changes of material manufactured at the previous site.

Further stability data are required as follow-up measure for the bulk product to reflect the anticipated storage time and conditions used during full production.

### ICH M3 R2

Acute toxicity will be assessed using single-dose toxicity studies in two mammalian species (one non-rodent) as follows;

1. mammal one - [*acute\_toxicity\_study\_report\_one.pdf*](demo)
2. mammal two - [*acute\_toxicity\_study\_report\_two.pdf*](demo)

In these studies, both the clinical and parenteral route of administration will be used (intravenous). The minimum and maximum dosages (3 - 18 mg/kg) to be administered over 90 minutes without short-term adverse effects

Each study will be conducted under GLP.

Acute toxicity results will be used in combination with the known toxicity for other mAbs to assess the potential consequences of human overdose and will be available to support Phase III.

**Table 1: Treatment Schedules for Hertumig** ….

## Part B: Clinical Plan

* Clinical Trial Protocol will be drafted for inclusion in the application for the above-mentioned Investigational Medicinal Product. In this we define the main points of the clinical trial protocol and consider a master protocol.[Ledford 2013](http://www.nature.com/news/master-protocol-aims-to-revamp-cancer-trials-1.13176) reports on “‘Master protocol’ aims to revamp cancer trials” [7] and [Woodcock and LaVange 2017](http://www.nejm.org/doi/full/10.1056/NEJMra1510062#t=article) on requirements to “Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both” [8]. Consider[*PRIME*](https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines)and[*Breakthrough Designations*](https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-breakthrough-therapies) (for comparison see FAQ 24. [here](https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies)).
* Guidance and reference is found in the ICH harmonised guideline: ***Integrated addendum to ICH e6(r1): guideline for good clinical practice*** ***E6(r2)step 4 version 2016*** (<https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf>) [5].

## Part C: Chemistry, Manufacturing and Controls, CMC

Here we will write a clear CMC plan on the work that needs to be done and included in the application for the above mentioned Investigational Medicinal Product. Emphasize the level of detail required.

Guidance and reference can be found at

* European Commission: ***EudraLex Volume 10 clinical trials guidelines*** (<https://ec.europa.eu/health/documents/eudralex/vol-10_en>) [2].
* European Commission ***EudraLex Volume 10 clinical trials guidelines***: ***Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states; To guidance for the conduct of good clinical practice inspections 2008***. (see chapter 4 <https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en> or PDF <https://health.ec.europa.eu/system/files/2016-11/18540104en_en_0.pdf>) [2].

## Part D: Pre-IND Meeting / Scientific Advice

Here we will include a summary of the project background, the questions with the opinion of the company, number of attendees, and the time for the meeting (ideally).

Advice can be found at

* Paul-Ehrlich-Institute, Federal Institute for Vaccines and Biomedicines webpage (<https://www.pei.de/EN/information/license-applicants/advice/scientific-advice/scientific-advice-node.html>).
* EMA Human Regulatory webpage for Scientific advice and protocol assistance (<https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance>).

## Part E: Inspection Readiness

Here we will write a summary of the work that a company needs to have ready before the inspection to ensure compliance to GxP. Extract some details from the Week 3 presentation. Important is to know the points the inspector normally go through during an inspection.

Guidance can be found at

* European Commission ***EudraLex Volume 10 clinical trials guidelines***: ***Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states; To guidance for the conduct of good clinical practice inspections 2008***. (see chapter 4 <https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en>) [2].
* European Commission: Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states. ***Guidance for the conduct of good clinical practice inspections*** (<https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2008_11/vpl10_an5_10-2008_en.pdf>).

## Overall strategy

Hints – With the above plans on the domains of preclinical, clinical and CMC, how would you accelerate submission process in Germany, with minimum questions from the health authorities and EC/IRB, and obtain rapid HA and EC/IRB approvals?

## Advice to Management

Hints – A short cover letter to the management on the Development Plan.

## Conclusion

Hints – A very short (two paragraphs) on why you think the regulatory strategy is well thought through and has the maximum chance of success.

# Supplemental

## Introduction on therapeutic mAb

Monoclonal antibodies (mAb) are well established as cancer therapies. As early as 1890, the neutralizing effect on diphtheria was known [9]. In 1980, human trials of mAb therapy for the treatment of lymphoma were performed and with the advent of antibody humanization later that decade, this treatment strategy became a powerful tool for precision medicine [9].

The advent and rise of mAb is a triumph for clinical medicine. Since the beginning of their modern understanding, the applications for mAb have been recognized; “a 1975 Nature paper reported how cell lines could be made that produce an antibody of known specificity” [10]. While these early days of antibody production - relying on hybridoma technology - were challenging, today mAb are often produced by isolation or transformation of Ab-producing cells taken directly from immunized animals or humans. The immunoglobulin genes responsible for the Ab of interest are subsequently transplanted into cell lines [10].

Recently (2021), the FDA approved the 100th mAb product [11]. The timeline starts in 1986 with the majority of products consisting of canonical antibodies, and a small number of alternative constructs including antibody–drug conjugates, bispecific Abs, fragment Abs, and others. While a high potential exists, the hurdles for biological drug approvals limit the number of products available thus far. “Just ten targets… account for 42% of the approvals to date”: PD1/PDL1, CD20, TNF, HER2, CGRP/CGRPR, VEGF/VEGFR, IL-6/IL-6R, IL-23 p19, EGFR, and CD19 [11].

The pharmacokinetics (PK) of monoclonal antibodies is generally well understood. The major drug disposition processes relevant for mAbs can be estimated in preclinical development. The product-specific and patient-specific factors that can affect PK behavior can be considered for successful clinical therapy [12].

Each particular mAb has unique risks. The steps to identify and minimize potential adverse effects must be clear and accurate. preclinical and clinical protocols must be established to avoid infusion reactions [13]. Preclinical validation of in vitro safety using human tissues is necessary to predict potential outcome for administration to humans. For clinical trial volunteer safety, communication must be maintained between scientists and clinicians both in phama/biotech companies and those performing clinical studies [13].

The serious risks of off-target antigen binding are well-known, particularly after the adverse outcome seen during the phase 1 trial of anti-CD28 mAb TGN1412 resulting in systemic inflammatory response in all six volunteers [14].

Despite the known potential for first-in-human studies there is no current robust way to ensure complete safety. Therefore, adherence to guidance and regulatory protocols are vital for safe and successful trials.

mAb are recognized as versatile platforms for cancer immunotherapy by directly stimulating or inhibiting immunological protein pathways [15]. The induction of antitumor immune responses can be exploited to develop new cancer treatment strategies based on tumor-specific response of natural or engineered mAb [15].

The nomenclature for our drug is defined according to the WHO International Nonproprietary Names (INN) (Programme and Classification of Medical Product) [16]. The current state of the art in anti-cancer monoclonal antibodies (mAbs) is overviewed by [Chiavernna, et al](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5319201/). [17].

Diagram

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Figure 1. Signal transduction by the HER family and potential mechanisms of action of trastuzumab. Abbreviations: EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal–related kinase kinase; PI3K, phosphoinositide 3-kinase; SOS, son of sevenless; VEGF, vascular endothelial growth factor. Reprinted from Hudis CA. Trastuzumab—Mechanism of action and use in clinical practice.

# N Engl J Med 2007; 357:39-51 DOI: 10.1056/NEJMra043186

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