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# A Key Opinion Leaders Analysis of the Critical Success Factors for the Market Potential of Genetically Modified Vaccines

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**ABSTRACT:**Conventional vaccines have been very successful in preventing and controlling many diseases. One of the next steps in vaccine innovation is the introduction of genetic modification, which provides various novel opportunities in the vaccine field. Although the market potential for conventional vaccines has been evaluated in detail, the market potential of genetically modified vaccines has not been investigated yet. Interviews with key opinion leaders were conducted to extract critical success factors, which subsequently were quantified, weighed, and prioritised by a ranking survey. Results of this study revealed that critical success factors could be classified into four categories: technical, commercial, rules & regulations, and societal. The key opinion leaders indicated that the category “rules & regulations” requires immediate attention and consideration. Additionally, the “societal potential” category demands intervention measurements, as both these categories included highly prioritised barriers. They further indicated that genetically modified vaccines provide new market opportunities against previously untargeted diseases.

**KEYWORDS:**Genetically modified vaccines, Novel vaccine technologies, Critical success factors, Innovation barriers, Market potential, TAM, SAM, TM.

### I. INTRODUCTION

The astonishing success of vaccines in disease control and prevention is and remains undeniable. The global eradication of smallpox and rinderpest exemplifies the outstanding achievements that vaccination has made so far[1, 2]. Moreover, vaccination is considered the most cost-effective medical tool to control infectious diseases[3]. Despite successes achieved by conventional vaccines, there are still a lot of diseases that are difficult to target[4, 5, 6]. These untargeted diseases include ‘the big three’: malaria, tuberculosis, and HIV/AIDS [7]. ‘The big three’ are responsible for the occurrence of 217,9 million new infections each year [8], emphasizing the necessity and urgency of vaccine development against these diseases. Furthermore, this need provides not only business opportunities[9, 10] for vaccine manufacturers to expand their vaccine repertoire and cover new markets in the vaccine field but it also makes a great contribution to global public health benefit.

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According to WHO facts, the global vaccine market tripled in value from 5 billion US dollar in 2000 to almost 24 billion in 2013. In 2010, only 3% of the global pharmaceutical market could be allocated to vaccine revenues. Furthermore, the vaccine market undergoes a spectacular growth rate of 10-15% per year as opposed to the 5-7% of the global pharmaceutical market. The global vaccine market is becoming an engine for the pharmaceutical industry and is expected to reach 100 billion US dollar by 2025 [11].

The introduction of novel technologies such as genetic modification in the vaccine field can provide numerous opportunities. Genetically modified (GM) vaccines could lead to the generation of vaccines against virtually all pathogens[12, 13]. Furthermore, GM technology allows generating more complex vaccines like, vector-based vaccines, DNA vaccines, RNA vaccines, virus like particles, and virosomes[5, 12, 14]. The application opportunities in the medical field go beyond infectious diseases, e.g., tumour immunology [15].

Although the market potential of conventional vaccines has been evaluated in detail [16, 17] that of the GM vaccines has not been investigated yet. The market potential of GM vaccines differs from conventional vaccines due to their novelty and specific characteristics. Furthermore, different barriers need to be taken into account including one of the most profound and well-known hurdles against genetic modification technology in general: public perception.

GM vaccines are considered as the next step in vaccine development [14]. Hence, gaining knowledge about their market potential is considered essential, as many new GM vaccines will enter the market in the near future[6]. Furthermore, our prior study showed the strengths of one of the most promising GM vaccine platforms, the modified vaccinia virus Ankara (MVA)[13]. The aim of this study is to provide a quantitative key opinion leaders (KOLs) analysis of the GM vaccine market potential, by presenting a consensus overview of the critical success factors (CSFs) for successful introduction of these novel vaccines.

CSFs were first described by Rockart in 1979, as a tool for chief executive officers' information needs. This concept was based on an idea described earlier by Daniel (1961) and was applied in the 1980s to identify the success components indicating why some companies were more successful than others. CSFs are the key areas in which good results will secure a successful competitive performance, and where 'things must go right' if a company wants to be successful[18, 19]. It is described to provide information measures that reflect critical areas providing a set of requirements. CSFs are applied in different ways in a large variety of industries, especially in combination with enterprise resource planning implementation [20, 21, 22, 23, 24].

CSFs are variables, which can affect the competitive position of various businesses within an industry. More importantly, CSFs vary from industry to industry and are influenced by management decision-making [25]. According to Leidecker and Burno (1984)[26] CSFs are applied at three levels of analysis: economic/socio-political environment, industry, industry/firm-specific.

