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Review

Lessons learned during the development and transfer of technology related to a new Hib conjugate vaccine to emerging vaccine manufacturers

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ABSTRACT

The incidence of Haemophilus Influenzae type b (Hib) disease in developed countries has decreased since the introduction of Hib conjugate vaccines in their National Immunization Programs (NIP). In countries where Hib vaccination is not applied routinely, due to limited availability and high cost of the vaccines, invasive Hib disease is still a cause of mortality. Through the development of a production process for a Hib conjugate vaccine and related quality control tests and the transfer of this technology to emerging vaccine manufacturers in developing countries, a substantial contribution was made to the availability and affordability of Hib conjugate vaccines in these countries. Technology transfer is considered to be one of the fastest ways to get access to the technology needed for the production of vaccines. The first Hib conjugate vaccine based on the transferred technology was licensed in 2007, since then more Hib vaccines based on this technology were licensed.

This paper describes the successful development and transfer of Hib conjugate vaccine technology to vaccine manufacturers in India, China and Indonesia. By describing the lessons learned in this process, it is hoped that other technology transfer projects can benefit from the knowledge and experience gained.

1. Introduction

The World Health Organization (WHO) estimated Haemophilus Influenzae type b (Hib) to cause at least 3 million cases of serious disease and 400,000–700,000 deaths each year in young children in 1998 [1], almost all in developing countries. Hib was the leading cause of non-epidemic bacterial meningitis and the second leading cause of bacterial pneumonia [2]. Developing countries have been hesitant to introduce the vaccine in their NIP's because of its relatively high price and their limited awareness about the disease burden. In addition, in the absence of sufficient clinical evidence about the effectiveness of Hib vaccine in developing countries there was no clear strategy of WHO about the use of the vaccine in these countries [1]. Local production of Hib vaccine would solve the supply problem and lower the price. However the Hib technology was not accessible to Developing Countries Vaccine Manufacturers due to patents and proprietary know how about the Hib production technology.

Given the longstanding history of Intravacc (The Institute for Translational Vaccinology, originating from the former Research and Development Unit of the National Institute of Public Health (RIVM) and the Netherlands Vaccine Institute (NVI)) in technology transfer [3–12], it was decided to develop a process for the production of a Hib conjugate vaccine and transfer the technology to manufacturers in developing countries.

The Hib technology transfer project, started at Intravacc in 1998. The primary objective was to develop and transfer Hib conjugate vaccine technology to a number of emerging manufacturers in Indonesia, India and China in order to ensure a sustainable supply of affordable Hib conjugate vaccine. This project was unique compared to other technology transfer activities organised by

Abbreviations: Hib, Haemophilus Influenzae type b; DTP, Diphtheria Tetanus and Pertussis; HepB, Hepatitis B; GAVI, The Global Alliance for Vaccines and Immunisation; WHO, World Health Organisation; RIVM, The National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu); NVI, Netherlands Vaccine Institute; Intravacc, Institute for Translational Vaccinology; SII, Serum Institute of India; NIP,BE, Biological E; SIBP, Shanghai Institute of Biological Products, National Immunization Program; FTE, Full Time Equivalent.

