MASTER'S THESIS-MASTER INNOVATION SCIENCES

Innovative appetite for snakebite antivenom: the assessment of facilitated regulatory pathways for providing access to innovative therapies for LMICs

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Abstract

Few innovative therapies for neglected diseases, such as snakebite, are being developed for LMICs. Due to regulatory voids for specific treatments in the current regulatory system, uncertainty for developers pursuing the development of these treatments arises. Recently the largest manufacturer of qualitative snake venom has withdrawn from the African market, leading to an unmet medical need. Monoclonal antibodies could be a viable alternative to the current treatments for snakebite, but the regulatory void currently disincentivizes development. However, a monoclonal antibody replacement was recently developed and approved for Rabies, despite the presence of a regulatory void. Therefore, this research retrospectively and prospectively analyzed the regulatory discussion for the two cases by interviewing stakeholders and experts in the field in order to identify which points of discussion are present in the regulatory approval process of both treatments. Insights were then linked to principles for the design of facilitated regulatory pathways in order to examine how these principles are viewed and how these can be used in the regulatory discussion to facilitate regulatory approval.

Three main points of discussion were found for both cases: (1) Regulatory categorization of a treatment, (2) A difficult to define Standard of car, and (3) How to correctly access the efficacy of the treatment. In a comparison, the potential categorization of the treatment and heterogeneity in the standard of care were perceived to have more severe consequences for the access to the snakebite treatment than the rabies treatment. The correct efficacy assessment was discussed evenly in both cases as both cases had various points of uncertainty. The discussion provided implications for the formulation of a possible facilitated regulatory pathway for mAb antivenom in LMICs. Moving the burden of clinical benefit and evidence to the post-authorization phase could be used in order to speed the time to market for snakebite victims without access to specific treatment. Increasing the level of communication and commitment between the regulator and developer could be used in order to enhance the transparency in the regulatory pathway to counteract the strategic use of the ambiguity surrounding the standard of care. Sophisticated patient stratification methods, pan-specific antivenom, and the use of workable and verifiable surrogate clinical endpoints could be used to correctly assess the efficacy. Finally, increasing the role of medicines' effects on surrogate endpoints, allows expedited access based on preliminary clinical data by counteracting uncertainty.

Keywords: Snakebite, Rabies, Monoclonal Antibodies, unmet medical need, tailor-made regulation

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List of used abbreviations and definitions

- EMA: European Medicines Agency
- EUNDS: Extraordinary Use New Drugs
- FDA: Food and Drug Administration
- FRP: Facilitated Regulatory Pathway
- HICs: High-income countries
- LMICs: Low and Middle-income countries
- MAb: monoclonal Antibody
- MAPPs: Medicines Adaptive Pathways to Patients
- Me-too products: Product mimics
- MSF: Médecins Sans Frontières
- NGO: Non-Government Organization
- NVIVO: Qualitative research software tool.
- PEP: Post-exposure prophylaxis
- SoC: Standard of Care
- SRA: Strict Regulatory Authority
- IG: Immunoglobulin
    - RIG: Rabies Immunoglobulin
        - eRIG: Equine Rabies Immunoglobulin
        - hRIG: Humanized Rabies Immunoglobulin
- RCT: Randomized controlled trial
- RFFIT: Rapid Fluorescent Focus Inhibition Test
- UMMS: University of Massachusetts medical school
- WHO: World Health Organization

1. Introduction

The development of innovative pharmaceutical treatments for neglected diseases prevalent in low- and middle-income countries (LMICs) is limited (Doua & Geertruyden, 2014). The cause of this is two-fold. First, market failure is present due to a lack of individual financial resources and the lack of a social reimbursement system in LMICs. Consequently, there is little or no incentive for manufacturers to research and develop innovative treatments for diseases that exist exclusively in these countries if patients are simply not able to afford them (Kremer, 2002; Trouiller et al., 2002; WHO, 2018c). Second, a systemic failure is present due to inadequacies in regulatory frameworks (WHO, 2018c). These inadequacies are the result of the fact that LMIC regulatory authorities, both national and supranational, are underequipped and are therefore not able to assess innovative therapies (Ndomondo-Sigonda et al., 2017) as they do not have the resources and technological means to do so (Bunnik et al., 2018). As a result, LMICs rely on the regulatory assessment and approval procedures of high-income countries (Bunnik et al., 2018) or on facilitated regulatory pathways (FRP) (Liberti, 2017).

Stringent regulatory authorities (SRAs) extrapolated existing frameworks or developed new ones for the assessment of innovative treatments for LMICs (Saidu et al., 2013). An example of such a framework is Article 58 of the European Medicines Agency (EMA) (European Parliament and Council, 2004). This framework allows the EMA's capabilities to be combined with local expertise, helping LMICs to approve innovative treatments that are perceived to be too complicated for the evaluation by local national or regional regulatory authorities in LMICs (EMA, 2013). Unfortunately, these special developed frameworks are used on a limited basis as these frameworks have standards believed to be too high for LMICs, or because LMICs do not trust the outcomes of these frameworks (Bunnik et al., 2018; EMA, 2013). For example, article 58 specifically targets LMIC markets but does not grant approval for western markets. Consequently, these initiatives are met with skepticism as local governments suspect a double standard (Bunnik et al., 2018).

In the case that generic regulation is available but inapplicable, several classes of treatment still cannot be effectively assessed by current regulatory pathways, resulting in the inconsistent and unpredictable approval of potential life-saving therapies in LMICs (Bunnik et al., 2018). Treatments that have no applicable generic regulation as it is not appropriate for the context of use and lack a tailor-made regulatory pathway are deemed to be in a regulatory void (Short, 2013). For treatments that are in such a regulatory void, a change in assessment practice is required in order to foster innovation. The lack of regulation leads to uncertainty for developers who try to develop innovative products (Foote & Berlin, 2004; Williams et al., 2018).

One class of treatment in such a void seeking approval in LMICs is monoclonal antibodies (mAb) for antitoxin purposes. The WHO noted that no regulation exists for this class of product, and that they are searching for regulatory possibilities as horse-derived immunoglobulin-based serums against toxins are being reviewed for replacement in the near future (Kaplan et al., 2012; WHO, 2017). Recently, the largest manufacturer of high-quality African snake antivenom withdrew their product from the market, leading to an unmet medical need (MSF, 2015). A new monoclonal-based treatment could help relieve this medical need by providing high-tech, affordable, safe, and efficient treatment (Laustsen et al., 2016; Laustsen et al, 2017; WHO, 2018c).

So far, only a few studies investigated how regulatory pathways can be used to authorize innovative therapies targeting neglected diseases in LMICs. At this moment, it is unknown how to assess the approval process of innovative pharmaceutical treatments for LMICs. In other words, this research intends to fill the gap in research regarding approval pathways for the fostering of innovative pharmaceutical treatments for LMICs, whilst guaranteeing standards of safety and efficacy in regulatory pathways. In order to do this, this research will study a case which has had successful approval despite such a regulatory void. Despite the mentioned difficulties for tailor-made regulatory pathways for LMICs,

Rabishield™, a monoclonal antibody-based post-exposure prophylaxis (PEP) for rabies, has had successful evaluation via a facilitated regulatory pathway for LMICs (Health Canada, 2014). This case will be used as a retrospective case study to serve as casuistic help for future treatments like mAb antivenom.

To do so, this study aims to investigate the related contemporary regulatory discussion which contributed to the successful regulatory trajectory of Rabishield™ (retrospective case) in order to translate the lessons learned to a treatment, mAb antivenom (prospective case), that currently lacks an adequate regulatory pathway and is thus in a regulatory void. The research will therefore be guided by the following research question:

How was the development process of Rabishield™ regulated with a tailor-made approval process and how can we translate the corresponding principles and learnings to the approval of innovative therapies?

Theoretically, literature (e.g. Rothwell, 1980; Wagner, 2003) mostly analyzed the impact of regulation on innovation (Ambec et al., 2013; Bason, 2018; Butenko & Larouche, 2015). This research, however, focusses on how new innovative regulation that promotes innovation can be developed by researching how to establish or adapt regulation that fosters innovation, and the process and guidance behind this regulation. This is done by investigating the regulatory discussion on the division between generic and tailor-made regulation in the facilitated regulatory pathways for both the retrospective and prospective case. As Faulkner (2009) and Hirsch et al., 2016 mention that regulation usually trails innovation, insight in the co-evolution of innovative development and regulation can help the development of regulation that promotes innovation.

Practically, a solution is required for the systemic failure as some classes of treatment still cannot be effectively assessed by current regulatory pathways. The retrospective assessment of the process leading up to the marketing approval of Rabishield™ will allow a clear overview on the discussion on evidence versus access by identifying the parts of the regulatory pathway that were standard and the parts that were tailor-made by examining the viewpoints and arguments that influenced the discussion. The information provided by this assessment can support policy advice by identifying lessons learned from the outcome of the discussion on the regulatory trajectory during the regulatory trajectory. This will then be applied to mAb antivenom: a class of treatment currently without a fit regulatory pathway. This assessment will allow for policy advice regarding development of innovative pharmaceutical treatments in a regulatory void seeking regulatory approval for LMICs.

This paper is outlined as follows: the next section describes the case in further detail. Hereafter an overview of literature discussing regulation and innovation is given, zooming in on regulation and innovation in the pharmaceutical industry, and then focusing on regulation and innovation for innovative pharmaceutical treatments in LMICs. Next, the theories used are discussed, along with a synthesis of all the elements of the theories in a conceptual model. After this the method section will explain the research design, data collection, body of evidence, data analysis, and quality protocol used to conduct the research. This is followed by the results of the research and the comparison between the cases. Finally, the discussion and conclusion of this research are presented.

2. Case description

This part will elaborate upon the cases specified in the research, starting with a basic explanation of monoclonal antibodies (mAbs). After this, the prospective case is shortly discussed in further detail, followed by the retrospective case. Finally, the regulatory background for monoclonal snake antivenom is discussed.

What are monoclonal antibodies?

Monoclonal antibodies (mAbs) are antibodies created by immune cell clones. Specified mAbs can be created to bind to almost any substance. Because of the specific targeting nature and clonal properties, mAbs can be very effective at targeting the antigen on which they are specified (Gogtay et al., 2017). As cocktails based on monoclonal antibodies are homogeneous in nature, the immune system response to a monoclonal antibody cocktail can be more advantageous (Figure 1 part B) when compared to a product which is less specific such as animal derived immunoglobulins (Figure 1 part A)(Gogtay et al., 2012; Laustsen & Dorrestijn, 2018; Kini et al., 2018). However, biological pharmaceutical products, including mAbs, are inherently different from traditional small-molecule medication due to their size and therapeutic potency. Consequently, they bring different unique regulatory issues and questions, as the assessment of their safety risks is changed as it is difficult to delineate the benefit-risk profile of mAbs (Ebbers et al., 2013; See Appendix A for generic mAb development pathway).

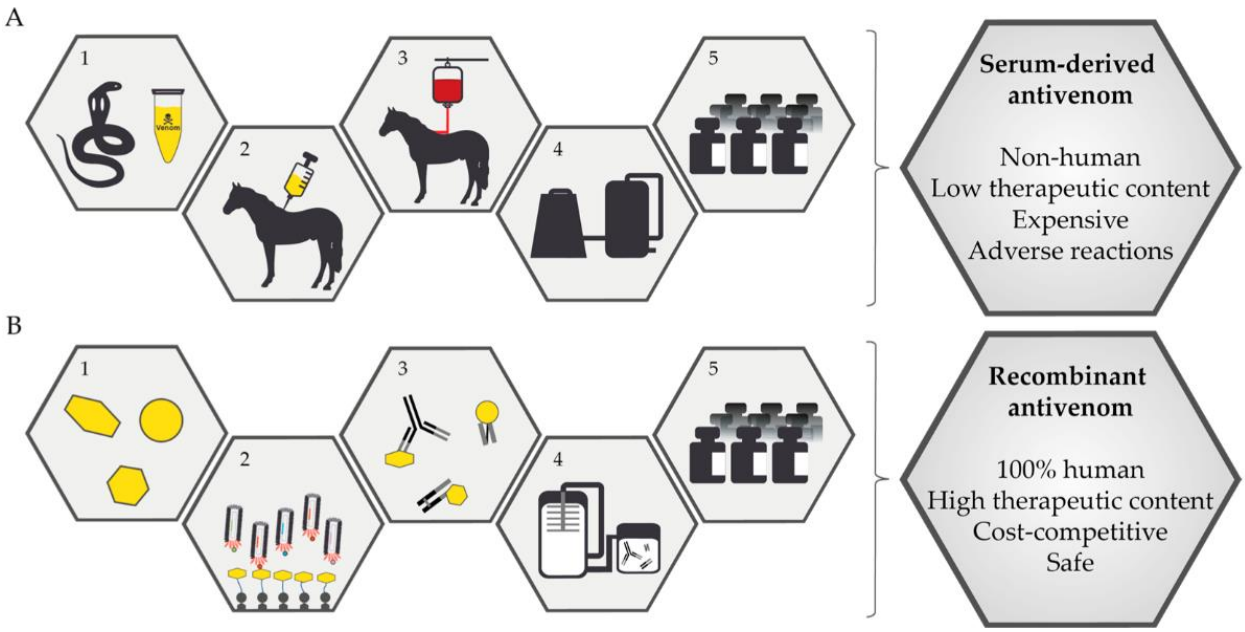

Figure 1: Serum-derived- vs recombinant (e.g. mAb) antivenom (Kini et al., 2018)

A recent WHO meeting discussing access to blood-derived immunoglobulins concluded that replacing immunoglobulins with mAbs has potential (WHO, 2018a). The meeting discussed four diseases, including both snakebite and rabies. Recently a mAb replacement for Rabies immunoglobulin, the mAb Rabishield™ has been approved despite the presence of a regulatory void, making it a suitable retrospective case for this research. Snakebite has recently been declared a neglected tropical disease by the WHO (WHO, 2019b) making it a suitable prospective case in this research.

Prospective case description: Snake monoclonal antivenom.

The prospective case in this research is represented by snake monoclonal antivenom. Snakebite is a neglected tropical disease which is estimated to cause between 81.000-138.000 deaths per year (WHO, 2019a) and leaving about three to four times as many people permanently disabled and/or disfigured (WHO, 2018b; WHO, 2019a). Snakebite is a difficult disease to treat, as snake venom differs between species, and even within species, depending on the age of the snake and their geographical location (Casewell et al., 2014; Chippaux et al., 1991; Tan et al., 2015). Because of the venom heterogeneity the quality of the antivenom is related to its match with the snake venom encountered.

The standard treatment for snakebite is an antivenom based on horse serum derived immunoglobulins that counteracts or inactivates the snake toxin (Warrell et al., 2013). However, due to the production stop and subsequent market withdrawal of the most qualitative snake antivenom, FAV-Afrique, the availability of effective and qualitative snake antivenom has dropped considerably in the African continent (MSF, 2015). As local stocks of FAV-Afrique run dry, Indian-made polyvalent antivenom is being imported into Africa. Although the Indian antivenom is specifically targeted at African snakes, it remains largely ineffective due to a low therapeutic content fraction, which detrimentally affects efficacy (MSF, 2015; Warrell et al., 2013). This results in health centers needing to using large quantities of the antivenom when victims are bitten (Warrell et al., 2013). As the antivenom contains horse-derived immunoglobulins and serum, which are foreign to the human immune system, the use of large quantities of antivenom lead to a higher chance of side effects, serum reactions, and life-threatening anaphylactic reactions in victims (Warrell et al., 2013).