CSFs are generally used in the field of management information systems and business strategy research with various views including strategic planning and decision-making, identification and prioritization in business strategies, market description, and performance models [22, 23, 27].

Comprehensive evaluation of GM-vaccine-CSFs requires investigating both benefits and barriers from the field. In this study, the benefits of GM vaccines are referred to as the 'added value', which GM vaccines introduce over conventional vaccines. It is those CSFs that should make GM vaccines superior over conventional vaccines, thereby defining the theoretical potential of GM vaccines. Nevertheless, in order for GM vaccines to become successful, barriers need to be overcome. Hence, these barriers play an essential role in successful application of GM vaccines and thus are included in the CSFs repertoire. Application of this customized concept, combining both the added value and the barriers to describe the CSFs, provides an overview of the market potential of GM vaccines.

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## II. RELATED WORK

This study comprised three data collection stages. Fig.1 shows research methods applied in this study and three specific data collection moments. First, literature was collected in order to obtain background information on genetically modified (GM) vaccines. Then, exploratory interviews were conducted with key opinion leaders (KOLs), to identify the critical success factors (CSFs) for a successful introduction of GM vaccines. Finally, a survey was used to quantify, weigh, and prioritize the importance of the collected CSFs.

## III. TEXT INPAINTING

### I. LITERATURE

A literature study provided specific search terms on GM vaccines and the concept of CSFs. Our previous study, which provided a quantitative SWOT analysis about the market implementation of the MVA platform for influenza vaccines [13] formed a quantitative basis for evaluating the market potential of all GM vaccines. The collected information, together with data gathered from consulting experts, was used to develop a set of questions for the interviews.

### II. INTERVIEWS

In order to attain most recent opinions and views on the market potential of GM vaccines, semi-structured interviews were conducted. The interview candidates were experts and KOL in the vaccine field. Interview candidates from different backgrounds (academia, industry, regulatory) were purposively selected to provide a diverse and comprehensive overview of the market potential of GM vaccines. Additionally, interviews were conducted with ethics-committee-experts and an independent advisory body (which advises the Dutch government on the risk of the use and production of GMOs on human health and the environment). Table 1 provides background information on KOLs that were approached for the interviews and survey.

Background	Interviews	Survey
Academia	4	12
Industry	4	8
Regulatory	4	1
Other	3	0
<b>Subtotal</b>	<b>15</b>	<b>21</b>
<b>Total</b>	<b>36</b>	

Table 1. Background of the KOLs.

The semi-structured interviews were conducted to allow for probing in order to gain more in-depth answers. The questions were structured in six categories, which created a context for the questions and guaranteed the completeness of the data gathered. The categories include; ‘vaccine development’, ‘vaccine manufacturing’, ‘vaccine registration’, ‘hurdles’, ‘societal’, and ‘general questions’ (Appendix A). Multiple researchers conducted the interviews through which investigator triangulation was achieved. Data was analyzed anonymously, in order to remove any reticence from the interviewees.

Qualitative research requires data collection until reaching a point of data saturation. As before [28, 29] we achieved saturation when the collection of new data does not provide new information on the research [30, 31]. The saturation curve of this study was constructed based on new CSFs mentioned during the interviews. To determine the saturation point, the total amount of CSFs was used, irrespectively of the category they belong to. Interviews were conducted until no new CSFs were obtained in three consecutive interviews. Hence, the saturation determined the research sample size.

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All interviews were transcribed, data based, and analyzed in order to gain insight from the data collected to formulate CSFs for GM vaccines. Moreover, their implementation potential mentioned by KOLs from various fields with different perspectives was codified. Interview transcripts were open-axial coded according to the grounded theory [32]. By applying the grounded theory, interview analysis resulted in 174 open codes. These codes were subsequently categorized into 4 axial codes, which are constructed by means of categorising open codes identified in the previous step; Technical Potential, Commercial Potential, Rules & Regulations and Societal Potential.

### IV. RANKING SURVEY

The ranking survey was used to quantify, weigh and prioritise the CSFs gained from the interviews. Additionally, the survey was used to verify the results of the interviews. The top 10 CSFs in each category were determined using a frequency count on their prevalence in the interviews, and compiled into a survey. This survey was sent to 87 KOLs around the world, which were selected based on their expertise in the vaccine field. Furthermore, KOLs from different backgrounds were selected (academia, industry, and regulatory) in order to include different perspectives on the market potential of GM vaccines. The KOLs were asked to rank the CSFs based on their importance. This was achieved by allocating 20 points amongst 5 factors in each category. Additionally, the KOLs were asked to indicate whether a CSF is a short-, mid-, or long-term concern.