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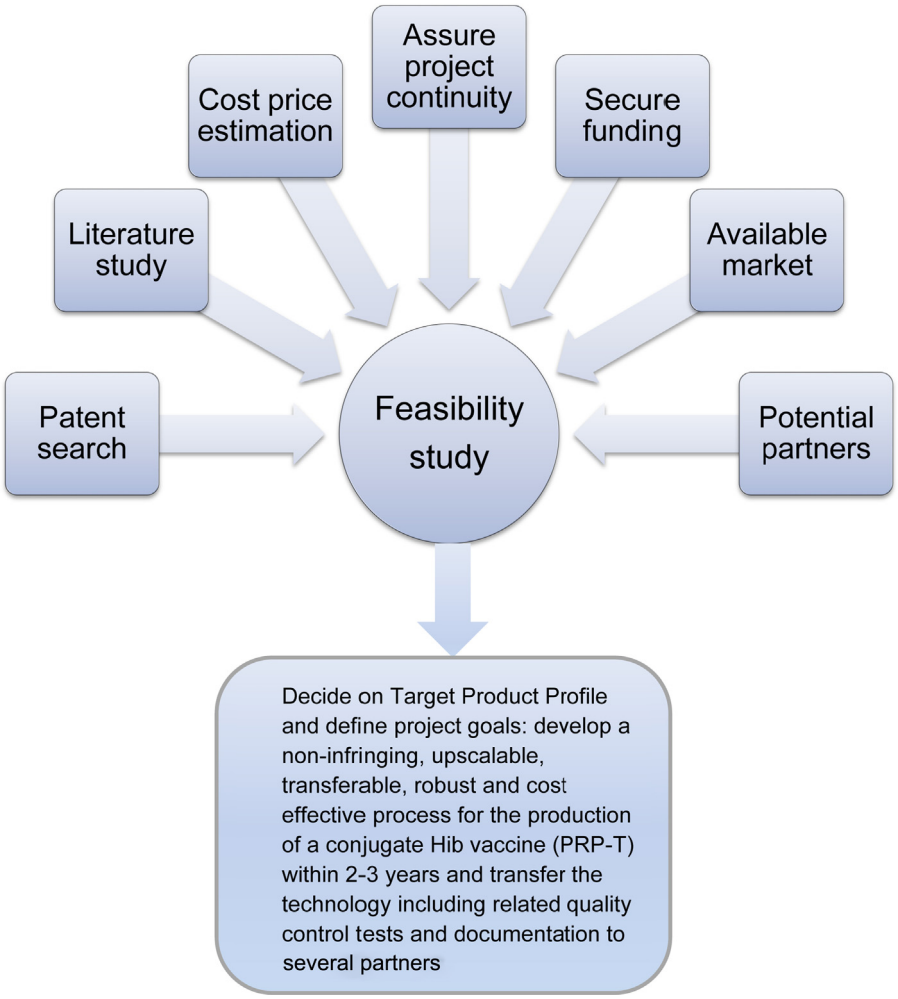

Fig. 1. Schematic representation of the feasibility study performed before starting the Haemophilus Influenzae type b project at Intravacc: by studying the project feasibility at an early stage, taking several aspects into consideration it was possible to define a realistic Product Target Profile and thereby acceptable project deliverables.

Intravacc until then. The main difference being that the technology that had to be developed was not directly needed for the Dutch Immunization Program. The project was mainly financed by the technology transfer partners after a seed capital was made available by Intravacc to start.

This paper will focus on the lessons learned within the framework of the Hib conjugate vaccine development and technology transfer project at Intravacc.

2. General aspects

Project feasibility and project management are two aspects that can be considered general, relatively independent of the project type, but of great influence on the progress.

2.1. Project feasibility

Before starting the Hib project at Intravacc a feasibility study was performed in order to evaluate the national and international importance of the Hib project and to see if it was possible to start such a project. All technologies transferred until then were already being used routinely to produce and/or test vaccines for the Dutch NIP. What made the Hib project different was that it was solely intended for technology transfer. As part of the feasibility study (Fig. 1), different aspects were studied: freedom-to-operate, Prior Knowledge, expected cost price of the vaccine, project continuity including impact on on-going projects, funding, potential partners and available market.

Based on this feasibility study it was concluded that it was possible to develop a non-infringing, scalable, transferable, robust and cost effective Hib process within 2–3 years and to transfer the process and related quality control tests and documentation to several partners. Based on the cost-price calculations performed at that stage of the project it was concluded that a very competitive cost price was possible ($\leq$1.00 $/dose). The Hib project was considered feasible and the main preconditions were defined:

- Assuming that the potential partners did not had any Prior Knowledge related to polysaccharide/conjugate vaccines, the Hib vaccine had to be developed solely by Intravacc.
- Technology transfer had to start at an early stage of the project to allow the partners to make certain choices that may be of importance for their own situation: depending on the partner; attention was required for retention of staff, setting up a research and development infrastructure and/or building a production facility.
- Intravacc had Prior Knowledge on polysaccharide and conjugate vaccines [13–16], this knowledge had to be evaluated and used as much as possible for the benefit of this project.
- The process to be developed had to be non-infringing with existing patents.

- The concentrated conjugate bulk had to be stable in order to allow the possible production of a liquid stand-alone or combination vaccine at a later stage; therefore stability testing of intermediate products had to be part of the project.
- The process had to be as much as possible free from raw materials from animal origin.
- The process had to be scalable since it was decided that not all unit operations could be scaled up at Intravacc. This was mainly due to a limited availability of large-scale capacity because of other high-priority projects.
- The vaccine had to comply with both European Pharmacopeia and WHO requirements [17–19]; local requirements did not exist at that time.
- The process had to use as much as possible "conventional" equipment that is already available at partner's facility.