As the immunoglobulins are increasing in cost, ineffective, and contain a high degree of possible side effects, continued use is not sustainable and desirable (Laustsen & Dorrestijn, 2018). The development of new snake antivenom based on monoclonal antibodies is progressing, but there is no specific regulatory pathway for this kind of treatment yet. Whilst there is regulation for serum-derived animal immunoglobulins, and for therapeutic mAbs, there is no regulation for antivenins on mAb basis as antitoxins are not considered for mAb regulation. This regulatory vacuum disincentivizes mAb antivenom development as manufacturers encounter regulatory uncertainty (Foote & Berlin, 2004; Williams et al., 2018).

Retrospective case description: Rabishield™.

Recently a monoclonal antibody against the rabies virus, Rabishield™, was approved despite the lack of specific regulation for this class of product. Due to its successful development despite the regulatory uncertainty Rabishield™ has been chosen as the retrospective case. Rabishield™ is a mAb alternative to rabies immunoglobulin (RIG) that has been developed by the University of Massachusetts medical school (UMMS) in partnership with the serum institute of India. Rabishield™ is a product developed for immediate protection against the Rabies virus, which is spread by contact with infected mammals that is almost always fatal, estimated to cause around 60.000 deaths per year (Hampson et al., 2015).

Whilst preemptive vaccination is available, possible exposure always requires booster shots for long term protection against the virus, and in severe cases RIG or Rabishield™ for immediate protection against the virus (WHO, 2018a; see appendix B for a treatment roadmap). Rabishield™ is a mAb alternative to serum-based immunoglobulins with higher hypothesized potency, specificity, and availability than the immunoglobulin-based products. As no specific regulation was available for this type of product, it did follow an adaptive approval pathway via the Canadian extraordinary use new drug submission (EUNDS), which has led to approval for Rabishield™ in India in 2017. As Rabishield™ is a product that was approved without specific regulation, it is fit to be used as a retrospective case in this study.

3. Theory

This section will first discuss an overview of literature on innovation and regulation in the pharmaceutical sector, which will then be specified for LMICs. Next, the theories and related principles that will be used to facilitate the work will be specified: The facilitated regulatory pathways presented by Liberti (2017) and the MAPPs principles provided by Eichler et al. (2018) to examine the regulatory discussion within the facilitated regulatory pathway.

3.1. Literature overview on the relation between innovation and regulation

Innovation and regulation have a precarious relation in most sectors (Ashford et al., 1985; Jaffe & Palmer, 1997; Wagner, 2003). This is because regulation was, and sometimes is still seen as having a debilitating effect on innovation by inhibiting progress and restricting freedom via compliance costs and restricted incentives (Rothwell, 1980; Ambec et al., 2013). This relation between regulation and innovation is especially prevalent in the pharmaceutical industry, where the market approval of new products is strictly regulated. This strictness is the result of historical disasters with drugs, such as the thalidomide case in 1950s (Foote & Berlin, 2004). The main aim of the strict regulation is to guarantee consumer safety as it reduces the chances of dangerous treatments reaching the market (Abraham, 1995; Scherer, 2000; Watkins, 2011). Consequently, the safety and quality need to be proven by manufacturers in various stages throughout the development process of a drug.

However, this high regulatory burden based on risk aversion also has the possibility to filter out possibly efficacious treatments. Eichler et al. (2013) mentions that false negative decisions in denying drug licenses ultimately leads to negative consequences for public health. Furthermore, Blind (2012) found that, among other regulatory practices, product and consumer safety is one of the most important regulatory practices when reviewing innovative performance, but there is no consensus on this in the pharmaceutical industry (Grabowski et al., 1978; Grabowski et al., 1983; Bax & Green, 2015). Dubois et al. (2015) notes that the compliance costs required to adhere to regulation in the pharmaceutical industry are so high that it effectively creates a barrier of entry for new companies and thus new innovations. It has also been mentioned that strict regulation discourages radical innovation in favor of incremental improvements (Scannell et al. 2012), leading to a proliferation of me-too products as opposed to new, innovative products aimed at unmet medical need (Fojo et al., 2014; Hollis, 2004; Lee, 2004). And finally, and for LMICs specifically, large compliance costs prevent the access to potential life-saving drugs or cause high out-of-pocket costs for patients (Okpechi et al., 2015. The out-of-pocket costs can result in a cycle of perpendicular poverty, as the out-of-pocket costs lead to loss of income or housing, worsening the situation for the patient and relatives (Faden et al., 2011; Wagner et al., 2011).

As a result, multiple approval pathways have been developed specifically for LMICs in response to facilitate access. However, the standards for approval are relatively stringent and HIC guidelines do not necessarily correspond with LMIC demand (Doua & Geertruyden, 2014), leading to a mismatch in the system as experiences in HICs cannot be directly converted. As current approval pathways appear deficient for the approval of innovative pharmaceutical therapies in LMICs (Bunnik et al., 2018), further insight in the relation between regulation and innovation can help the development of efficient approval pathways for LMICs. The relation between innovation and regulation is moderated by certain directional principles like unmet medical need. As this moderating function is not clear for the LMIC context two situations are researched in which an unmet medical need influences the regulatory discussion.

3.2. Theoretical approaches

The following parts discuss the theoretical approaches used in this research. First the facilitated regulatory pathways (FRPs) by Liberti (2017) are discussed. FRPs are tailor-made pathways which are studied to view

the effect that the regulatory discussion has on regulation, and thus innovation. Hereafter, the Medicines Adaptive Pathways to Patients (MAPPs) principles provided by Eichler et al. (2018) are discussed. The MAPPs principles can be used to examine the discussion surrounding the unmet medical need and the effect that the unmet medical need has on the regulatory discussion within the FRPs.

3.2.1 Facilitated regulatory pathways

Regulatory pathways can facilitate access to new medicines. When regular regulatory approval pathways fail to provide guidance or are to slow for new treatments such tailor-made expedited pathways can be used. For example, accelerated access programs are aimed at facilitating timely access to innovative drugs. They allow drugs to reach the market earlier when significant medical benefit can be achieved, by decreasing review time, requiring less clinical data, and/or additional guidance from regulatory authorities (Pace et al., 2018).

Therefore, when an unmet medical need is encountered there is a proposition to change or adapt the regulatory system in order to foster innovation. This can be done via the facilitated regulatory pathways (FRPs) (Liberti, 2017) as these are used to facilitate access to new medicines when regular approval pathways fail to provide guidance or are to slow for new treatments (Liberti, 2017). The intended goal of FRPs is to speed the assessment and development programs of new medicines which can provide a possible impact to an unmet medical need by creating tailor-made regulation.

Facilitated regulatory pathways are defined by Liberti (2017) as *"regulatory pathways designed to accelerate product development, the submission of market applications, and regulatory reviews".* FRPs can be tailor-made and adapted to the specific characteristics of the therapy and the context of its development where standard regulation or guidelines cannot be used. Liberti (2017) identified general characteristics of existing FRPs, and three ways that FRPs use to accelerate product development, namely by (1) increasing the level of communication and commitment between the regulator and the developer, (2) increasing the role of medicines' effects on surrogate endpoints, and (3) moving the burden of clinical benefit and evidence to the post-authorization phase. These ways of development acceleration can be used when an unmet medical need is encountered in order to speed assessment. A change in the regulatory system could lead to higher interest in the development of innovative products, and thus result in higher innovative performance of the sector. An overview of the product acceleration methods used by FRPs can be found in table 1.

Table 1: Product acceleration methods of FRPs (Liberti, 2017)

PRODUCT ACCELERATION METHODS	USE CASE
INCREASING THE LEVEL OF COMMUNICATION AND COMMITMENT BETWEEN THE REGULATOR AND THE DEVELOPER	Used to increase the exchange of information with open discussions between the regulator and the developer in order to enhance transparency within the regulatory pathway.
INCREASING THE ROLE OF MEDICINES' EFFECTS ON SURROGATE ENDPOINTS	Used to speed the review process by employing surrogate clinical endpoints within clinical trials that are reasonably likely to predict the clinical benefit for a drug to allow expedited assessment of preliminary clinical data.
MOVING THE BURDEN OF CLINICAL BENEFIT AND EVIDENCE TO THE POST-AUTHORIZATION PHASE	This way can increase the time-to-market and thus patient of a new treatment by shifting the burden of the clinical evidence generation to the post-authorization phase (phase IV clinical trials) when this is feasible.

3.2.2 Medicines Adaptive Pathways to Patients

Another theoretical approach used in this piece is the Medicines Adjusted Pathways to patients (MAPPs) as presented by Eichler et al. (2018). The MAPPs principles are aimed at discussing evidence versus access when regarding unmet medical needs and are used as an elaboration of the principles on which an FRP can be based. The MAPPs principles provide a guideline for which criteria are fundamental in FRPs, and thus influence the discussion on the division between generic and tailor-made regulation.

In this research MAPPs is used to explore and examine important themes present in the regulatory discussion. When regarding drug development, ideally, a high standard of evidence is presented by the manufacturer, and fast market access is authorized by the regulatory authority. Considerations need to be made with regards to the amount and quality of the evidence, and the time to market access, in order to provide timely access, which is neither too fast nor too slow.

An overview of these considerations is provided by the principles mentioned by Eichler et al. (2018) in the MAPPs principles. MAPPs is composed of 8 principles: (1) unmet medical need, (2) timely access, (3) iterative development and assessment, (4) an increase of the evidence-to-uncertainty ratio, (5) the use of real-world data, (6) the expansion of treatment eligible population, (7) adaptive pricing and reimbursement, and (8) assurance of appropriate utilization. All the principles are explained in table 2.

Table 2: MAPPs principles (Eichler et al., 2018)

PRINCIPLE	EXPLANATION
UNMET MEDICAL NEED	*"Focus on the promise to address an unmet medical need: Target well-defined patient population(s) with life threatening or severely debilitating conditions with no treatment or no satisfactory treatments. This means focusing on products with a high probability of considerable effect size." (Eichler et al., 2018; p2)*
TIMELY ACCESS	*"Focus on patients with a limited time-window who cannot wait until all relevant research questions have been addressed" (Eichler et al., 2018; p2)*
ITERATIVE DEVELOPMENT AND ASSESSMENT	*"Align evidence generation plan with pre-planned regulatory and P&R re-assessment time points across entire product life-span." (Eichler et al., 2018; p2)*
INCREASE OF THE EVIDENCE-TO-UNCERTAINTY RATIO	*"Progressively increase the ratio by aligning known unknowns, pre-plan and modify, where needed, the evidence generation plan across product life-span, including the post-launch phase." (Eichler et al., 2018; p2)*
REAL WORLD DATA	*"Use real world data to inform iterative decision making: Acknowledging the high internal validity of RCTs, use entire methodology toolbox for on-market knowledge generation. "(Eichler et al., 2018; p2)*
EXPANSION OF TREATMENT ELIGIBLE POPULATION	*"Amend regulatory label population in line with incoming information about product's benefits and harms in relevant (sub-) populations." (Eichler et al., 2018; p2)*
ADAPTIVE PRICING AND REIMBURSEMENT	*"Flexible price points and reimbursable populations, adapted to pre-agreed milestones, incoming new information and environmental changes." (Eichler et al., 2018; p2)*
ENSURE APPROPRIATE UTILISATION	*"Ensure appropriate utilization by managing risks and monitoring use. This allows for the education of prescribers about identified risks and uncertainties. "(Eichler et al., 2018; p2)*

3.2.3 Conceptual model

This study researches the relation between regulation and innovation and the moderating function of unmet medical need on this relation. The regulation in an FRP is tailor-made to adapt to the specific context and characteristics of the therapy as generic regulation and guidelines are not applicable. There is discussion because there is no consensus between on the stakeholders on the balance between the standard and the tailor-made parts within the FRP and to what extent it needs to be tailor-made. From the generic regulation and guidelines some aspects can be used or altered, whilst for other aspects no alteration might be possible. There is no consensus on the use of altered or tailor-made regulation as stakeholders have different viewpoints on the relation between the acceptance of uncertainties regarding timely access and required evidentiary standard.

Therefore, this study researched how the principles are used and how they influence the regulatory process. Because stakeholders have different interests when regarding regulatory frameworks, the expected outcome is that the stakeholders have different viewpoints, arguments, and might disagree on the importance of the principles. This disagreement between stakeholders translates into discussion on the division of generic versus tailor-made regulation. The choices made in this division affect therapy development, and thus affect an FRP.

This is done by researching the regulatory discussion in an FRP via the MAPPs principles for two cases and the relative importance of the principles for both to provide a guideline for which criteria are fundamental in FRPs for LMICs. The retrospective case is examined to view what points of discussion were present, and how this influenced the MAPPs principles and consequently the FRP. Hereafter the prospective case is examined to view how it could be done, using the lessons learned from the retrospective case by using the MAPPs principles and points emanating from the regulatory discussion.

By studying which points are present in the discussion, which viewpoints are held, and which arguments are used the present similarities and differences can be examined, giving insight in the discussion of the tailor-made process for innovative treatments for LMICs. With this a situational overview can be given of how the tailor-made mAb antivenom pathway could look like.

By examining the MAPPs principles proposed by Eichler et al. (2018) for the regulatory discussion on the division between the generic and tailor-made regulation, the choices regarding regulation can be researched, as well as how the choices are influenced by the principles. These choices ultimately influence the regulation, and consequently development of a new therapy and innovation as a whole. The conceptual model used in this study can be seen in figure 2 below.

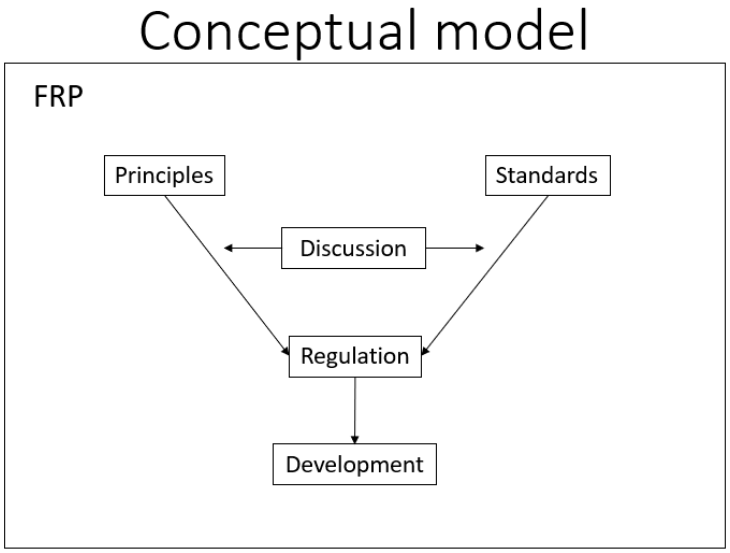

Figure 2: Conceptual model

4. Methods

This part will elaborate on the methods used in this research, starting with the research design, followed by the data collection approach used and bodies of evidence collected for both cases. Finally, the data analysis is explained.