### V. SURVEY ANALYSIS

The survey developed for this study was based on 4 x 10 CSFs (4 Categories, 10 CSF in each category) in combination with three different priority periods, including short-, mid-, and long-term period. The respondents were asked to indicate the level of importance for each CSF by allocating 20 points amongst 5 factors in each category. During the analysis, the points of each CSF were accumulated, thereby generating an importance level for each CSF. Priority periods were determined using a frequency count for each period of each CSF.

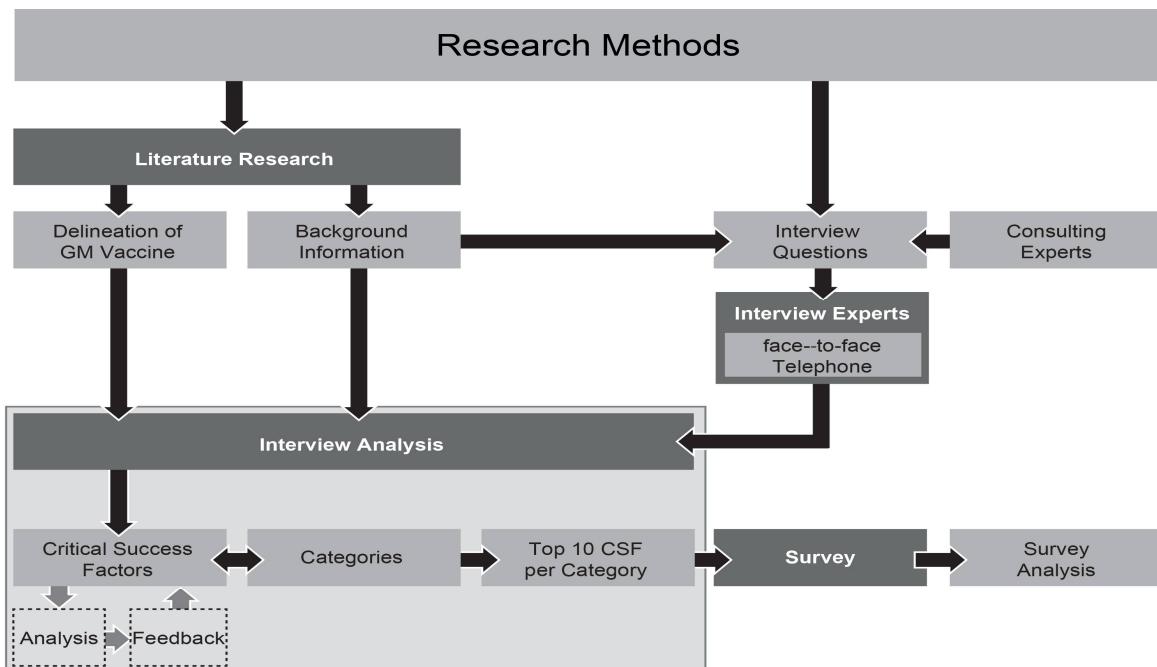


Fig.1. Research methods applied in this study. Literature Research, Interview Experts and Survey are the three specific data collection stages.

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### VI. EXPERIMENTAL RESULTS

#### I. INTERVIEWS

The 4 categories identified in exploratory interviews with the experts and KOLs are presented in Fig. 2. Subsequently, the interviews were used to extract a top 10 CSFs of each category. Fig. 2 presents the number of times each category was mentioned and the variety of arguments within these categories. The category “technical potential” is mentioned most often, 156 times. Categories “commercial potential” and “societal potential” are mentioned almost equal, 119 and 117 respectively. The category “rules & regulations” is mentioned slightly less, 104 times.

The variety of argument in “technical potential” and “commercial potential” is practically equal, 61 and 58 times, respectively. Comparing these categories to “rules & regulation” (29) and “societal potential” (26) less variety of arguments is identified.