It was decided to develop a PRP-T vaccine (Hib polysaccharide conjugated to tetanus toxoid), as similar vaccines were already licensed and extensively used in various NIP's worldwide. In addition, lot release criteria were already available for this vaccine and the conjugation process was published by Robbins [20,21] and not patented. Further, tetanus toxoid was being routinely produced by most of the potential partners and clinical trials, to demonstrate the effectiveness of this vaccine, were relatively simple to perform as a serological correlate of protection was available.

2.2. Project management

In order to manage the project in an efficient way a dedicated project team was assigned at Intravacc (seven FTE's for at least 2–3 years). Further, a project management software ("Microsoft-project") was used to plan and manage the tasks and activities related to the project. An integrated project planning, including both the activities at Intravacc and at partner's site, was updated regularly in coordination with each individual partner. The deliverables, milestones and go-no-go decisions were clearly defined in the planning and discussed with the partners.

Further, both Intravacc's and partner's management team had regular meetings in order to discuss the progress of the project.

Thus, in general the management approach followed was partner- and regulatory-driven: every decision taken was evaluated from an applicability point of view, at the partner's site, as well as from a regulatory point of view and possible impact on the time-to-license.

2.3. Project specific aspects

Beside the general aspects mentioned above, some specific aspects were found to be very important for a successful Hib technology transfer project. These aspects are mainly related to the nature of this project.

2.4. Intellectual property

The Hib technology that was developed and transferred had to be non-infringing with existing patents in order to guarantee freedom-to-operate after the completion of technology transfer. A preliminary patent search took place at a very early stage of the project followed by a regular consultation of the relevant patent literature during different development stages of the process. A couple of patents were considered to be of relevance in the development of the Hib process. Several conjugation methods used in the production of licensed Hib conjugate vaccines were already patented [22–26], so these methods were not used. A conjugation method patented by intravacc was not used as this method was never applied for the production of a licensed vaccine [27]. A conjugate purification method that gave relatively high yields appeared to be patented as well [28], a different purification method had to be chosen, accepting thereby a lower process yield. Processes for the formulation of combination vaccines including Hib were also patented [29]. Therefore, the partners were advised to stay as close as possible to their own DTP and/or DTP-HepB formulation, which was also preferred for regulatory reasons. Ultimately, a non-infringing process was developed and implemented [9].

It was decided to file a "protective" patent application on the Hib process developed by Intravacc since the innovative aspects of this specific process were not covered in the (patent) literature. This was also done in order to protect this new knowledge from being patented by a third party and to guarantee the access of the Hib partners to the technology developed by Intravacc during and after the finalization of the transfer of the technology. In the meantime, the patent is granted in all countries where one or more of the Hib partners are present, in Europe and US. The partners were given a license on this patent [30–32].

2.5. Regulatory aspects

When Intravacc started with the Hib project, a number of safe and effective Hib conjugate vaccines were already licensed [33]. One of these vaccines (PRP-T) was produced according to the Robbins conjugation method [20,21]. As this technology was not patented and already well-established resulting in safe and effective Hib conjugate vaccines, this conjugation method was selected in order to produce a 'me-too' product, following the published information.

Further, lot release criteria had been already established for this Hib conjugate vaccine [17–19]. In case a new conjugation method would have been chosen, which was technically quite feasible, as Intravacc owned a patent, new product specifications should have been investigated in extensive clinical trials to support the lot release criteria. That was considered as unethical, costly and time consuming.

Further, during the process of development and transfer of the Hib technology it was noticed that local regulatory authorities did appreciate additional information on conjugate vaccines. This was provided by Intravacc through Hib training courses and workshops on quality control and lot release aspects in collaboration with WHO. In addition, local regulatory authorities were involved in crucial decision-making's from the very beginning of the project.

2.6. Strategic aspects

Investing in a Hib conjugate vaccine was very critical for most of the emerging vaccine manufacturers, since DTP-HepB-Hib combination vaccines were replacing DTP and DTP-HepB. Further, in most developed countries acellular pertussis vaccine was being introduced while in developing countries, whole cell pertussis was still the vaccine of choice. To anticipate any shortage of combinations based on whole cell pertussis vaccine, local production of these vaccines was needed. This was the incentive for many emerging vaccine manufacturers to expand their product portfolio by introducing new combination vaccines [34].