4.1. Research design

This research has the aim to analyze tailor-made approval processes for LMICs by answering the following research question:

How was the development process of Rabishield™ regulated with a tailor-made approval process and how can we translate the corresponding principles and learnings to the approval of innovative therapies?

To answer this question, this research retrospective and prospectively mapped the discussion surrounding the regulatory division in facilitated regulatory pathways for LMICs by interviewing stakeholders and experts in the field in order to study how the principles are used and how they impact the division when regarding clinical evidence between generic and tailor-made regulation. This gives insight in the product acceleration methods used in the regulatory process which has been performed, and how these methods could influence how the regulatory process could be performed. Additionally, this provides insight on how the tailor-made process works and which similarities and differences are present by identifying which points of discussion are present, which viewpoints are held, and which arguments are used. The retrospective case study in this research is represented by the rabies immunoglobulin (RIG) replacement Rabishield™ to study the regulatory discussion surrounding the facilitated approval pathway. This allows to identify the lessons learned during development to be translated to the prospective case of snake antivenom mAbs in order to be able to identify the relation between innovation and regulation for treatments aimed at LMICs. The research was performed in three sequential stages.

The first stage of the research used scoping interviews to gain basic knowledge and to identify suitable interview candidates for both cases. This is accompanied by a literature review on the relation between innovation and regulation for pharmaceutical treatments in LMICs (see section 3).

The second stage of the research is deductive, with the use of the MAPPs principles to identify viewpoints and arguments in the discussion on the division of generic versus tailor-made regulation in regulatory approval pathways for LMICs. These principles are then analyzed by performing a retrospective case study of Rabishield™. Rabishield™ has been approved using an adaptive approval pathway, because assessment was not possible in the context of a standard approval pathway. The regulatory discussion on the approval process is studied by examining the MAPPs principles and their relative importance for the tailor-made process through grey literature, literature, and semi-structured interviews with stakeholders and experts in the regulatory approval pathway.

The third stage of the research is inductive, as the insights provided by the principles in the assessment of Rabishield™ are used to perform a prospective case study on monoclonal snake antivenom. This study is performed with grey literature, scientific literature, and semi-structured interviews. The obtained insights for both cases are then compared and connected to the MAPPs principles. The observations from the connection are then used to research the relation between innovation and regulation in the context of LMICs and formulate stakeholder advice for the assessment of monoclonal antivenins in LMICs.

Finally, in the fourth stage a possible FRP for monoclonal snake antivenom is formulated based on the results of the regulatory discussion, comparison and connection of the discussion with the MAPPs principles.

4.2. Data Collection.

The study used desk research combined with multiple stages of semi-structured interviews for the data collection.

4.2.1. Desktop Research.

The first part of the data collection consisted of a systematic search for articles and pieces of grey literature that were of interest to the cases. The articles for the Rabishield™ case were found by using "*Rabishield™*", "*clinical trial Rabishield™*", "*Rabies monoclonal*", and "*Rabies monoclonal antibody"* in Google, Google scholar, and PubMed. The references of articles found with this query were searched as well (i.e. snowball sampling). Articles for the Rabishield™ case were found to be of use when they provided knowledge on (1) the development, (2) regulation, and/or (3) background of monoclonal antibodies for Rabies. In total four peer-reviewed articles were found to be of interest for the case.

The articles for the monoclonal snake antivenom case were found by using search queries with combinations of the words "*Snake*", "*Antivenom*", "*Immunoglobulin*", "*Monoclonal*", and "*Monoclonal antibody"* in Google, Google scholar, and PubMed. Sources of the articles found with this query were scanned for further articles that might be of interest. Articles were considered useful when they provided insight on (1) the problems of snakebite, (2) the development of immunoglobulins for snakebite, (3) monoclonal antibody development for snakebite, and (4) regulatory background of therapies for snakebite. In total 13 articles were found to be of interest for the case.

4.2.2. Scoping and semi-structured interviews

Recruitment of the respondents

In order to obtain basic information on the field, and for the identification of suitable candidates for interviews, scoping interviews were performed with experts and influential actors in the sector. The scoping interviews have been performed with a pharmacology expert on mAbs and vaccines and a biochemical and biotechnological expert to get insight in the technologies, the sector, and development strategies in the field. The experts were found via a central actor in the field.

The second round of interviews were held with actors knowledgeable on the Rabishield™ case to give a retrospective view on the facilitated approval pathway, the points present in the discussion, the viewpoints held, and the arguments used in the discussion on the MAPPs principles in order to identify the similarities and differences present in the discussion. The third and last round of interviews on the prospective snake anti-venom mAb case and were used to identify gain a prospective view on the discussion on the possible facilitated regulatory pathway.

Interviewees from both the retrospective and the prospective case were recruited using the scoping interviews, snowball sampling from interviews, and via a central actor in the field. Interview groups that were of interest were those working for regulatory bodies, in monoclonal development, for non-government organizations (NGOs), research institutions, or for health care facilities. The identified interviewees were approached via e-mail. The e-mail shortly explained the research and stated the that the focus in the interviews was on retrieving information regarding the MAPPs principles, regulatory discussion, possible perceived improvements, and implications regarding the fostering of innovation surrounding one or both cases. If the respondents agreed to an interview, they were assumed to be knowledgeable on the subject and thus valuable to the research.

Interview guide and template

An interview protocol was created beforehand for each case which had a general focus on retrieving information regarding: (1) General information on the respondent, (2) Open questions on the possible barriers encountered during the regulatory process , (3) Possible solutions for these problems, (4) The

viewpoint of the interviewee and the viewpoints of the interviewee on other actors, and (5) The MAPPs principles. The full interview protocols can be found in appendices D (for Rabishield™) and E (For Snake Antivenom).

The MAPPs principles were concretized for the interview questions so they could be used in the research. By using interview questions based on concretized principles the heterogeneity in the actors' understanding of the principles was reduced. In the case that the principles were still unclear to the interviewee, a list of definitions is included in both interview protocols as a backup. Table 3 shows the MAPPs principles with related example questions.

Table 3: MAPPs Principles and related questions

PRINCIPLE	**QUESTIONS**
UNMET MEDICAL NEED	How is the concept of unmet medical need considered in your opinion?
TIMELY ACCESS	How is the timely access considered in your opinion?
ITERATIVE DEVELOPMENT AND ASSESSMENT	How are the iterative development and assessment considered in your opinion?
INCREASE OF THE EVIDENCE-TO-UNCERTAINTY RATIO	How is an increase of the evidence-to-uncertainty ratio considered in your opinion?
REAL WORLD DATA	How is the use of real-world data considered in your opinion?
EXPANSION OF TREATMENT ELIGIBLE POPULATION	How is the expansion of treatment eligible population considered in your opinion?
ADAPTIVE PRICING AND REIMBURSEMENT	How are adaptive pricing and reimbursement considered in your opinion?
ENSURE APPROPRIATE UTILISATION	How is appropriate utilization ensured in your opinion?

The preformed interviews were semi-structured, which allowed the interviewer to guide the interview in a general direction whilst at the same time to digress where applicable. Additionally, the interviewees were encouraged to be profound in their answers and explanations, to avoid misunderstanding. The interviews were recorded when permitted and then transcribed in full. The transcript or interview report was sent to the interviewee for validation, allowing the interviewee to add, adjust, or retract when needed.

4.3. Body of evidence for the Rabishield™ case

All pieces in the body of evidence were given a code starting with R to identify them for the Rabishield™ case. The body of evidence used in the Rabishield™ consists of five interviewees (R1-5), three presentations (R6-8), four peer-reviewed articles (R9-12), one background paper (R13), one meeting report, and one meeting transcript (R15). Of the five interviewees three (R1, 2, and 3) are regulatory experts, one interviewee is a public health professional (R4), and the last interviewee is a toxicology researcher with knowledge on monoclonal antibodies (R5). The interviewees were interviewed in person, or via phone, skype, or Webex if there was no possibility to perform the interview face-to-face.

The next part of the body of evidence consists of an FDA workshop (July 2017) (R15) on monoclonal antibodies for a rabies post-exposure prophylaxis (PEP), for which the full transcript and all presentations were published on the FDA website. At this meeting, a total of twenty-four participants were present and several aspects of preclinical and clinical development, such as in-vitro studies, in-vivo studies, and phase I, II, and III studies of Rabishield™ as well as requirements for future Rabies monoclonal antibodies were discussed. Furthermore, several presentations were given during this workshop, of which three were identified to be relevant for the research (Connelly, 2017; on ethical considerations (R6), Sparrow, 2017; on the WHO perspective (R7), and Gunale, 2017; on the development experience (R8).

Continuing, the published articles for the performed (pre-)clinical trials are included: Sloan et al., 2007 (R9) for the preclinical studies, Gogtay et al., 2012 for phase I clinical trials (R10), and Gogtay et al., 2017 (R11) for the phase II/III pivotal trial. Lastly, the article by Sparrow et al., 2018 (R12) and the WHO background paper on rabies vaccines and immunoglobulins (R13) were included. The body of evidence is summarized in Table 4 below.

Table 4: Body of evidence for the Rabishield™ case

NO	SOURCE	EXPLANATION
R1	Interview 1	Interview 1; Interviewee employed by a national regulatory authority with knowledge on drug research, clinical pharmacology, and both early- and late-stage (pre)clinical development
R2	Interview 2	Interview 2; Interviewee employed by an ethical regulatory body with knowledge on scientific development, safety in regulation, and regulatory improvement
R3	Interview 3	Interview 3; Interviewee employed by a national regulatory authority, with knowledge on the development of vaccines and monoclonal-based therapies for infectious diseases
R4	Interview 4	Interview 4; interviewee employed by a non-government organization with knowledge on the regulatory process and product specifics of Rabies monoclonal antibodies and monoclonal antibodies in general.
R5	Interview 5	Interview 5; University researcher with specific knowledge on the discovery phase for monoclonal antibodies and monoclonal antivenom
R6	Connelly, 2017	Presentation on the ethical considerations of monoclonal Rabies antibody development
R7	Sparrow, 2017	Presentation on the WHO perspective of monoclonal rabies antibodies
R8	Gunale, 2017	Presentation on the clinical development experience of monoclonal Rabies post exposure prophylaxis
R9	Sloan et al., 2007	Peer-reviewed article on the preclinical studies of Rabishield™. Discusses the neutralizing potency of the mAb against different Rabies strains in vitro and in vivo.
R10	Gogtay et al., 2012	Peer-reviewed article on the phase I clinical trial of Rabishield™
R11	Gogtay et al., 2017	Peer-reviewed article on the phase II/III pivotal trial of Rabishield™
R12	Sparrow et al., 2018	Peer-reviewed article on advances in the development of monoclonal antibodies for post exposure prophylaxis
R13	WHO, 2017	Background paper on rabies vaccines and immunoglobulins
R14	WHO, 2018b	WHO meeting on monoclonal antibodies against Rabies and evaluation of mechanisms to improve access to other blood-derived immunoglobulins
R15	FDA Transcript, 2017	Transcript of FDA meeting on monoclonal Rabies antibodies in July 2017.

4.4. Body of evidence of the monoclonal snake antivenom case

All the pieces of evidence used in the monoclonal snake antivenom case were given a code with S, and some of the sources of the Rabishield™ case were included as well when the information in the source was applicable to both cases. The body of evidence used in the snake antivenom case consists of 10 interviewees (R1-R5, S1-S5), twelve peer-reviewed articles (S6-S8, S10-S17, S19), one correspondence piece (S9), and one WHO report (S18). Of the ten interviewees (R1-R5, S1, and S2), four (R1, R2, R3, and S1) are regulatory experts, two interviewees are public health professionals employed at non-governmental organizations (R4 and S2) and one interviewee is a toxicology researcher with knowledge on monoclonal antibodies (R5). Two interviewees (S3 & S4) were scoping interviews with relevant knowledge, and one interviewee (S5) was a validation interview. The interviewees were interviewed in

person, or via phone, Skype, or Webex if there was no possibility to perform the interview face-to-face. The body of evidence for the mAb snake antivenom case is summarized in Table 5 below.

Table 5: Body of evidence for the monoclonal Snake antivenom case

NO	SOURCE	EXPLANATION
R1	Interview 1	Interview 1; Interviewee employed by a national regulatory authority with knowledge on drug research, clinical pharmacology, and both early- and late-stage (pre)clinical development
R2	Interview 2	Interview 2; Interviewee employed by an ethical regulatory body with knowledge on scientific development, safety in regulation, and regulatory improvement
R3	Interview 3	Interview 3; Interviewee employed by a national regulatory authority, with knowledge on the development of vaccines and monoclonal-based therapies for infectious diseases
R4	Interview 4	Interview 4; interviewee employed by a non-government organization as a public health professional with knowledge on the regulatory process and product specifics of Rabies monoclonal antibodies and monoclonal antibodies in general.
R5	Interview 5	Interview 5; University researcher with knowledge on the discovery phase for monoclonal antibodies and monoclonal antivenom
S1	Interview 6	Interview 6; Interviewee employed by a national regulatory body with a focus on preclinical drug safety.
S2	Interview 7	Interview 7: Interviewee working as a policy advisor employed by a non-government organization with a focus on public health and microbiology
S3	Interview 8	Interview 8; Scoping interviewee employed by a university. Pharmacology expert on mAbs and vaccines.
S4	Interview 9	Interview 9; Scoping interviewee with expert biochemical and biotechnological knowledge
S5	Interview 10	Interview 10; validation interview with non-government organization employees with focusses on public health and vaccines.
S6	Habib & Brown, 2018	Peer-reviewed article on the health-economic perspective of snakebite and the antivenom crisis
S7	Laustsen & Dorrestijn, 2018	Peer-reviewed article on the integration of engineering, manufacturing, and regulatory considerations in the development of antivenoms
S8	Laustsen et al., 2017	Peer-reviewed article on the cost competitiveness of recombinant antivenoms
S9	Laustsen, 2016	Correspondence piece on the price of recombinant antivenoms
S10	Lee et al., 2015	Peer-reviewed article on monoclonal antibody possibilities for a specific snake species
S11	Lee et al., 2017	Peer-reviewed article on monoclonal antibody possibilities for a specific snake species
S12	León et al., 2018	Peer-reviewed article that gives a perspective on current technology fit for the industrial manufacturing of snake antivenoms
S13	Longbottom et al., 2018	Peer-reviewed article focused on the mapping of global hotspots of snakebite envenoming vulnerabilities
S14	Ralph et al., 2019	Peer-reviewed article on reducing snakebite deaths in Asia
S15	Scheske et al., 2015	Peer-reviewed article on the relevance and application of international guidelines of snake antivenoms
S16	Williams et al., 2018	Peer-reviewed article on the effectiveness and safety of antivenoms
S17	Kini et al., 2018	Peer-reviewed article on biosynthetic oligoclonal antivenom and next generation snake treatments
S18	Theakston et al., 2003	Report of a WHO workshop on antivenoms
S19	Gutiérrez et al., 2017	Peer-reviewed article on snakebite envenoming

4.5. Data analysis

The data collected for both cases was analyzed using NVivo (QSR International Pty Ltd). In the first round of coding, parts of the transcribed interview reports were categorized according to three main discussion points brought up by the interviewees, namely: (1) product definition, (2) standard of care, and (3) efficacy assessment. These three main discussion points were not initially predefined, but similarities and the reoccurrence of those discussion points in both the prospective and retrospective case allowed for a first broad round of coding according to these discussion points. Secondly, open coding was applied, meaning that all text within one of the discussion points was divided in substantial codes that described (1) involved actors, (2) their views, (3) arguments to support their views, (4) potential regulatory and non-regulatory effects or outcomes of a specific view and/or (5) possible solutions for the articulated effects. In the next round of coding these substantial codes were linked where possible based on their context, possible causal relationships, and patterns of interaction on the development and/or approval process of Rabishield™ or monoclonal snake antivenom. Finally, the discussion points were also linked to the MAPPs principles as outlined in the theory: (1) unmet medical need, (2) timely access, (3) iterative development and assessment, (4) evidence-uncertainty ratio, (5) real world data, (6) expansion of treatment eligible population, (7) adaptive pricing and reimbursement, and (8) appropriate utilization. In other words, the three discussion points found were first examined in detail to enable a clear understanding of all viewpoints of the involved actors, whereas the link and thus potential presence of the MAPPs principles allowed for the design of new regulatory pathways to facilitate market approval in the conclusion. The complete overview and comparison of the cases finally allows the teachings derived from the Rabishield™ case to formulate principles that need to be considered when setting up facilitated regulatory pathways in LMICs, and to translate the lessons learned from the Rabishield™ case to the monoclonal snake antivenom case. The quality protocol used to perform this research can be found in Appendix E.