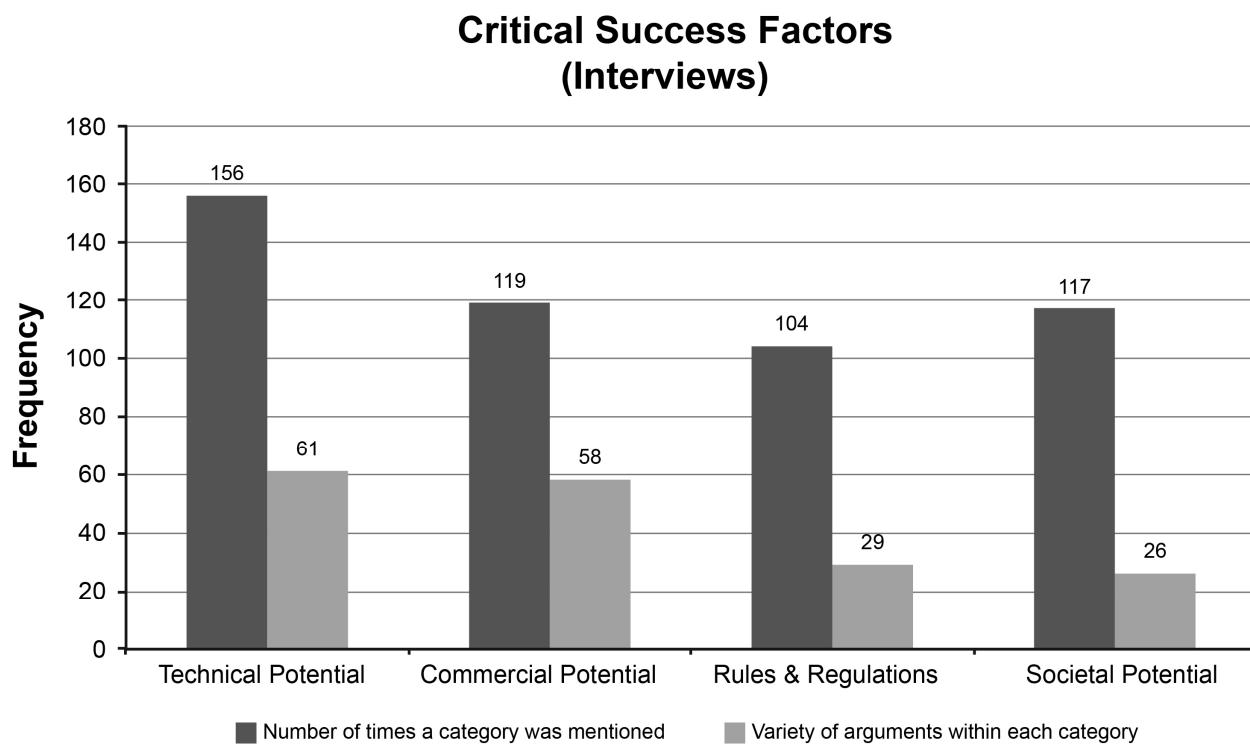


Fig.2. Results of the interviews, both the amount of times a category was mentioned and the variety of arguments within the category.

Saturation of CFSs, mentioned by the KOLs, was reached after 15 interviews, as indicated in Fig. 3. The total number of CSFs presented in the saturation curve, 161, differs from the total of the variety in arguments, 174, visualized in Fig. 2 due to the fact that 13 CSFs were applicable in multiple categories.

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### Saturation Curve (Interviews)