Further, it was very important to decide on the selection of potential partner(s). The first selected partner was Bio Farma, Indonesia. Bio Farma's management was very committed to the Hib project and competent staff was available. In addition, Bio Farma was WHO pre-qualified and had thereby access to the global market.

Intravacc decided together with Bio Farma about the Target Product Profile: a freeze-dried stand-alone Hib conjugate vaccine to be combined with a quadravalent vaccine (DTP-HepB) just before

injection. In addition it should be possible in the future to develop a liquid stand-alone or liquid pentavalent (DTP-HepB-Hib) combination vaccine starting with concentrated bulk conjugate.

Since the partner was willing to produce the Hib vaccine both for local as well as for global (through UNICEF) use, it was decided that the product should meet the European Pharmacopeia and WHO requirements. Local requirements did not exist at that time.

None of the potential partners had previous experience with conjugation technology, getting access to Hib conjugation technology have given Hib partners the opportunity to get familiar with conjugate vaccines in general and invest in the necessary infrastructure [35,36]. Further, one of the conditions to enter into a Hib technology transfer agreement with Intravacc was to invest in the research and development infrastructure locally. As Intravacc is not a routine producer of Hib vaccine, troubleshooting had to be taken over by the partners after a couple of years from finalizing the technology transfer. In addition, Intravacc identified many triggers for further process optimizations, but not all could be implemented because of the relatively short duration of the project. Partners were therefore advised on aspects related to optimization and scaling up of the process. Intravacc did develop the process at pilot scale (cultivation up to a 500 L bioreactor scale and conjugation up to 20 000 doses) including related quality control tests and transferred this technology to all partners. The partners were responsible for further scaling up in their own facilities. The large scale technology developed by the individual partners was considered to be proprietary know how and not shared between partners. Intravacc was involved in the implementation and scaling up of the process at partner's site. The choice to follow this approach was made taking the available resources into account; a turn-key project up to commercial scale (including all clinical data) would take more time and money and was only relevant in case the product to be developed was to be licensed through Intravacc. Further, Intravacc generated relevant materials, documentation and data, including preclinical data, and transferred all the materials and information to the individual partners.

Comparability of the batches produced at different scales and different production sites was assessed based on the lot release criteria. Whenever needed, data were duplicated by Intravacc and additional tests were used to assess consistency and comparability of the batches. To facilitate the comparability studies performed by Intravacc, all the technology transfer partners used (raw) materials of the same quality (documents related to (raw) material specifications were provided by Intravacc in the framework of the Hib project). Further, Intravacc provided the individual partners with seed lot, reference samples and reagents and Bio Farma (the first partner) produced the first clinical lot (used for (pre)clinical studies) in close cooperation with Intravacc [9], this lot was used as a "golden standard" for all technology transfer partners.

2.7. Financial aspects

Getting external financial support was not possible. After exploring several possibilities, it was clear that receiving financial support would have been seen as an unfair competition vis-à-vis Hib conjugate vaccine manufacturers who already had a licensed product. Consequently the whole project was financed by the partners and a seed capital from Intravacc.

2.8. Marketing aspects

The Global Alliance for Vaccines and Immunization (GAVI) has played a very important role in creating a Hib market, resulting in the routine use of the vaccine in many developing countries. 83% of the GAVI eligible countries were using Hib conjugate vaccine in 2009 [37,38].

This approach has attracted new manufacturers and created more competition, to supply Hib vaccine at a lower price to developing countries. Although GAVI has played an important role in making the necessary funds available, to allow UNICEF to buy the vaccine (the so called "pull strategy"), GAVI did not support new manufacturers to develop Hib vaccines ("push strategy"). This was done by Intravacc by means of the Hib project. At least two partners of the Hib project contribute significantly to the global supply of Hib vaccine to UNICEF. So both strategies are needed to achieve a sustainable supply of affordable and quality vaccines to developing countries.

Further, the availability of data from multiple burden assessment studies followed by the publication of a revised WHO position paper [39] in 2006, recommending global use of Hib vaccine, played a critical role in a growing demand for Hib vaccine in developing countries.