5. Results

5.1. The retrospective case: Rabishield™.

This part describes the results of the retrospective case, Rabishield™. Firstly, the development process of Rabishield™ is described, starting with the discovery phase and ending at the phase III clinical trial. Hereafter, the main three discussion points surrounding the regulatory trajectory will be presented.

5.1.1. The development process of Rabishield™

Rabishield™, under the development name RMAB 1, was the result of a research goal set in 2003 by Massbiologics of the University of Massachusetts Medical School (UMMS) with the aim to identify mAb(s) which could be used as efficacious alternative to Rabies Immunoglobulin (RIG) in places where the disease burden is high, as very few people who need RIG have access to it (R10). The mAb, then still named HuMAb 17C7, proved to be promising as it was able to neutralize the majority of known Rabies isolates in an in vitro rapid fluorescent focus inhibition test (RFFIT) performed by UMMS in a number of potential candidates (R9).

Only one rare Peruvian bat isolate which quantitatively represents 0.07% of all Rabies isolates was not neutralized by the mAb (R11, 13 and 14). Whilst a problem, this failure rate is comparable with contemporary used hRIG, which fails to neutralize two isolates, albeit both different from the monoclonal escapee (R11). The neutralizing potency held in an in-vivo PEP model; a Syrian hamster challenge performed by UMMS. This challenge demonstrated that HuMAb 17C7 provided non-inferiority in neutralizing potency when compared to contemporary humanized rabies immunoglobulin (hRIG) both in a model with only PEP, as well as a model including PEP and vaccine (R9).

The strong pre-clinical data allowed the UMMS to seek a partner for the further development of the Rabies mAb. The Serum institute of India private limited (SIIPL) was interested in the potential, and a collaboration was established in 2006 (R8). The collaboration included a tech transfer of the monoclonal cell bank to the SIIPL in 2007, allowing the institute to create the first clinical lot in 2008 and thereby to start the clinical development phase (R8).

The SIIPL funded the Phase 1 study, which was conducted from 2009 till 2010 in India and consisted of a randomized, open label, dose-escalation study in 74 adults between the age of 18 and 45 of which four were entered in a safety cohort. The study started with the lowest possible dose in two adults following a previous safety calamity with a monoclonal tested in the UK. The endpoints of the study were safety assessments of (1) adverse events, (2) clinical parameters, and (3) anti-drug antibodies. This study showed that the mAB, now called SII RMAB, was found to be safe, tolerable, and comparable to hRIG when used in a PEP regimen (R10).

After a favorable phase 1 study, a phase 2/3, randomized, single-blind, noninferiority, controlled study was funded by the SIIPL and conducted in India between 2012 and 2015. The study was split in two phases. The first part contained 50 participants with WHO category three exposures on lower extremities only. After reviewing the data, the clinical trial data safety monitoring board (DSMB) concluded that futility of the trial was not met, and an additional 150 participants were recruited for the second phase. The second phase contained WHO category three exposures of all extremities, whilst also including children and women of childbearing age. The primary end point of the study was the geometric mean concentration of titers (concentration of specific antibodies in the blood), which were measured via RFFIT. This two-phased study concluded that the SII RMAB was safe and non-inferior to a hRIG PEP regimen, and thus would be a valid substitute. This led to market authorization in India by the CDSCO in 2016 (R11, R13), no other nations have authorized it as of now. The history of Rabishield™ is shortly outlined in Table 6 on the next page.

Table 6: History of Rabishield™ (HuMAb17c7/SII RmAb)

YEAR	PHASE	SPECIFICS	SOURCE
2003	Research started at UMMS		Sloan et al., 2007, Gunale, 2017
2006	Preclinical studies at UMMS	In vitro (RFFIT, ELISA) and in vivo studies (Syrian hamster challenge) of monoclonal candidates	Sloan et al., 2007
2006	Collaboration started with SIIPL and licensing agreement signed		Gunale, 2017
2007	Tech transfer of cell bank to SIIPL		Gunale, 2017
2008	First clinical lot created		Gunale, 2017
2009-2010	Phase I (CTRI/2012/05/002709)	Open label, dose-escalation study with a simulated PEP regimen in 74 participants (Adults between 18 and 45 years of age). Endpoint(s): Safety evaluations of adverse events, and the measurement of clinical parameters and anti-drug antibodies	Gogtay et al., 2012
2012-2015	Phase II+III Pivotal (CTRI/2009/091/000465)	200 Eligible respondents, antibody and serological response measured. Part 1: 50 respondents (only WHO category three exposures on lower extremities. Part 2: 150 respondents, all WHO category 3 exposures, including children and women of child-bearing age. Endpoint: ratio of day 14 geometric mean titers of antibodies measured via RFFIT	Gogtay et al., 2017
2016	Market Authorization by CDSCO+ Start of Phase IV		Gunale, 2017;

5.1.2. Regulatory discussion

This section will discuss the regulatory discussion for monoclonal replacements for rabies immunoglobulins, which entails both the parts in the process that could be completed with existing guidelines and parts that deviated from the guidelines during the regulatory process. R4 mentioned that that Rabishield™ had a fairly standard, "textbook" preclinical process for immunoglobulins and vaccines from the FDA as UMMS was based in the United States. This means that all known isolates needed to be tested in-vitro (R8) and the in-vivo studies need to measure "pharmacokinetics, half-lives and interaction of mAbs, toxicity, dose ranging and vaccine interaction/inhibition" (R12). Massbiologics demonstrated the neutralizing potency of its mAb across as many isolates as possible in vitro (laboratory strains as well as "street" circulating isolates) (R3, R4). For the in vivo studies, Syrian hamster challenge studies were performed as these are used to measure any added benefit of a new combination, as Syrian hamsters are susceptible to many viruses (R15). Other animal models can be added when deemed necessary by regulatory authorities (R12).

Blood product or monoclonal antibody?

The first point of discussion identified was the exact product definition of Rabishield™ as there was no agreement on the regulatory specification of the product profile. The clinical standards depend on the classification of the new treatment. In summary, Rabishield™ is a monoclonal antibody PEP vaccine replacing an immunoglobulin blood product. Whilst the preclinical process was identical to immunoglobulin or vaccines, the clinical regulation for monoclonal antibodies and immunoglobulins differs. Blood products almost never perform clinical studies, as R5 mentions that "*a vigorous phase 1,2,3 trial has only been done for one or two antivenoms*" (products), whilst monoclonal antibodies need to

adhere to strict regulatory standards (R2, 3, 4, and 5). Consequently, the exact definition and regulatory categorization of the product has a great effect on the required clinical trials as blood product regulation is more lenient when compared to monoclonal regulation.

Some interviewees specified it first and foremost as a blood product (R3 and R5), others as a monoclonal antibody (R2 and R4). As Rabishield™ was deemed a direct replacement for a blood product with the same method of neutralization, some sources (e.g. R3 and R5) stated that the monoclonal is an update to the existing treatment and should thus be regulated as such. For example, R3 mentions that a monoclonal in this case could be considered as a "*very tiny fraction of a blood product*", or even an "*in vitro sensitized blood product*". This means that it should not even be regulated as tightly as a blood product due to the specified therapeutic fraction, whilst blood products are more loosely regulated than monoclonal antibodies in the first place. As the product definition determines the clinical requirements set in the approval process, developers could have advantages when the more lenient blood product regulation would be applicable and therefore face lower development costs and a faster time-to-market.

The question is how different national regulatory authorities consider the quality of the clinical evidence. In the end the manufacturer chooses what clinical data to provide. An extensive clinical trial across multiple nations can allow multiple regulatory authorities to have access and contact during the development of clinical data, meaning they will be more comfortable to approve the product after its licensed (R3). The downside for such a trial is the high cost, which is especially relevant for treatments in LMICs as it determines the access to those products (S3).

Historical safety failures have led to strict regulatory and safety standards for monoclonal antibodies (R2). Whilst blood products have known safety issues, healthcare workers have experience in dealing with the expected issues that they possess (R3). However, despite the hypothesized improvements monoclonal antibodies bring their own host of problems. However, most of the safety concerns of monoclonal antibodies are related to endogenous off-target toxicity (R5). Rabishield™ with its aim on the rabies virus targets an exogenous target which are far less prone to off-target toxicity (S4, R5). Nevertheless, R3 mentions that a monoclonal antibody remains a monoclonal antibody, regardless of what it replaces or targets (R3), so clinical blood product regulation will not be applicable when monoclonal antibodies are being discussed (S5).

In the end a phase I and phase II/III pivotal trial was done for Rabishield™ by the manufacturer, meaning blood product regulation was not used. The effect of this was that the time-to-market was longer, and thus more costs were made for the regulatory trajectory. On the other hand, this meant that the regulatory evidence was stronger.

An overview of the arguments from the blood product or monoclonal discussion for the Rabishield™ case can be found in Table 7 below.

Table 7: Summary of the Rabishield™ blood product or monoclonal discussion

POINT OF DISCUSSION	ARGUMENT FOR BLOOD PRODUCT REGULATION	ARGUMENT AGAINST BLOOD PRODUCT REGUALTION	ARGUMENT FOR MONOCLONAL REGULATION	ARGUMENT AGAINST MONOCLONAL REGULATION	DECISION
SHOULD THE PRODUCT BE DEVELOPED ACCORDING TO THE GUIDELINES OF A BLOOD PRODUCT OR A MONOCLONAL?	The monoclonal is actually only a small piece of the blood product, and thus purer.	Monoclonal antibodies possess a safety profile which require adequate evidence, regardless of what they replace	Monoclonal antibodies have historical safety failures, leniency in safety is unwanted	Safety issues with monoclonal antibodies are related to off-target toxicity, monoclonals targeting exogenous targets are not prone to this	Monoclonal antibody regulation used, as the product remained a monoclonal first.

Standard of care

Clinical trials aimed at testing the therapeutic dose in randomized controlled trials comparing the new intervention against placebo are unethical in severe and fatal diseases such as rabies (R1, 2, 3, 4, 5), and

therefore no placebo can be used when dealing with possible infections. A placebo can only be used in a simulated PEP when the volunteer is not at risk of developing rabies.

R8 mentions that the mAb should be (pre)clinically compared to the current standard of care (SoC) whenever possible. However, defining the SoC is difficult as this differs across nations and regions (R15), because different products are available for rabies post-exposure prophylaxis (PEP) treatment. The basic form of contemporary used rabies immunoglobulin (RIG) PEP has been around since the 1950s (R12). Although the RIG has been used effectively in the past the basic product design is now outdated or even archaic (R7). Whilst many iterative improvements have retrofitted the sera for present-day use, the introduction of new and innovative technology is desirable.

Currently, rabies immunoglobulins are available in different formulations in two main groups: Equine (eRIG) and Humanized (hRIG) in different levels of purification. Other groups are available but used far less (>1%), and thus not considered in this research. ERIG and hRIG are not considered to be ideal treatments due to supply, financial, and safety issues (R10). According to R12, only 1-10% of patients recommended to receive PEP actually received it due to a lack of availability or cost constraints. In general, eRIG is more affordable than hRIG but less efficacious, with a higher degree of side-effects (see Appendix F for a more comprehensive comparison of PEP products).

Whilst the standard of care in many western nations entails the use of hRIG after a possible rabies infection, other countries might use eRIG or may not have access to any form of immunoglobulins (R15). In order to assess the product on safety and efficacy a comparison between the mAb and a form of RIG needs be made, even if the RIG is scarce. However, as eRIG and hRIG have documented side effects (S5), using RIG in healthy volunteers exposes them to potentially harmful side-effects (R2 and R4). Adding to this, it is questionable to subject clinical trial participants to a certain product (eRIG, with its known shortcomings) if it is known a better product is available (hRIG), albeit not locally (R2).

Finally, as there is a form of treatment available, the incorporation of children and pregnant women into the clinical trial is a point of discussion. On the one hand they should not be exposed to something they might not have benefit from if treatment is available (R15), on the other hand the currently available RIG products are far from perfect (R2, 4 and 14).

For the preclinical trials a complete comparison with all products is feasible, although the use of both eRIG and hRIG is questionable as hRIG is more efficacious and the current best standard, meaning that if a product in non-inferior to hRIG it will also be non-inferior to eRIG. In the case that the product would be inferior to hRIG but superior to eRIG it could still be useful as the supply of hRIG is very limited, and thus access to a qualitative alternative is an improvement.

Rabishield™ was ultimately compared to hRIG, the highest standard of care possible in the phase I studies and phase II/III pivotal trial. The preclinical work of Rabishield™ was done by UMMS in the United States of America, which has hRIG as the standard of care. Therefore, in order to retain the validity of the comparisons throughout the clinical testing hRIG was used in the phase I and phase II/III pivotal trial as well. Whilst in India eRIG is used more frequently due to its lower cost, hRIG is considered to have less side effects (R10). Safer versions of eRIG exist, but these are unavailable in developing countries, meaning that hRIG was the safest available comparator. The use of hRIG during the clinical trials meant that the price went up, and the duration of the study increased, as hRIG was the most expensive competitor available and the availability is scarce. Furthermore, children and women of childbearing age were only involved after the first 50 participants of the pivotal trial proved that the futility of the clinical trial was not met. An overview of the arguments from the standard of care discussion for the Rabishield™ case can be found in Table 8 on the next page.