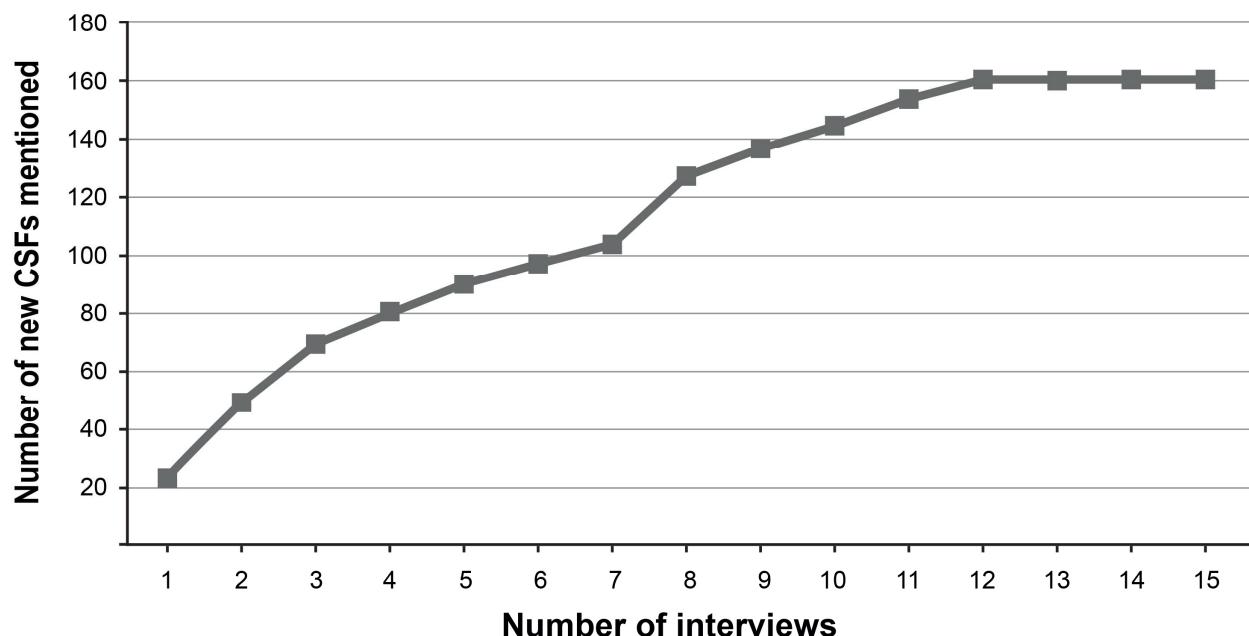


Fig. 3. Saturation curve of the interviews. Cumulative number of new CSF mentioned in the interviews, irrespective of the category. Saturation was reached at 15 interviews.

### VII. SURVEY

Forty CSFs that were identified in prior exploratory interviews are presented in Fig. 5 and will further be discussed per category. The name of the CSF will be given in an *italic* front. The response rate was 24%, well within acceptable limits [9, 28, 29]. Fig. 4 provides the number of added values and barriers of the top 5 of each category from the survey, identified in exploratory interviews with the experts and KOLs. Furthermore, Fig. 5 shows the results of the survey including the total amount of points given to the CSFs by the KOLs, percentage of the total points in the category given to the CSFs, and an indication on each CSF's priority in the future (short-/mid-/long-term).

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### Added Value vs. Barriers

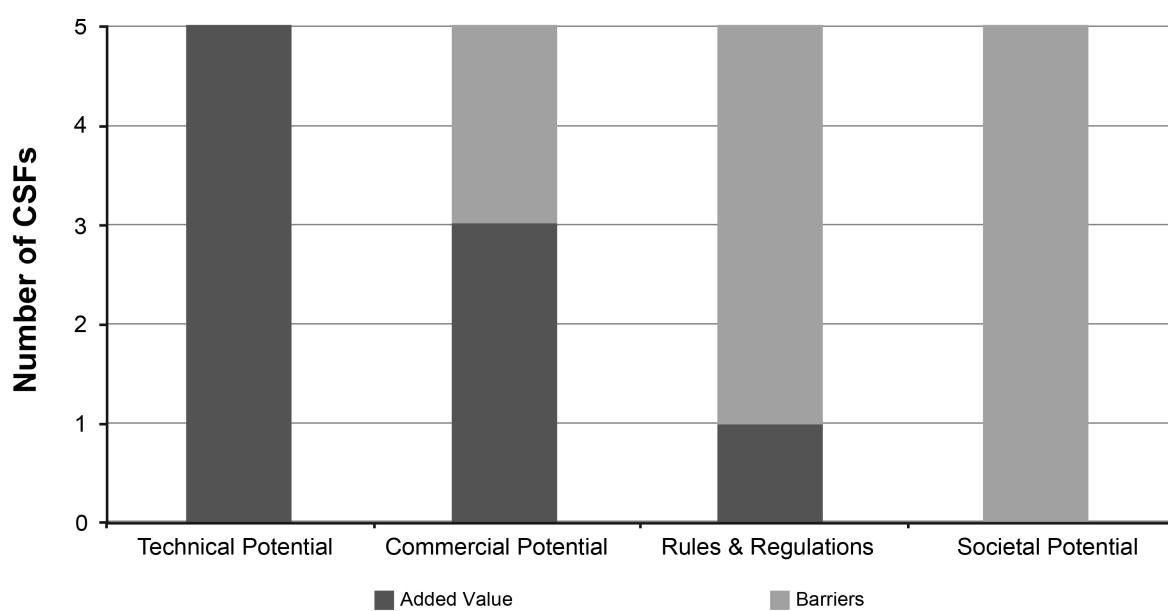


Fig. 4. Number of added values and barriers of the top 5 of each category from the survey.