2.9. Technology Transfer aspects

The technology transfer approach chosen for this project was one that covers all the phases of a technology transfer process: preparation, start-up, implementation, evaluation and troubleshooting (Fig. 2). During the preparation phase enough information was exchanged in order to have a license agreement in place, the partner had to make sure that funding is secured and that the continuity of the project could be guaranteed. This was followed by appointing a dedicated project team, preparing an integrated project planning and a work plan, exchanging technical information and training partner's staff on both the process and quality control tests at Intravacc's facility. During the implementation phase, the partners had to order all the materials needed, setup their own documentation system (based on Intravacc's documentation) and setup a seed lot system using the seed lot produced by Intravacc, prepare experimental batches and receive training in their own facility. Further, Intravacc provided the individual partners with a well characterised Hib seed lot with a known history, sufficient quantities of reference samples and reagents to be able to implement the transferred knowhow. During the evaluation phase, Intravacc tried to identify the gaps for each individual partner, based on the available data and information and decide together with the partner on further training needs. If necessary, Intravacc was willing to train the partner multiple times. Depending on the progress made, advice and support was given during the scaling up, clinical trials and registration. Intravacc was involved during the troubleshooting phase and helped generating additional information and data, duplicate testing and if needed plan additional trainings.

Intravacc's Hib technology was ultimately transferred to four different partners [9]. Bio Farma (BF, Indonesia), Biological E Ltd. (BE, India), Serum Institute of India (SII, India) and Shanghai Institute of Biological Products (SIBP)/Glovax (China). Many other vaccine manufacturers showed interest in this project but it was decided from the very beginning to transfer the technology to a selected group in order to have enough focus and to achieve the pre-set goals. Unnecessary competition at an early stage would not encourage emerging manufacturers to invest in a new product.

Further, within the framework of the Hib project, people from Birmex (Laboratorios de Biologicos y Reactivos de Mexico) and UMC (Universitair Medisch Centrum Utrecht) were trained on more generic conjugation know-how. In addition, a Hib course was developed in collaboration with WHO to train both production and regulatory staff from several countries on quality control aspects related to conjugate vaccines.

During the technology transfer of Hib technology from Intravacc to the individual partners, a couple of key features were determined that can be considered to be decisive factors for the