Table 8: Summary of the discussion on the standard of care for Rabishield™

POINT OF DISCUSSION	ARGUMENT FOR DIFFERENTIATION PER NATION	ARGUMENT AGAINST DIFFERENTIATION PER NATION	ARGUMENT FOR THE USE OF HRIG	ARGUMENT AGAINST THE USE OF HRIG	DECISION
STANDARD OF CARE DIFFERS PER LOCALE; DOES THIS MEAN THAT A LOCAL STANDARD NEEDS TO BE USED?	The standard of care differs per region and nation, thus a different standard needs to be used depending on the nation, even if this means using no immunoglobulins.	Comparing with Placebo or a substandard comparator is unethical for severe or fatal diseases when better comparators are available for non-simulated clinical trials	HRIG is the current gold standard, if a new product is non-inferior or superior to hRIG it will also be superior to eRIG	HRIG is no comparison if it is not available locally	Comparison with hRIG as this is the highest possible standard, if hRIG is "beaten", so are the others

Assessing efficacy

The final point that was brought up in the regulatory discussion was the problem of assessing the efficacy of the new intervention. In order for a clinical trial case to be included the rabies infection needs to be verified (R1, 4; and 16), because the absence of a rabies infection would simply allow every treatment to be effective (R1). For example, the animal could have bitten without being rabid (R2, 4, and 15), or without shedding rabies virus (R15). The WHO uses a system which classifies the risk of developing rabies in three categories, which are further detailed in appendix B. Additionally, the quality of care delivered prior and during the clinical trial uptake needs to be assessed because a comparison between PEPs can only be done if other factors are kept constant. The risk of developing rabies is thus determined by multiple factors.

However, there is still a factor of uncertainty as the risk of developing rabies increases when the bite is in close proximity of the nervous system, head, or both (R10, 11, 14, and 15). Furthermore, the risk is increased when the bite is not identified and washed accordingly, or the antibody is not appropriately delivered (R15). This means that cases of the same severity need to be used, wound cleaning as recommended by the WHO is done properly, and the vaccines are appropriately delivered (R6).

When these factors cannot be controlled a problem arises with the statistical power of the clinical trial. Interviewee R4 and participants in the FDA workshop (R15) mentioned that additional participants could be added to the clinical trial in order to retain statistical power. However, a participant in the FDA workshop (R15) noted that in order to satisfy the statistical demands for a disease as rabies with the current statistical gold standard (mortality endpoints 99%-100%) one would need around 30.000 participants per arm, which would be entirely unfeasible for any clinical trial (R15). Furthermore, increasing the number of participants also negatively affects the duration and cost of the clinical trials, which in turn affect the final time-to-market and price of the treatment (R2). Manufacturers are expected to be opposed by this, especially in resource limited settings (R4). It could also be considered to be unethical, as supply of the RIG products is limited, and thus extensive testing of new products could be inadvertently keeping a promising new product from its patient population if they do not have access to an alternative (R2).

Another option that was brought up for the clinical trials was measuring the serological response (neutralizing titers) (R14) to the PEP instead of using mortality endpoints. By analyzing neutralizing titers, which would neutralize the virus if it would be present, a comparison can be made between the PEP options without confirming rabies infection. This was done in the phase II/III pivotal trial of Rabishield™, and the product was approved by the Indian regulatory authority (CDSCO) based on this trial. Interestingly, one interviewee mentioned that it is questionable that the FDA would approve the product based on the same studies as the number of participants in the study (50+150) would probably not be enough to convince the FDA (R4). In conclusion, when uncertainty is present, steps need to be taken to assure that the efficacy is correctly assessed. This can be done by negating the uncertainty, increasing the number of trial participants, and measuring alternate endpoints for the clinical trials. An overview of the arguments from the assessing efficacy discussion for the Rabishield™ case can be found in Table 9 on the next page.

Table 9: Summary of the discussion on the assessment of efficacy for Rabishield™

POINT OF DISCUSSION	ARGUMENT FOR ADDING PARTICIPANTS	ARGUMENT AGAINST ADDING PARTICIPANTS	ARGUMENT FOR ALTERNATE ENDPOINTS:	ARGUMENT AGAINST ALTERNATE ENDPOINTS	DECISION
HOW TO CORRECTLY ASSESS EFFICACY?	In order to retain statistical power in clinical trials, participants must be added when a rabies infection cannot be confirmed	The number of participants that need to be added is unfeasible, and would dramatically increase costs and time-to-market	By analyzing neutralizing titers, the antibody response against a possible infection can be measured and confirmed, regardless of possible rabies transmission	N.A.	Neutralizing titers were analyzed to allow a comparison regardless of infection.

5.2. Snake antivenom monoclonal antibodies

Blood Product or monoclonal

The first point brought up during the discussion of monoclonal snake antivenom was the product definition, much like Rabishield™. If the new snake antivenom would be classified as a blood product this would provide advantages for the manufacturer due to lower regulatory requirements reducing costs and the time-to-market. On the other hand, if the product is designated as a monoclonal, the ensuing clinical trials would be able to provide the manufacturer the evidence required to convince multiple stringent regulatory authorities (SRAs). As regulatory guidelines are not legally binding, it is up to the manufacturer what kind of evidence to present to the regulatory authority or authorities (S1). If a manufacturer wants to divert from certain points in the guidelines they can do so if they have a convincing reason (S1). If there is no guideline, scientific advice can be requested from regulatory authorities (S1).

Multiple interviewees mentioned that monoclonal products provide inherent benefits due to their purity when compared to immunoglobulins and therefore extensive clinical evidence would not be warranted (R3 and S2). As immunoglobulins have low regulatory requirements, the purer monoclonal antibodies would not need additional requirements when compared to the less pure immunoglobulins. Regulatory interviewees (S1, R1, and R2), however, do not share this view, and stated that the stricter monoclonal regulation is a consequence of historical safety failures. Despite the fact that the monoclonal snake antivenom would target exogenous snake venom (S4), the risks of off-target toxicity as experienced in the past provide precedent for regulatory requirements that are stricter than those of immunoglobulins.

Stricter regulatory requirements were discussed in terms of their economic and time-to-patient implications. As snakebite is a disease most prevalent in lower socioeconomic communities, the possible price level of the product is critical (S11, S19). If monoclonal regulation needs be used this could prove problematic according to S7, as "*demonstrating efficacy and safety in clinical trials is difficult, expensive, and time-consuming".* This is extra problematic when dealing with treatments aimed at low income patient populations (S16). S6 mentions "*antivenoms costing more than £3 per treatment may be unaffordable".* According to S8 a typical African snakebite could be treated for between 60-250 dollars with a recombinant antivenom, as opposed to the current $60-640 (S6, S8, and S9) for a qualitative immunoglobulin treatment. This means that a monoclonal replacement could be a cheaper alternative to the current immunoglobulin products, but still possibly unaffordable.

S7 mentions that an option would be to reduce the amount of (expensive) clinical activities and replace these with more (inexpensive) preclinical activities. This partly coincides with the thoughts of R3, who states that emergency protocol needs to be considered after safety and efficacy is demonstrated and S16 who states: ***"****For antivenom manufacturers that currently operate with relatively small markets and products that, by necessity, have to maintain a low price to assure affordability to those most in need, there is little if any incentive to undertake such a rigorous pathway during development".* This could

especially relevant for cases for which no antivenom exists. As no current regulation is ideal a consideration needs to be made that includes both an acceptable degree of safety and clinical trial requirements that are feasible for the intended purpose of the product (R5). An overview of the arguments from the blood product versus monoclonal discussion for the monoclonal snake antivenom case can be found in Table 10 below.

Table 10: Summary of the discussion on blood product versus monoclonal for the monoclonal snake venom

POINT OF DISCUSSION	OPTION 1/OUTCOME? /PROBLEM?	OPTION 2	OPTION 3
SHOULD THE PRODUCT BE DEVELOPED ACCORDING TO THE GUIDELINES OF A BLOOD PRODUCT OR A MONOCLONAL?	Extensive clinical trials will make the product more expensive due to increased regulatory demands. The balance between regulation and affordability is a trade-off, as extensive clinical testing can convince multiple SRAs, increasing possibilities in the long run.	Guidelines are not legally binding, and the manufacturer can present whatever evidence they want to regulatory authorities if solid argumentation supporting their point can be presented. If there is no guidance for a certain part scientific advice can be requested from regulatory authorities.	Regardless of the chosen regulatory pathway phase I clinical trials are advisable.

Standard of care

The discussion on the standard of care is also relevant for monoclonal snake antivenom. The SoC for snakebite is heterogenous, with the use of various products with various degrees of efficacy. This is due to the interspecies, intraspecies, and geographical heterogeneity of snake venoms. As the venom composition changes depending on this heterogeneity, the antivenom can have a varying effect. Additionally, the composition of venom that snakes produce also depends on their geographical location, meaning that the antivenom for the correct snake can something fail to mitigate the effects of the venom in a different location (S7, S10, and S17) meaning that products need to be made for various geographical regions.

Currently, the selection of snake species used as a venom source for the immunoglobulins is related to their medical importance (S12). The result of this is that some regions have highly effective products, whilst other regions might not have any antivenom available at all. At the moment, specific antivenom is unavailable for 43% of all venomous snake species (S13) and treatment thus consists of polyvalent or paraspecific antivenoms (S13). Failing to neutralize the toxins in snake venom can have severe consequences, including death, so the possibility of receiving a placebo is not ethical for real bite victims (S16). Therefore, the use of placebo in phase II/III clinical trials is not warranted (S16).
Furthermore, the use of substandard products is disputable when better comparators are available, even if they are not available locally. Substandard products could bring additional unwanted side-effects, which could be considered unethical for phase I volunteers, and is not advisable in phase II/III.

Whilst a comparison with the current best standard is desirable, problems arise when no antivenom is available for a certain snake or region. A comparison for these cases would equal the use of placebo or non-specific antivenom products, both of which are unwanted for potentially deadly snakebites. In these cases, an emergency protocol can be considered after the product is demonstrated to be safe. This would then be a unblinded single product study, not unlike those often used for immunoglobulin-based antivenom (S16). Although authors denote that an agreement needs to be made on suitable trial endpoints in order to improve these studies (S16). An overview of the arguments from the standard of care discussion for the monoclonal snake antivenom case can be found in Table 11 below.

Table 11: Summary of the discussion on the standard of care of snake monoclonal antivenom

POINT OF DISCUSSION	OPTION 1	OPTION 2	OPTION 3
WHAT IS THE STANDARD OF CARE OF SNAKEBITE?	Heterogeneity in the venom composition means that the standard of care is heterogeneous. Some snake species	The use of the best available comparator is advisable if it is logistically possible, even when it is not usually available locally. Some snakebites do not have specific treatment, prompting the	For snake species for which no specific treatment exists

	might have effective antivenom, whilst others might have nothing at all.	use of placebo as best available comparator. Placebo is unethical when discussing snakebite due to the severe consequences related to the lack of treatment.	emergency protocol can be considered

Assessing efficacy

Problems with the correct assessment of efficacy are mentioned during the snakebite discussion. Uncertainty is prevalent with snakebite as the biting snake often cannot be identified. As many species of venomous snakes exist, people caught in the moment often cannot recall an exact visual definition. Additionally, snakes tend to make dry bites in which no venom injected, with the percentage of dry bites at around 50% (S18) depending on the species. These facts combined with the diverse venom consistency makes assessing the efficacy of snake antivenom difficult. This means that unless the species of snake can be identified, and a "wet" bite can be established, confirmation of the biting species is uncertain.

To mitigate this, the number of participants in clinical trials can be increased. This would however increase the cost and time-to-market of the product, which is undesirable given the intended patient population. Alternatively, the use of "*venom or toxin detection kit*" can be of help (S7 and S16) as this kit can detect the kind of injected venom. On the basis of the result, the antivenom with the corresponding profile can be administered accordingly. This kind of patient stratification can help mitigate the issues of uncertainty in the clinical trials. The final option mentioned in the body of evidence would be the development of a pan-specific monoclonal snake antivenom (R5), which would remove the requirement of species identification. An overview of the arguments from the assessing efficacy discussion for the monoclonal snake antivenom case can be found in Table 12 below.

Table 12: Summary of the discussion on the assessment of efficacy for the monoclonal snake antivenom

POINT OF DISCUSSION	OPTION 1	OPTION 2
HOW CAN THE EFFICACY OF SNAKE ANTIVENOM CORRECTLY BE ASSESSED?	Uncertainty is prevalent in snakebite. The diversity of species, heterogeneity of the venom, and possibility of a "*dry bite*" means that correct assessment of efficacy is difficult	The uncertainty needs to be accounted for in clinical trials. This can be done by adding participants, identification via toxin detection kits, or the development of antivenom that is not species specific.

6. Comparison and connection

This part will compare the regulatory discussion between the retrospective and prospective cases to identify similarities and dissimilarities within the discussion. These allow for lessons to be derived, which can be translated to the monoclonal snake antivenom case by formulating principles that need to be considered when setting up facilitated regulatory pathways in LMICs.

6.1. Blood product or monoclonal case comparison

Starting with the product definition, there are some similarities when looking at the regulatory discussion as interviewees for both cases mentioned that monoclonal antibodies are a purer form of product and that the regulatory requirements should mirror this. Immunoglobulins have had an historical advantage that they have been approved when the regulatory requirements were less strict. The safety tests were basically done in humans (R3), and it has been proven to be safe enough the millions of times they have been administered. This is not feasible for new drug products.

Although the economic perspective was mentioned as a reason for choosing blood product regulation in both cases it was highlighted more often in the discussion of snake venom. Both rabies and snakebite are diseases most prominent in poorer nations. Snakebite is a disease impacting the most impoverished in these poor nations, making the price of a possible product critical to its uptake. Extensive regulatory requirements can be a barrier to affordability and thus access, but vice versa too lenient requirements can mean that the regulatory evidence is lacking, and the drug might not be safe.

MAPPs connection to the blood product or monoclonal discussion

The points mentioned during the discussion link the discussion to the MAPPs principles of timely access and adaptive pricing and reimbursement. R5 mentions that one needs to consider timely access as it is an emergency medicine. R3 states that if the antivenom has shown to be well-tolerated and phase I safety data is available you can consider an emergency protocol. R4 states that timely access would not be relevant for the Rabishield™ case, as there was already a product on the market. This sentiment is shared by R2, stating that it not a new disease *"This exists since snakes exist, it is not a new problem"*. Thus, when connecting timely access to the discussion points of the cases it can be connected to the blood product versus monoclonal discussion. Timely access is relevant for the blood product versus monoclonal discussion as timely access in influenced by the decision on the regulatory specification. If timely access is required, the demanding extensive clinical evidence might be detrimental to that effort.

The principle of adaptive pricing and reimbursement is one that is articulated as extremely relevant for treatments that are aimed at LMICs. The price of a product is partly determined by the extent of the clinical trials as these can add costs, so if the less lenient monoclonal regulation is used this could impact affordability. On the other hand, additional clinical evidence can convince multiple parties, possibly enabling reimbursement. This principle was mostly discussed in the discussion surrounding monoclonal snake antivenom as snakebite is a disease of the most impoverished and can result in a circle of poverty.

6.2. Standard of care comparison

The second part of the discussion on Rabishield™, the standard of care, was also discussed for the monoclonal snake antivenom. For Rabies PEP different products are available which have a different degree of safety and efficacy and therefore determining the SoC is difficult. The products available for snakebite also differ in terms of safety and efficacy. But where the standard of care of Rabies mostly depends on the region, snakebite not only depends on the region but also on the biting snake as snake venom is heterogenous depending on the species, region, and age of the snake. Therefore, defining a standard of care for snakebite is considered to be more difficult. In the case of rabies PEP products, a best-

case SoC can be defined as the diversity of the products is related to their efficacy, and hRIG is the current best. In the case of snake venom some species have multiple antivenom products, whilst other species might not have a single antivenom available and treatment is dependent on paraspecific antivenom.