#### *Technical Potential*

The most important CSF, as indicated by the KOLs, in the category of technical potential is the *opportunity to target previously untargeted diseases*. The amount of points given to this CSF was 103 points, representing 25% of the total amount of points. The majority of KOL indicates this added value of mid-term priority.

The *possibilities to produce multi-targeted* and *safer vaccines* are ranked to be the second and third most important factors with 65- and 62 points. It is notable that the *possibility to produce multi-targeted vaccines* is mainly a long-term concern, according to the KOLs. Moreover, developing *safer vaccine* is indicated to be of a short-term concern. *Offers safer vaccines* was described as a statement that GM vaccines offer safer vaccines comparing to the conventional vaccines.

Notable, although, the *lack of efficacy* was mentioned five times during the in person interviews, it has not received any scores and thus not ranked by any of the KOLs in the survey. The top 5 CSFs in technical potential are all added values of GM vaccines (Fig. 4).

#### *Commercial Potential*

Commercial potential is prioritized predominantly as short- and mid-term concerns. The *new market opportunities* is ranked as most important with 76 points, 18% of the total points. According to the KOLs, GM vaccines open up many new markets due to the high unmet need that currently exist. The *high market potential* is ranked as second important CSF within this category, representing 16% of the points. Furthermore, *required financial investments*, is not ranked higher, as it was the second most mentioned CSF from the interviews. Also remarkable is that *GM vaccines are the future* is ranked only with 41 points.

The three highest ranked CSF in this category are added values, followed by two CSF which could be assigned as barriers, resulting in a 3:2 ratio of added value against barriers in the top 5 (Fig. 4).

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### *Rules & Regulations*

It is noteworthy that most CSFs in rules & regulations are indicated as a short-term concern. *Rules and guidelines are available* is ranked as most important with 16% of the points, resulting in 66 points, and indicated as a short-term concern. Second, with 15% of the points (61 points) is *first products will be difficult*, which is indicated as short-term concern. Third is *GMO required environmental assessment* and fourth, *rules and regulations could be a barrier* with 57 and 54 points, respectively. Both are indicated primarily as a short-term priority. Although the highest ranked CSF in this category is an added value, the others in the top 5 are barriers (Fig. 4).

### *Societal Potential*

*Acceptance* is indicated as the most important CSF within this category with 73 points. *Acceptance* was described as a hurdle in the survey. *No alternative vaccines are available*, was ranked as the second most important CSF with 65 points, which is 15%. Both CSFs will be in the mid-term future. The third, fourth en fifth CSFs are closely ranked representing 14%, 13% and 12%, respectively. These three CSF are all indicated to be of short-term concern. However, *people forgot the need for vaccinations* is also indicated to be a long-term concern. It is remarkable that the top 5 of societal CSFs are all hurdles (Fig. 4).

	Total	% of the Points	Short-term	Mid-term	Long-term
<b>Technical Potential</b>					
Offers opportunities against previously untargeted diseases	103	25	5	8	3
Possibility to produce multi-targeted vaccines	65	15	1	7	10
Offers safer vaccines	62	15	6	3	2
Time saving	51	12	6	2	2
Creates possibilities to improve efficacy	49	12	2	9	3
Creates possibilities to improve specificity	35	8	0	6	3
Cross protection	34	8	2	5	3
Creates flexibility	16	4	2	2	1
Lack of safety	5	1	1	0	0
Lack of efficacy		[ 5* ]			
	420	100	25	42	27
<b>Commercial Potential</b>					
New market opportunities, high unmet need	76	18	6	8	5
Market potential is high	66	16	3	6	4
Need for added value	57	14	6	2	3
Costs go down	48	11	3	5	3
More financial investments are required	46	11	8	2	1
Low hanging fruits are picked	45	11	7	3	3
GM vaccines are the future	41	10	2	6	3
Two parallel markets: Traditional vs. GM	24	6	1	4	4
Economical mechanisms; Market control volume, market controlled profit	11	3	1	1	1
Oriented on high-end market	6	1	0	2	1
	420	100	37	39	28
<b>Rules &amp; Regulations</b>					
Rules and guidelines available	66	16	9	2	2
First products will be difficult to get market approval	61	15	10	0	0
GMO requires environmental assessment	57	14	8	3	4
Rules and regulations could be a barrier	54	13	8	4	1
Additional requirements complicate the registration process	45	11	10	3	1
Central registration procedure (EMA)	38	9	6	4	2
GMO requires more testing and has stricter requirements	35	8	8	5	2
Streamline of regulations required	35	8	3	3	1
No difference in registration process between GM and traditional	19	5	2	4	2
Registration requirements are no hurdle	10	2	3	1	1
	420	100	67	29	16
<b>Societal Potential</b>					
Acceptance	73	17	5	8	4
No alternative vaccines available	65	15	6	8	2
Lack of knowledge/awareness	59	14	8	5	4
Adverse opinion against GM vaccines	56	13	9	5	2
People forgot the need for vaccinations	49	12	7	3	7
GM discussion needs to be held	36	9	10	2	1
No adverse opinion against GM vaccines	25	6	2	1	1
Don't provide information solely because it is GM	20	5	3	3	2
GM discussion will gradually disappear	19	5	2	1	3
Collaboration on multiple levels	18	4	2	1	1
	420	100	54	37	27