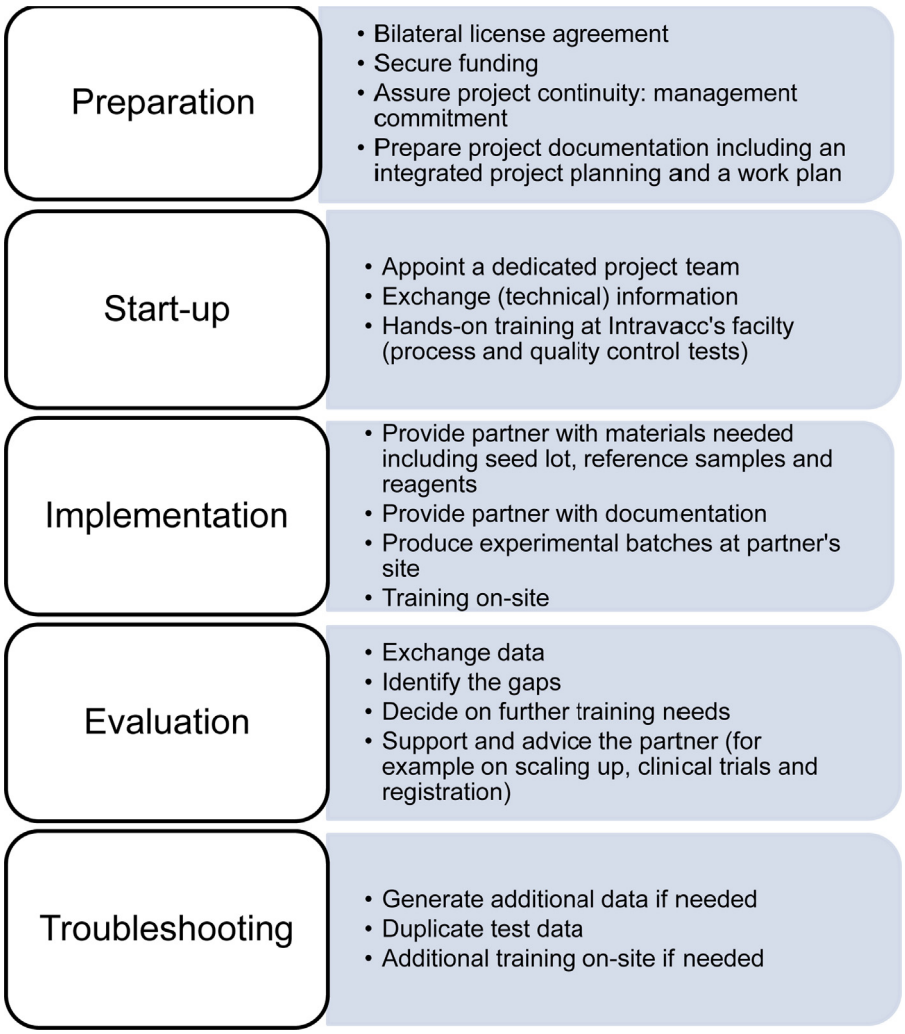

Fig. 2. Schematic representation of the "overall technology transfer approach" followed for the Haemophilus Influenzae type b project at Intravacc including main activities: this approach covered all the phases needed for a technology transfer process; preparation, start-up, implementation, evaluation and troubleshooting.

success of the Hib technology transfer project: commitment of all personnel involved, including the management, competent and dedicated team both at Intravacc and at each individual partner and clear communication between Intravacc and the partners including timely sharing of data and information.

3. Discussion

The Hib project was the first technology transfer project at Intravacc which was solely meant for technology transfer purpose and not for the Dutch National Immunization Program. For that reason many lessons were learned in the course of this project. A committed, multidisciplinary, competent and dedicated team was needed both at the technology owner and at the technology recipient side. Having such a team at Intravacc made it possible to develop a non-infringing, scalable, transferable, robust and cost effective Hib production process including quality control tests, within 2–3 years. In addition, preclinical data were generated within 4 years realizing a proof-of-concept for the process to be transferred. A committed management willing to invest in the new product was crucial in order to have a fast and efficient technology transfer. An example was Serum Institute of India (SII). The transfer of technology started in 2001 and already in 2007 SII was able to license and prequalify Hib conjugate vaccine. To achieve this, SII had to invest in its production facilities and research and development infrastructure. An open communication with the Hib project team in SII did help to insure an efficient transfer of the technology. The delay that other partners experienced was mainly because of the difficulties to keep competent/trained personnel and managerial issues.

In line with the primary objective of the Hib project; two partners have played an important role in the global price reduction and sustainable supply of large quantities of Hib conjugate vaccine: Biological E Ltd. (BE) and Serum Institute of India Ltd. (SII). SII supplies pentavalent vaccine (DTP-HepB-Hib) through GAVI for $1.75 starting from 2011 and BE decided to cut the GAVI price to $ 1.19 per dose starting from 2013. SII and BE are committed to supply about 600 Million doses of this vaccine in the coming years. A decade ago, GAVI had only one European supplier and the price of pentavalent vaccine was $3.56 per dose [40,41].

Through this Hib project, Intravacc's partners were provided with general conjugation knowhow, and related quality control tests, resulting in a broadening of their research and development portfolio with several conjugate vaccines including meningococcal and pneumococcal vaccine, beside several Hib combination vaccines.

Emerging vaccine manufacturers consider technology transfer to be the fastest route to develop a vaccine and to get access to the

know-how needed [42]. In general technology transfer has been proven to be an efficient tool in increasing a sustainable vaccine supply and consequently in improving population health [43].

The approach followed for this Hib technology transfer project was successful and can be followed for other technology transfer projects. Before starting the project an extensive and detailed feasibility study was needed in order to evaluate most important aspects: freedom-to-operate, Prior Knowledge, expected cost price of the vaccine, project continuity including impact on on-going projects, funding, potential partners and available market. Based on the outcome of the feasibility study, key factors influencing the success and effectiveness of the project were defined. By defining most of the elements having an impact on the project and identifying the project priority position for both the transferee and transferor, it was possible to decide on the project preconditions and thus the mechanism to be followed during the process development and technology transfer.

The partner selection has taken place at an early stage and was mainly based on the management commitment to the project, the capability to keep competent personnel and the willingness to invest in the new product. The Target Product Profile and thereby the product requirements to be met were decided in collaboration with the technology transfer partners and could be partly based on the anticipated market. The availability of an integrated project planning facilitated the communication between the technology owner and recipient. Further, the data, materials and documentation that was generated and transferred by the technology owner was discussed with the local regulatory authorities at an early stage of the project to avoid unnecessary delays in the licensure of the vaccine. Training of staff from local regulatory authorities was considered because the product was relatively new.

Funding source

The Hib technology transfer project was funded entirely by the various partners (BF, BE, SII and Glovax/SIBP), through bilateral license agreements. In the beginning a seed capital from Intravacc was used to study the feasibility of the project and generate proof-of-concept data.

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