For both cases the question of ethics is applicable. Comparison with placebo in both cases cannot be ethically justified due to the severe consequences related to a lack of treatment in both cases. This creates problems in snakebite when antivenom is being considered for species which do not currently have antivenom, or to a certain degree specific antivenom, available. The discussion surrounding the standard of care is related to the MAPPs principles of unmet medical need, the expansion of treatment eligible population, adaptive pricing and reimbursement, and ensure appropriate utilization.

MAPPs Connection to the standard of care discussion

The unmet medical need is contested between the interviewees for both cases, with the viewpoints on the monoclonal snake antivenom case ranging from *"There is no discussion on that if you ask me"* (R2) to *"There are some unmet needs for sure, but there is good equine antivenom"* (S2). R5, R1 and S2 state that it depends on the species of snake, venom type, region, availability, and quality of the currently available products. This means that in some cases it could be considered an unmet medical need, whilst in others it is not the case due to the availability of efficacious antivenom. R1 states that for both cases it could also be viewed as an issue of logistics, as efficacious treatments exist, they just aren't accessible locally. When connecting the regulatory discussion to unmet medical need, it is related to the standard of care, as the standard of care partly dictates the need that is experienced. If there is a low standard or no standard the need is high and vice versa.

The expansion of the treatment eligible population principle is also connected to the standard of care as the possibilities of incorporating risk groups in the clinical trial population depend on the standard of care. Clinical trials should be started in healthy adults, and risk groups like children or child-bearing females be added to the clinical trial only when efficacy is proven. On the other hand, if there is no established treatment, early incorporation of these risk groups needs to be evaluated when it is deemed feasible. If a form of treatment is available, the incorporation of these risk groups is only feasible when safety is demonstrated.

The next link is the principle of adaptive pricing and reimbursement, as part of countering unmet medical need is to counteract catastrophic health costs (R5). The standard of care depends on the availability and accessibility of qualitative products and affects the pricing and reimbursement strategy. If products are unavailable due to cost constraints the principle of adaptive pricing and reimbursement is relevant. R5 denotes that similar types of schemes are already being implemented for certain vaccines and expects that antivenoms can fit well in a similar type of scheme.

As the principle ensure appropriate utilization is related to the uncertainty that healthcare workers face, it can be connected with the standard of care. R2 denotes that ensuring appropriate utilization not really affects monoclonals as they will be delivered by highly skilled professionals. However, R3 noted that healthcare workers can be reluctant to use contemporary antivenoms due to the extent of their side effects. If the degree of side effects of monoclonals is demonstrably lower, this could have an effect on the morale and willingness of health care workers faced with the decision of administering the product. Additionally, when people close to treated patients see that a treatment has a positive or negative effect on the patient, they are influenced as well (R3). This means that a poor product could have negative effects for antivenom in a whole community, whilst a good product might do the opposite.

6.3. Assessing efficacy

The final part of the discussion of the cases surrounded assessing efficacy. In Rabishield™ certain uncertainties meant that the correct assessment of efficacy was difficult and therefore the statistical power of the clinical trials would be low. Animals can bite without being rabid, or without shedding the virus. Furthermore, the severity of the wounds beyond WHO level 3 exposure was still heterogeneous. This meant that the clinical trials needed to be adjusted to mitigate these issues. Rabishield™ was approved with relatively small clinical trials which measured neutralizing titers. This uncertainty was also present in the monoclonal snake antivenom case, as snakebite also has issues with uncertainty. This is because snake venom is heterogenous and snakes tend to dry bite. This uncertainty generates issues for the clinical trials. In order to mitigate this, the number of participants can be adjusted, or patient stratification can be improved with toxin detection kits, pan-specific antivenom, or alternate clinical trial endpoints.

MAPPs connection to the assessing efficacy discussion.

The first principle that in connected to assessing efficacy is timely access. It is related to assessing efficacy as the uncertainties inherent to a disease influence the clinical trials, and the clinical trials determine the evidence that is required. Multiple factors determine the risk that rabies and snakebite have on patients, and uncertainties that influence these factors can make correct assessment difficult, and thus influence the possibilities that timely access can provide.

The second principle that is connected to assessing efficacy is iterative development and assessment. Iterative development concerns the use of the post-licensing knowledge generation, which is affected by uncertainties which are present when assessing efficacy. It considers a starting point and possible expansions for the phase IV clinical trials.

The last principle that is connected to assessing efficacy concerns the use of real-world data. Whilst real world data normally is used in phase IV clinical trials, R2 mentioned that the use of real-world data is valid throughout the entire development of a product. R5 mentions that is could be appropriate but questions whether it would be possible. The use of placebo is rejected by all interviewees as it not considered to be ethical. The use of real-world data is a method to measure efficacy, but its use before phase IV clinical trials is questionable as it often includes unequal settings possibly unfit for use in clinical trials. If it is possible to use real-world data without placebo then it could be appropriate.

The connections between the MAPPs principles and the discussion points from the regulatory discussion are summarized in Table 13 below, along with the relative importance of the principle for each of the cases (X= is no discussion, and 0 to ++ implies the relative importance).

Table 13: Summary of the connection of the MAPPS principles and the discussion points

MAPPS PRINCIPLE	BLOOD PRODUCT VERSUS MONOCLONAL *RABIES/SNAKEBITE*	STANDARD OF CARE *RABIES/SNAKEBITE*	ASSESSING EFFICACY *RABIES/SNAKEBITE*
UNMET MEDICAL NEED	++/++	++/++	++/++
TIMELY ACCESS			+/++
ITERATIVE DEVELOPMENT AND ASSESSMENT			X/0
REAL-WORLD DATA			++/++
EXPANSION OF TREATMENT ELIGIBLE POPULATION		+/++	
ADAPTIVE PRICING AND REIMBURSEMENT	0/++	+/++	
ENSURE APPROPRIATE UTILIZATION		0/++	

7. Conclusion and Discussion

Conclusion

This research was performed to answer the following research question:

How was the development process of Rabishield™ regulated with a tailor-made approval process and how can we translate the corresponding principles and learnings to the approval of innovative therapies?

This question yielded three points that were of specific concern for the regulatory discussion: (1) Blood product or monoclonal, (2) Standard of care, and (3) Assessing efficacy.

The blood product or monoclonal discussion, or regulatory categorization of treatments, was found to affect the amount of evidence needed for market approval. In turn, the required evidence influences the design of the clinical trials needed to gain market approval, and consequently the involved costs and development time of the treatment. The use of blood product regulation was articulated by respondents to allow for a lower amount of clinical evidence required for market approval, and thus lower the development costs and time-to-patient. However, higher amounts of clinical evidence, in the case when categorized as a monoclonal treatment, would have a greater chance of convincing multiple regulatory authorities. Stakeholders interested in lower evidentiary requirements focused on the possible product improvement over immunoglobulins, prompting lower requirements.

This discussion can be related the research of Ozcan & Gurses (2018) on the regulatory categorization of dietary supplements, which moved between regulatory categories before creating their own category. They found that firms attempt to *"disrupt unfavorable regulation"* via their intended audience in order to lower development costs and time. In this case this the developer could reiterate those afflicted by an unmet medical need in order to try to lower development costs and time, which would coincide with the findings by Hoekman & Boon (2019), who found that unmet medical needs *"were not driving utilization, but a means to justify approval"*.

However, when connected to the MAPPs principles, this means that the blood product versus monoclonal discussion is connected to the principles of timely access and adaptive pricing and reimbursement. This implies that regulatory categorization of treatments can not only be in favor of the manufacturer of the drug and used as a tool to justify limited data collection but has also the possibility to determine the degree of access to patients. This matter is especially important in LMICs where a lack of individual financial resources can pose a burden to potential life-saving products.

In a comparison, the discussion on the possible product price was more prominent during the snake antivenom discussion, and thus the principles of timely access and adaptive pricing and reimbursement were more prominent. This means that the potential categorization of the antivenom as a monoclonal treatment was perceived to have more severe consequences for the access to this treatment than Rabishield™. Consequently, regulatory authorities need to, as described in detail by Eichler et al. (2008), carefully balance the need of evidence which can result in a delayed market access at one side, but higher levels of uncertainty on effectiveness and safety at the other side.

A potential solution to accelerate market approval while monitoring safety and efficacy is to move the burden of clinical benefit and evidence to the post-authorization phase and shortening the pre-market approval development process. This alternative market approval process equals the third product acceleration method as described in the theory section where less evidence for market approval can speed the time to market and counteracts the unmet medical needs of snakebite victims without access to specific treatment whilst monitoring safety on the basis of real world data.

Whilst additional safety issues would be expected with such a method due to limited clinical evidence, Boon et al. (2010) found no special safety issues with early approval instruments in Europe, and

Richey et al. (2009) found that accelerated approval programs for oncology indications in the US were safe. Although, whilst evidence was found that the clinical development period could be shortened by Boon et al. (2010), Richey et al. (2009) found no evidence that development times were decreased. Consequently, the nature of the accelerated approval program determines whether earlier market access can be achieved. If the clinical development period can be shortened, the related development costs could possibly also be reduced, meaning it's interesting in an LMIC setting.

The standard of care was the second point of discussion for the cases, as the standard of care was not globally definable. The presence and quality of the standard of care was found to directly affect the unmet medical need of a disease. When there is no standard of care or one of low quality, the unmet medical need and the necessity for a new innovative treatment will be high. Generally, a low standard of care would mean that there is a larger prompt for measures that would ensure mitigation of the unmet need. Stakeholders interested in lower evidentiary requirements would therefore be interested in an unmet medical need that is defined as high as possible.

When the standard of care for a disease is heterogenous and/or undefinable, there is room for ambiguity. As denoted by Mahoney and Thelen (2009), this ambiguity can be strategically used by actors to act according to their own interpretation. Thus, in the case of a heterogenous standard of care openings within the interpretation can be used by developers to contest the unmet medical need in their advantage, prompting more regulatory leniency.

When connected to the MAPPs principles the standard of care discussion could be connected to the principles of expansion of treatment eligible population, adaptive pricing and reimbursement, and ensure appropriate utilization. Comparing the cases, the expansion of the treatment eligible population was most discussed in the snakebite case, as the heterogeneity of snake venom has a great effect on the efficacy of a product. For the adaptive pricing and reimbursement, the economic implications of snakebite were also again more discussed than Rabishield™, as mostly the poor are affected.

When connected to an FRP, increasing the level of communication and commitment between the regulator and developer has the ability to enhance the transparency in the regulatory pathway to counteract the strategic use of the ambiguity surrounding the standard of care and speed up the review process. One FRP that uses this method is the FDA fast track designation (Liberti, 2017), which is aimed at allowing the possibility for drug approval after phase II trials via extended communication between the developer and regulator. A coral snake antivenom conference in 2009 denoted that the licensure of an antivenom in the case of absence of any licensed product may be facilitated by the use of fast track designation (Seifert, 2009), which might also be useful for other snakebites.

The final point of discussion articulated was the assessment of drug efficacy. Uncertainty was found to have an impact on the validity of the presented clinical evidence and should as such be mitigated as much as possible. Multiple options were presented in the bodies of evidence: (1) increasing the number of clinical trial participants, (2) improved patient stratification methods, and (3) alternative clinical endpoints. The advantage of a larger number of clinical trial participants would be that the outcome would be statistically significant without the inclusion of advanced methods, the disadvantage is the additional clinical development costs related to the additional number of participants. Additional development costs increase the price of a treatment and would therefore not be feasible for a treatment aimed at a LMICs. Improved patient stratification methods would lower the required number of clinical trial participants, lowering costs. This would, however, require that patient stratification methods (i.e. toxin detection kit or pan-specific antivenom) are available, and some methods could also have related additional costs. Reasonably effective snake venom detection kits have been developed for Australia but are reported to be too expensive for LMIC settings (Theakston & Laing, 2014), meaning the use will probably be limited.

Finally, alternative clinical endpoints could mitigate the requirement of additional trial participants, but suitable endpoints need to be identified as otherwise misuse is possible (Fleming, 2005).

When connecting the discussion surrounding assessing efficacy to the MAPPs principles it can be connected to timely access, iterative development and assessment and real-world data. Comparing the cases, the principle of timely access is pronounced in both cases, as both cases had inherent uncertainty. The principle of iterative development and assessment was only mentioned in the discussion on snakebite due to the heterogeneity in the disease. The final principle of the discussion, real-world data, was mentioned in both cases, but far more pronounced in the snakebite case as the heterogeneity in the case influences its ability to measure efficacy.

When connected to the FRP, a possible product acceleration method would be increasing the role of medicines' effects on surrogate endpoints, allowing expedited access based on preliminary clinical data by counteracting the uncertainty present in snakebite. However, as Fleming (2005) notes, the surrogate endpoints need to be a true alternative for clinical benefit, otherwise it can be misused. Gilbert & Hudgens (2008) and Richey et al. (2009) denote that surrogates can be used to shorten studies, reduce costs, and for *"bridging efficacy of a vaccine observed in a trial to a new setting*" (Gilbert & Hudgens, 2008). The last of which is especially relevant for snakebite due to the venom heterogeneity. A Coral Snake Antivenom conference held in 2009, denoted that surrogate endpoints could be used for licensure of a coral snake antivenom (Seifert, 2009).

Theoretical implications of the conceptual model

Theoretically, this research found that the principles influence and are influenced by unmet medical need, which acts as a moderator for the rest of the MAPPs principles. Unmet medical need drives and influences the demand for idiosyncratic regulatory possibilities in order to stimulate innovation when regulatory uncertainty is encountered for treatments in a regulatory void for LMICs. Therefore, this research identified that the discussion surrounding unmet medical need as a moderator for the MAPPs principles can be used to create tailor-made regulatory pathways for products in a regulatory void via the facilitated regulatory pathways. The discussion can help identify points affecting the division of generic and tailor-made regulation.

When comparing unmet medical need directly between the cases it was ultimately more pronounced during the monoclonal snake antivenom case, although it depended on the species of biting snake. When looking at the relative importance of the MAPPs principles, the principles were discussed more prominently in the monoclonal snake antivenom case, which is consistent with the more prominent discussion surrounding the unmet medical need of snakebite. Theoretically speaking, this would mean that for snakes without a specific antivenom, the division between tailor-made regulation and generic regulation would lean more to the tailor-made part in order to counteract this unmet need, and this should be visible in a possible FRP.

Practical implications

Practically, the issues discussed above provide implications for the formulation of a possible FRP for monoclonal snake antivenom and new drug products in LMICs. Regulatory interviewees noted that the chance is low that a snake antivenom mAb would be classified as an immunoglobulin. Whilst manufacturers can submit their chosen clinical evidence, and IG regulation would provide leniency to the manufacturer by reducing costs, it would not be convincing for regulatory authorities. Moving the burden of clinical benefit and evidence to the post-authorization phase could be used in order to speed the time to market in order to counteract the unmet medical needs of snakebite victims without access to specific treatment.