Fig.5. Results of the survey. Total is the total amount of points given to the CSF by the KOLs. % of the points means the percentage of the total points in the category given to the CSF. Short-/mid-/long-term gives an indication on the future period of the CSF, the points indicate the amount of KOLs that indicated this period. \*Times mentioned in the interviews.

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### VIII. TARGET MARKET

Fig. 6 depicts a prediction shift in target market once GM vaccines are introduced in the vaccine field. Target Market A illustrates the portion of the market of conventional vaccines that could be replaced by better GM alternatives. Target Market B represents the potential new markets that GM vaccines will create once there are vaccines developed for yet untargeted diseases.

#### Shift in Target Market after GM Vaccine Introduction

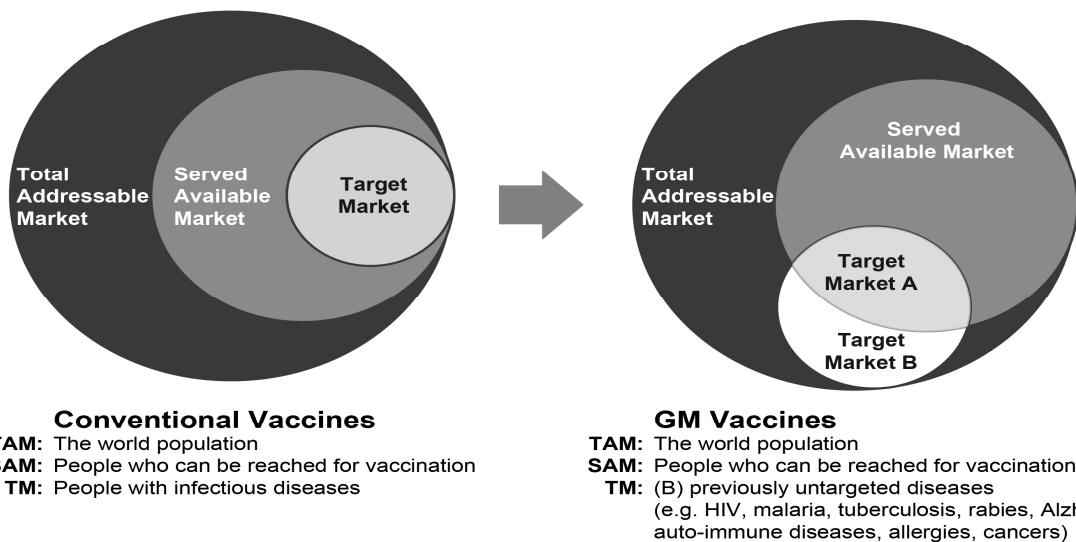


Fig.6. Shift in Target Market after introduction of GM in the vaccine field. Modified from Blank and Dorf(2012) and applied to conventional and GM vaccines.

### IX. CONCLUSION

This study provides a quantitative KOL analysis of the market potential of GM vaccines. Our analysis reveals that CSFs for successful market introduction of GM vaccines can be grouped into four categories: technical potential, commercial potential, rules & regulations, and societal potential. The category rules & regulations requires immediate attention and consideration. Subsequently, the societal potential demands intervention measurements. GM vaccines provide new market opportunities to combat previously untargeted diseases.

Currently certain rules and guidelines are available for GM vaccines. Nevertheless, acquiring the first approval and overcoming the initial obstacles for market introduction remains challenging. Additional requirements and stricter rules and regulations for GM vaccine approvals such as environmental assessment and additional safety files, complicate the registration process, which consequently creates a barrier. KOLs consider a central registration procedure (e.g. European Medicine Agency) as a provisional solution. Only for the category rules & regulations all CSFs are short-term prioritized by KOLs. Virtually every CSF within this category deserves immediate attention and consideration. Although a growing body of science on GM vaccines could help to overcome these regulatory hurdles [33] an immediate intervention is required within this category, as many emerging GM vaccines are currently advancing

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through different clinical trial phases. Furthermore, from a KOLs' perspective, taking actions on the short-term will result in the gradual disappearance of regulatory hurdles.