Due the heterogeneity in snake venom the definition of a universal standard of care for snakebite is improbable. Increasing the level of communication and commitment between the regulator and developer could be used in order to enhance the transparency in the regulatory pathway to counteract the strategic use of the ambiguity surrounding the standard of care. The start of the clinical development of a monoclonal snake antivenom could therefore be focused on a location or snake species that is currently unaccounted for to counteract an unmet medical need, and would possibly allow fast track licensure (Seifert, 2009). When safety is demonstrable the treatment eligible population can be expanded to another region, snake, or risk group.

In order to correctly assess the efficacy of a monoclonal snake antivenom the uncertainty inherent to snakebite needs to be mitigated. This could be done with sophisticated patient stratification methods, pan-specific antivenom, and the use of workable and verifiable surrogate clinical endpoints. Two proposed endpoints for coral snake antivenom included: *"(1) effect on venom levels in patients, as correlated with lack of onset/progression of neurological symptoms",* and (2) *"pharmacokinetics (PK) in humans related to PK and efficacy in animal models"* (Seifert, 2009). However, this is based on the incidence of coral snake envenoming in the US, and extrapolation to other snakes will not be straightforward. Increasing the role of medicines' effects on surrogate endpoints, allows expedited access based on preliminary clinical data by counteracting the uncertainty present in snakebite.

If phase I clinical trials are feasible and easy to perform for monoclonal antibodies there is no reason not to perform them. Furthermore, as phase I safety data is mandatory for monoclonal antibodies skipping this clinical trial is ill-advised. So regardless of the regulatory pathway, phase I clinical trials would be recommendable if they are achievable. All safety aspects of monoclonal clinical trials, even if the target of the monoclonal is exogeneous need to be considered. When early access is no option the phase II and III clinical trials need to be set up. There are guidelines for both the development of monoclonal antibodies and for the development of snake antivenom which can be used for preliminary reference. Where these conflict or lack guidance there might be a regulatory vacuum. However, guidelines are not a legally binding, and deviation is possible when solid argumentation is available. Whilst the SoC might differ between regions and nations a comparison with the best available product without placebo would be ethical and would strengthen the regulatory evidence. The use of alternative (i.e. serological) endpoints would allow the study to deal with the infection uncertainty. Concluding, there are multiple regulatory possibilities for an aspiring developer. Therefore, early stage discussions with regulatory bodies for scientific advice regarding the regulatory trajectory are highly advisable in order to correctly navigate the possibilities.

Limitations

Regarding the used theory and resulting conceptual model, the MAPPs principles used for the interview questions were not familiar to every interviewee and were sometimes considered as complex. Due to this, and despite the fact that the definition of the principles was included in the interview guide, the understanding of the principles could have been diversified between interviewees. Consequently, the discussion might not have based upon the exact same understanding. In order to mitigate this, the research did not only consider the viewpoints but the argumentation behind the viewpoints as well, in order to review the insights.

Regarding the used methodology, the focus on two specific cases and the involved specialism required to understand the cases could have led to a specific selection of interviewees that might not be representative of the entire field. The recruitment of interviewees was partially through snowball sampling, meaning the stakeholder groups were less diverse and that most interviewees were researchers or employed by NGO's or SRA's. However, this recruitment method allowed to identify respondents having profound knowledge of the chosen cases and were therefore able to provide detailed information and argumentation on their viewpoints. There is, however, the possibility that other important views of

other actors, such as healthcare professionals, are not included in the research. This does not imply that other actors do not have relevant views. For further research it would be of additional value to include other actors present in the development process, such as healthcare professionals and pharmaceutical companies.

Finally, the investigated discussion points identified in this research were similar for both cases, however this will not automatically mean that other treatments have the same points of discussion. Points of discussion might be the same, overlap partly, or be entirely different depending on the specific case, meaning that generalizability is not a given. Further research into additional cases for different indications, can be done to gain further insight in the tailor-made process of facilitated regulatory pathways, including other types of antivenom.

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Appendix A. Standard drug development pathway

In order for a therapy to be approved it needs to be able to satisfy regulatory demands. Regulatory demands differ per product category, with for example blood products and monoclonal antibodies differing in requirements. The regular drug development pathway as outlined in Table 14 below consists of five phases which will shortly be discussed below.

Table 14: Regular drug development pathway (Based on FDA (2019b)).

PHASE	DISCOVERY	PRECLINICAL DEVELOPMENT	CLINICAL DEVELOPMENT	APPROVAL	POST-LAUNCH
ACTIVITIES	-Lead Identification -Synthesis of new biologic	-Assess safety and biological activity -In vitro studies -In vivo studies	-Assess safety, dosage, and efficacy trough phase I, II, and III studies	-Review of all submitted data	-Phase IV studies

The discovery phase is often the first phase considered in drug development and entails the selection of a target and the identification and selection of a lead candidate.

The preclinical development consists of two main parts: In vitro, or lab testing, and in vivo studies, or studies in live animal models. These studies include toxicology studies, the effect of the drug on the human body, also known as pharmacodynamics (PD), and the effect of the human body on the drug, which is also known as the pharmacokinetics (PK). These need to be satisfied by study models that mimic the effect on and by the human body as close as possible.

The clinical development has three main parts: Phase 1, or first in human studies, phase 2 which includes limited effectiveness and safety studies and phase 3, which is composed of full-scale effectiveness and safety studies. As all clinical development studies have a degree of heterogeneity depending on the indication, the drug tested, and the type and number of patients available a generalized description is given below.

Regular phase I studies are used to assess the safety and test dose ranging in human volunteers (FDA, 2019a). Phase 1 studies are with small numbers of patients, usually between 20-100 (Friedman et al., 2010). Phase 1 studies are required for all mAb products (R3, R4) at the minimum, as safety and efficacy need to be demonstrated. In some cases, phase 1 studies are on non-healthy patients as the effect of the drug, even in minor doses, can have great effects on healthy individuals (Friedman et al., 2010). Once these requirements are fulfilled and a dose has been identified phase II studies can be started (FDA, 2019a; Friedman et al., 2010).

Regular phase II studies are aimed at testing the efficacy and safety on real patients with a therapeutic dose (FDA, 2019a). and usually include around 100-300 patients (Friedman et al., 2010). As phase II studies use clinical dosing the effort is aimed at identifying the biological activity of the drug. Trial design differs depending on the indication and the drug tested. Most phase II studies are randomized controlled trials, which compares the new treatment against placebo or best available treatment (Friedman et al., 2010)

Finally, Regular phase III studies include large scale clinical testing with around 300-3000 patients (Friedman et al., 2010) to determine the effectiveness of the new drug as a treatment (FDA, 2019a). Phase III studies are often randomized controlled clinical trials which determine the effectiveness of the treatment against the current standard of care (Friedman et al., 2010).

After successful phase III clinical studies, the phase IV, or post-launch studies can be started. These studies are used to exert post-market vigilance on approved treatments in order to retain safety after approval.

Appendix B: Rabies treatment roadmap

Rabies exposure is categorized in three different categories (I, II, and III) by the WHO, with category I defined as *"licks on intact skin"*, category II defined as *"nibbling of uncovered skin, minor scratches or abrasions without bleeding*", and category III defined as: *"single or multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membrane with saliva from licks, contacts with bats"* (WHO, 2018a). Only the most severe category (III) requires immunoglobulin or Rabishield™ when the patient has not been vaccinated prior to exposure (WHO, 2018a). The treatment of all three categories as defined by the WHO is shown in figure 3 below.

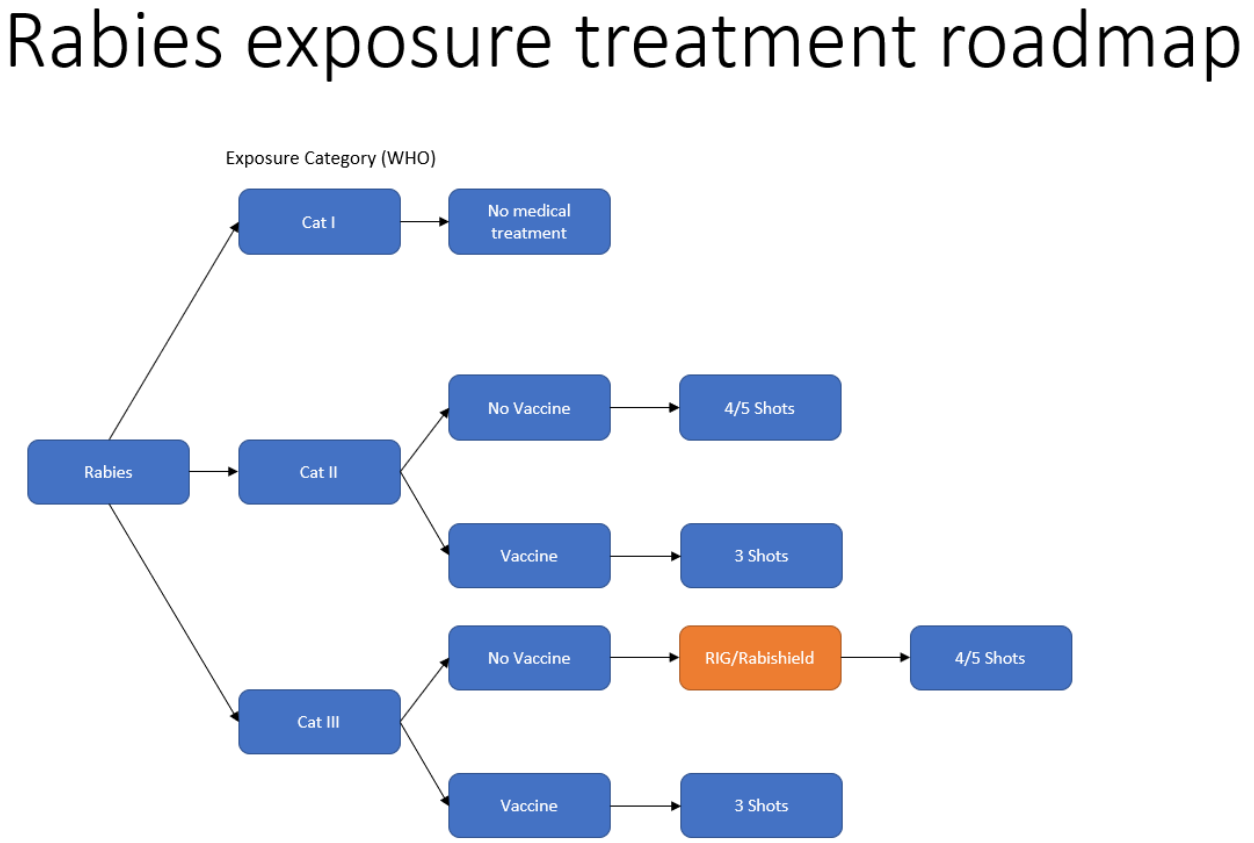

Figure 3: Rabies treatment roadmap (Authors own compilation, based on WHO, 2018a)

Appendix C: Rabishield™ Interview

Introduction

- Dear x, thank you for your interest in this research. Before we set off, I would like to ask you if this interview can be recorded for reference. A transcript or report of the interview will be sent to the interviewee to verify the data and allow adjustments and/or additions when deemed necessary. The interview will be semi-structured, meaning that it follows an interview protocol, but allows you to digress where applicable.

Short summary of the research:

- The study focusses on regulatory trajectories for monoclonal antibodies (mAb) for antivenin purposes against snake venom. As no specific regulation or guideline is currently available comparable approved mAb products were sought. The comparable products that were found included among others a mAb for tetanus and a mAb for Rabies (Rabishield™). The Rabishield™ mAb was found to have overlap with the mAb antivenin, and thus further researched. Regulatory wise there is non-specific regulation for mAb products, and regulation for snake antivenom based on horse serum. The WHO supports innovation of serum-based products, and research is currently being done to find ways to replace horse-based serum with a cocktail of monoclonal antibodies specified to toxins specific to snake venom. For the development of such a product it is deemed important to understand future requirements from regulatory authorities for market access.

- The research will therefore map regulatory approval pathways in order to study how they differ from the standard approval pathways. This will be done by interviewing diverse stakeholders and experts in the field. The study has two sequential stages, with first a retrospective study of an approved mAb cocktail aimed at Rabies (Rabishield™) to better understand the regulatory requirements and processes that resulted in the approval of this mAb. Subsequently a study of a prospective case (Snake antivenom mAb) will be conducted to better understand whether and how lessons learned from the Rabishield™ case can be applied to the Snake antivenom mAb case. This will then be used to formulate advice on the approval pathway for stakeholders involved in the process and allow insight in the development of regulation which fosters innovation.

- During the interview the principles will be shortly elaborated before the questions regarding those principles are asked to ensure equal understanding.

About the interviewee:

- What is your professional background?
- How were you involved with the Rabishield™ regulatory process?

Possible barriers

- What barriers were encountered when regarding the regulatory trajectory of Rabishield™?
- Were the dossier requirements changed when compared to a standard regulatory trajectory?
- What parts of the dossier could be completed without external consultation?

Existing regulation

- To what extent could existing regulation and guidelines be used in the development of Rabishield™?
- For which aspects of development were current regulation and guidelines unsuited?
- Who was consulted when regarding on how to proceed when regulation was found to be lacking? Why? Did this achieve the required goal?
- What strategies were used when lacking regulation was encountered, how was it dealt with?
- Why? Did this achieve the required goal?

Other Actors

- Did other parties contribute to the regulatory process? How?
- Was the media used to help further the process? Why? Did this achieve the required goal?
- To what extent could and did you learn from other products to understand the process?
- To what extent were patient groups, or other parties used as a mobilizing agent? Why? / Why Not?

Unmet medical need:

- Was this a product that addresses an unmet medical need?
- Would addressing an unmet medical need help further the development process?
- How was the concept of unmet medical need considered in phase X in your opinion?
- What has been done when regarding the concept of an unmet medical need in this phase?

Timely Access:

- Is this a product for which timely access is necessary?
- Why would timely access be necessary?
- How was timely access considered in phase X in your opinion?
- What can be done, and has been done by stakeholders with regard to timely access?

Iterative development and assessment:

- Is this a product for which iterative development and assessment is required?
- Why would iterative development and assessment be required?
- How was the iterative development and assessment considered in phase X in your opinion?
- What can be done, and has been done when regarding iterative development and assessment?

Real-world data:

- Is this a product in which the use of real-world data is necessary?
- Why would the use of real-world data be necessary?
- How was the use of real-world data considered in phase X in your opinion?
- What can be done, and has been done when regarding real world data in this phase?

Adaptive pricing and reimbursement:

- Is this a product in which adaptive pricing and reimbursement is considered?
- Why would adaptive pricing and reimbursement be considered?
- Is this dependent on the region for which the product is meant?
- How was adaptive pricing and reimbursement considered in phase X in your opinion?
- What can be done, and has been done in regard to adaptive pricing or reimbursement possibilities?

Ensure appropriate utilization:

- Is this a product in which appropriate utilization is important in this process?
- Why would this be a product in which appropriate utilization is important?
- How was appropriate utilization ensured in phase X in your opinion?
- What can be done, and has been done to ensure appropriate utilization?

List of definitions

Table 15: Explanation of the principles for the Rabishield™ case

PRINCIPLE	EXPLANATION
UNMET MEDICAL NEED	*"Focus on the promise to address an unmet medical need: Target well-defined patient population(s) with life threatening or severely debilitating conditions with no treatment or no satisfactory treatments. This means focusing on products with a high probability of considerable effect size." (Eichler et al., 2018; p2)*
TIMELY ACCESS	*"Focus on patients with a limited time-window who cannot wait until all relevant research questions have been addressed" (Eichler et al., 2018; p2)*
ITERATIVE DEVELOPMENT AND ASSESSMENT	*"Align evidence generation plan with pre-planned regulatory and P&R re-assessment time points across entire product life-span." (Eichler et al., 2018; p2)*
INCREASE OF THE EVIDENCE-TO-UNCERTAINTY RATIO	*"Progressively increase the ratio by aligning known unknowns, pre-plan and modify, where needed, the evidence generation plan across product life-span, including the post-launch phase." (Eichler et al., 2018; p2)*
REAL WORLD DATA	*"Use real world data to inform iterative decision making: Acknowledging the high internal validity of RCTs, use entire methodology toolbox for on-market knowledge generation. "(Eichler et al., 2018; p2)*
EXPANSION OF TREATMENT ELIGIBLE POPULATION	*"Amend regulatory label population in line with incoming information about product's benefits and harms in relevant (sub-) populations." (Eichler et al., 2018; p2)*
ADAPTIVE PRICING AND REIMBURSEMENT	*"Flexible price points and reimbursable populations, adapted to pre-agreed milestones, incoming new information and environmental changes." (Eichler et al., 2018; p2)*
ENSURE APPROPRIATE UTILISATION	*"Ensure appropriate utilization by managing risks and monitoring use. This allows for the education of prescribers about identified risks and uncertainties. "(Eichler et al., 2018; p2)*

Appendix D: Snake antivenom mAb Interview

Introduction

- Dear x, thank you for your interest in this research. Before we set off, I would like to ask you if this interview can be recorded for reference. A transcript or report of the interview will be sent to the interviewee to verify the data and allow adjustments and/or additions when deemed necessary. The interview will be semi-structured, meaning that it follows an interview protocol, but allows you to digress where applicable.

Short summary of the research:

- The study focusses on regulatory trajectories for monoclonal antibodies (mAb) for antivenin purposes against snake venom. As no specific regulation or guideline is currently available comparable mAb products were compelling. The comparable products that were found included a mAb for tetanus and a mAb for Rabies (Rabishield™). Regulatory wise there is non-specific regulation for mAb, and regulation for snake antivenom based on horse serum exists. The WHO supports the innovation of serum-based products, and research is currently being done to find ways to replace horse-based serum with a cocktail of monoclonal antibodies specified to toxins specific to snake venom. For the development of such a product it is deemed important to understand future requirements from regulatory authorities for market access.

- The research will therefore map regulatory approval pathways in order to study how they differ from the standard approval pathways. This will be done by interviewing diverse stakeholders and experts in the field. The study has two sequential stages, with first a retrospective study of an approved mAb (Rabishield™) to better understand the regulatory requirements and processes that resulted in the approval of this mAb. Subsequently a study of a prospective case (Snake antivenom mAb) will be conducted to better understand whether and how lessons learned from the Rabishield™ case can be applied to the Snake antivenom mAb case. This will then be used to formulate advice on the approval pathway for stakeholders involved in the process and allow insight in the development of regulation which fosters innovation.

About the interviewee:

- Professional background of the interviewee?
- Involvement with snake venom regulatory process?

Possible barriers

- Which barriers will be encountered when regarding the regulatory tract of mAb snake venom do you expect?
- What parts of the dossier can be completed with existing information?
- What parts of the dossier will require changing?

Existing Regulation

- For which aspects of (clinical) development do you expect that existing regulation and guidelines can be used
- For which aspects of (clinical) development do you expect that regulation and guidelines lacking?
- Who will need to be consulted when regulation is found to be lacking? Why?
- What strategies can be used when lacking regulation is encountered?

Other parties

- Can other parties contribute to the regulatory process? How?
- Can the media used to help further the process? Why?
- To what extent can we learn from other treatments to understand the process?

Unmet medical need:

- Is this a product that addresses an unmet medical need?
- Why would addressing an unmet medical need be necessary?
- How should the concept of unmet medical need be considered in phase X in your opinion?
- What can be done, and has been done when regarding the concept of an unmet medical need in this phase?

Timely Access:

- Is this a product for which timely access is necessary?
- Why would timely access be necessary?
- How should timely access be considered in phase X in your opinion?
- What can be done, and has been done by stakeholders with regard to timely access?

Iterative development and assessment:

- Is this a product for which iterative development and assessment is required?
- Why would iterative development and assessment be required?
- How should the iterative development and assessment be considered in phase X in your opinion?
- What can be done, and has been done when regarding iterative development and assessment?

Real-world data:

- Is this a product in which the use of real-world data is necessary?
- Why would the use of real-world data be necessary?
- How should the use of real-world data be considered in phase X in your opinion?
- What can be done, and has been done when regarding real world data in this phase?

Adaptive pricing and reimbursement:

- Is this a product in which adaptive pricing and reimbursement is considered?
- Why would adaptive pricing and reimbursement be considered?
- How should adaptive pricing and reimbursement be considered in phase X in your opinion?
- What can be done, and has been done in regard to adaptive pricing or reimbursement possibilities?

Ensure appropriate utilization:

- Is this a product in which appropriate utilization is important in this process?
- Why would this be a product in which appropriate utilization is important?
- How should appropriate utilization be ensured in phase X in your opinion?
- What can be done, and has been done to ensure appropriate utilization?

List of definitions

Table 16: Explanation of the principles for the Monoclonal snake antivenom case

PRINCIPLE	EXPLANATION
UNMET MEDICAL NEED	*"Focus on the promise to address an unmet medical need: Target well-defined patient population(s) with life threatening or severely debilitating conditions with no treatment or no satisfactory treatments. This means focusing on products with a high probability of considerable effect size." (Eichler et al., 2018; p2)*
TIMELY ACCESS	*"Focus on patients with a limited time-window who cannot wait until all relevant research questions have been addressed" (Eichler et al., 2018; p2)*
ITERATIVE DEVELOPMENT AND ASSESSMENT	*"Align evidence generation plan with pre-planned regulatory and P&R re-assessment time points across entire product life-span." (Eichler et al., 2018; p2)*
INCREASE OF THE EVIDENCE-TO-UNCERTAINTY RATIO	*"Progressively increase the ratio by aligning known unknowns, pre-plan and modify, where needed, the evidence generation plan across product life-span, including the post-launch phase." (Eichler et al., 2018; p2)*
REAL WORLD DATA	*"Use real world data to inform iterative decision making: Acknowledging the high internal validity of RCTs, use entire methodology toolbox for on-market knowledge generation. "(Eichler et al., 2018; p2)*
EXPANSION OF TREATMENT ELIGIBLE POPULATION	*"Amend regulatory label population in line with incoming information about product's benefits and harms in relevant (sub-) populations." (Eichler et al., 2018; p2)*
ADAPTIVE PRICING AND REIMBURSEMENT	*"Flexible price points and reimbursable populations, adapted to pre-agreed milestones, incoming new information and environmental changes." (Eichler et al., 2018; p2)*
ENSURE APPROPRIATE UTILISATION	*"Ensure appropriate utilization by managing risks and monitoring use. This allows for the education of prescribers about identified risks and uncertainties. "(Eichler et al., 2018; p2)*

Appendix E: Quality protocol

The quality protocol relies on four parts: Internal reliability, external reliability, internal validity, and the external validity (Bryman, 2016; Yin, 2013).

The internal reliability of this research is verifiability of the research, meaning that any researcher bias needs to be as minimal or absent. As only one researcher will partake in the research Internal reliability will be ensured by using three accepted theories provided by other authors, as well as source triangulation to verify statements. The external reliability will be ensured by documenting all used sources, all retrieved data from sources and interviews, all interview templates, and coding schemes used in the analysis.

The internal validity entails the match between observations and the resulting ideas and the avoidance of confounding. This is ensured with source triangulation and by mailing the transcripts to the interviewees for addenda or clarifications to verify the interview. The external validity is the generalizability of the research for other cases, sectors or situations. The external validity is reduced to the specificity of the case studies, but the outcome of the research might be transferable to other mAb cases and other LMIC cases.

Appendix F. Comparison of Rabies PEP products

The basic form of contemporary used rabies immunoglobulin PEP has been around since the 1950s (Baltazard & Bahmanyar, 1955; Sparrow et al., 2018). Whilst the RIG has been used effectively in the past the basic product design is now outdated as sera in general have been developed in the late 1800s. Whilst many iterative improvements have retrofitted the sera for present-day use, the introduction of new and innovative technology is beckoning. Rabies immunoglobulins are available in different formats under two main groups: Equine (eRIG) and Humanized (hRIG) in different levels of purification. Other groups are available but used far less (>1%), and thus not considered in this research.

Whilst the high degrees of severe adverse reactions related to impure immunoglobulin produce are now somewhat problems of the past (Madhusudana et al., 2013), other problems are still relevant today. ERIG and hRIG are still not considered ideal due to supply, financial, and safety issues (R10). According to Sparrow et al. (2018) only 1-10% of patients recommended to receive PEP actually receive it due to availability or cost constraints.

In general, eRIG is more affordable than hRIG but less efficacious. Some authors denote that purification has allowed eRIG to approach or be equal to hRIG in terms of safety and efficacy (Madhusudana et al, 2013). However, there appears to be no consensus on what degree of purification most eRIG products have as Gogtay et al. (2012) and Tsekoa et al. (2016) denote "more adverse effects" and "occasional allergic reactions" respectively. On the other hand, the WHO denotes that it is a "*misperception that scarce and costly hRIG is superior and safer*" as "*nowadays eRIG is highly purified and enzyme-refined*" (WHO, 2017). The preceding presents two implications: 1. eRIG is implied to have more adverse effects and 2. hRIG and eRIG can be equal in terms of efficacy and safety. ERIG that is currently being used appears to have various degrees of purification. Therefore, this research considers two theoretical kinds of eRIG: unpurified and purified, as apparently variants of both are being used.

The problem with the purification is that each additional step adds costs, and costs need be avoided as much as possible when dealing with destitute settings. In order to improve the financial situation, the price range of the mAb product needs to be under or equal to the cheapest contemporary product (WHO, 2017). It is believed that mass-produced mAbs can be a cheap alternative (R7), the SIIPL has committed to providing the price of Rabishield™ at approximately 20% higher than the price of eRIG (Sparrow et al., 2018). Whilst in destitute conditions any price is too high, every chance to lower the price should be considered an improvement. Furthermore, sources denote that large-scale production could allow the price of mAbs to be comparable or lower than eRIG in the future (R5; Sparrow et al., 2018).

When regarding the safety of the products the mAb is promising as mAbs are specified therapy proteins aimed at specific targets, as opposed to the partly specified combination in sera, meaning toxicity, especially off target toxicity, should be low (R3). The safety profile of regular eRIG is unfortunately worrying, with its use related to more adverse effects. Purified eRIG and hRIG suffer less of these adverse effects, but they are still reported, nonetheless. MAbs have the best safety profile due to the inherent purity and specificity of the cocktail relating to a low chance on adverse reactions (R3), meaning it could also maybe be used in clinical settings that used to be dangerous for antivenom due to the degree of adverse reactions (Boyer et al., 2013).

The efficacy of the RIG products also differs on the purity level of the produce. Regular eRIG is reported to have the lowest efficacy because of the low specific therapeutic content, which also explains the high percentage of adverse events reported with these products. The purified eRIG and hRIG have increased safety and efficacy compared to the unpurified products (Madhusudana et al, 2013), but are still not perfectly suited to their task. MAbs have high efficacy due to the inherent specificity of the cocktail (R3).

Potential for increasing the efficacy with monoclonal antibodies could also positively affect other factors in the process. S15 mentions that *"if snakebite victims keep getting treated with inappropriate*

antivenoms and as a result die or suffer permanent sequelae, their families and friends may not believe that antivenoms are indeed effective", which is a negative continuation of a lack of effectiveness. Not only family and friends of those affected might be skeptical though, as S14 mentions that *"Health workers in remote settings are also reluctant to treat snakebite because of apprehension about managing antivenom associated adverse reactions."*.

An additional problem related to the development of immunoglobulins is the risk of contamination (Gogtay et al., 2012). As sera are blood products there is chance of contamination with blood-borne pathogens, leading to a risk of infection. Whilst mAbs are not blood products, they are live products which are developed in live expression systems, meaning infection is also still possible (Casadeval et al., 2004). However, as sera are often pooled the chance of contamination is assumed to be higher in sera (Gogtay et al., 2012).

The pooling of sera is done because it allows the sera to minimize batch-to-batch variation to a certain degree, as there is a high degree of heterogeneity in blood products. For example, the study by Wilde et al. (1989) used two batches of the same product which had protein contents, commonly associated with adverse reactions, of 7.03% and 10.2% respectively. Another product used in the study had a protein content between 0.6%-2.8%, demonstrating the differences between products and between batches. This batch-to batch variation is a lot lower or non-existent in mAbs, as the products are clonal (R3). The only variation is in the formulation, which can be tailored to suit the required demands, allowing for more control over the product (R3).

The final major drawback of RIG is the lack of availability even if the financial means are available (Gogtay et al., 2012; Sparrow et al., 2018). MAbs would be able to help alleviate the supply shortage as they are easier to produce and mass production is available when needed (Gunale, 2017). A simplified disquisition of all specifics of Rabies PEP possibilities mentioned above is provided in Table 17 below.

Table 17: Product specifics of Rabies PEP (simplified from -- to ++)

RABIES PRODUCT	COMMON ERIG	PURIFIED ERIG	HRIG	MAB
AFFORDABILITY	++	-- to ++	--	+ to ++
SAFETY	--	- to +	+	++
EFFICACY	--	- to +	+	++
CONTAMINATION CHANCE	--	-	-	0
BATCH TO BATCH VARIATION	--	--	--	++
AVAILABILITY	0	-	--	++

As there is no clear consensus on the quality of the used and discussed eRIG, it is assumed that the pricing stated in articles considers the use of purified eRIG when comparing the product specifics. For Rabishield™ to have a practical use case it needs to be non-inferior or better in all of the specifics mentioned when compared to the best available treatment(s). Whilst Rabishield™ is significantly cheaper than hRIG, it is 20% more expensive than purified eRIG, meaning that it is non-inferior on affordability. Regarding safety and efficacy monoclonals are reported to be non-inferior or better than both purified eRIG and hRIG. Whilst there is a still a chance of the bioreactor getting infected this chance is deemed lower than the contamination chance of purified eRIG and hRIG. The batch-to-batch variation of a mAb and hence product control, is far better with an inherently homogenous monoclonal antibody, meaning that a mAb is non-inferior or better than purified eRIG and hRIG. Finally, the potential availability of mAbs is much better due to the easier production, and possibilities for mass production.

Concluding, Rabies PEP mAbs are non-inferior or better in all specifics when compared to hRIG, and non-inferior or better in all specifics except affordability than purified eRIG, with the SIIPL committing to a price that is around 20% higher than eRIG. Whilst this price hike compared to eRIG is unfavorable, the

price reduction compared to hRIG is an improvement. As mAbs also manage to outperform eRIG on safety, efficacy, batch-to-batch variation, and availability the product could prove a good competitor or replacement for immunoglobulins.