Currently, many barriers against GM vaccines are allocated to the category societal potential. Although no traditional vaccines are available to prevent, treat or cure diseases such as HIV and malaria, an adverse opinion exists against GM technologies. As such, awareness needs to be raised and the public needs to be educated about the advantages of GM technologies. A possible approach to increase awareness is emphasizing the successful accomplishments of GM technology in other fields. For example, GM techniques are used in production of medicines such as insulin, food such as cheese, and modification of bacteria to perform tasks as making biofuels, cleaning up oil spills, carbon and other toxic waste, and even to detect arsenic in drinking water [34, 35, 36, 37]. Vaccines have contributed to a significant reduction of many infectious diseases and the eradication of other diseases [38]. However, the general public seems to have forgotten the importance of vaccination. KOLs suggest that occurrence of discussion on GM vaccines is of short-term concern in order to address some of the CSFs in societal potential. Given the sensitive nature of GM, collaboration on multiple levels is required to introduce the subject for discussion.

The possibility to target previously untargeted diseases was ranked as the most prominent factor not only within its own category, but also among all other CSFs, irrespectively of the categories. Hence we would advocate that this factor might be the main driver behind research & development and public acceptance in GM vaccine field. Literature has acknowledged the huge scientific efforts and promising results concerning GM vaccine development for yet untargeted diseases like, HIV [39], malaria [40], tuberculosis [41], rabies [42], Alzheimer [43], auto-immunity[44], allergies [45], and cancer [15]. This potential added value of GM vaccines contributes to possible reduction in costs in healthcare worldwide. Although development of these vaccines is of high priority, from a KOLs' perspective, developing safe vaccines is still a prerequisite and a short-term priority.

It is remarkable that creating new market opportunities is considered to be a continuous added value and not time dependent. Fig. 6 illustrates how the GM vaccine market is positioned in comparison to the conventional vaccine market. GM vaccines are complementary to conventional vaccines and the two markets will exist parallel to each other. Nonetheless, according to the KOLs, these vaccines will probably make their first entrance in high-end markets due to financial interest of the companies developing vaccines. Target market B includes the most prominent CSF in technical potential, namely *offers opportunities against previously untargeted diseases*. This factor is also a required *added value* in the category commercial potential. Together with *no alternative vaccines available* from the societal potential category, these CSFs validate the *new market opportunities and high unmet need*.

In addition to development of vaccines for untargeted diseases, development of multi-targeted vaccines also has high priority. Furthermore, safety is considered one of the most important CSFs while developing GM vaccines. These vaccines should also save time and provide higher efficacy than current vaccines might offer. Other factors to keep in mind include, improved specificity, cross-protection, and flexibility. From a KOLs' perspective, developing safe vaccines against untargeted diseases that are time saving is a short-term matter. Remarkably, KOLs considered developing multi-targeted vaccines important, but a long-term concern. Challenging nature of development and production of these multi-targeted vaccines makes them not of short-term interest, as more research is required.

Relating back to the interviews, technical potential was the most prominent category. Regardless of the background of the interview candidates, they were all experts and/or KOLs in the vaccine field and thus possess extensive knowledge and expertise on technical aspects of GM vaccines. It appears that the experts from the industry are required to know the technical details of not only their product but also their competitors' products. Additionally, experts with an academic background seemed to know the technical details in a more fundamental way, while the regulatory experts must understand technical features to be able to make guidelines and regulations.

The specific nature of categories commercial and societal potential might be an explanation of the lower occurrence during the interviews. Compared to technical potential, these two categories are more dependent on the background of the interview candidates. However, the candidates, irrespective of their background, know some of the obvious

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arguments within these categories. The category rules & regulations was least mentioned by the interview candidates. Although guidelines and regulations are available for GM vaccines, they are constantly updated and sometimes practiced case-specific, which creates confusion.

A possible explanation for the high variety of arguments mentioned in the category technical potential is the diverse background of interview candidates, as they bring different arguments and perspectives to the table and view these from different angles. Remarkably, the variety of arguments mentioned in technical and commercial potential are comparable. Furthermore, the variety of arguments mentioned in rules & regulations are comparable to those from societal potential. This might be due to the fact that technical and commercial arguments are established and well defined, thus more tangible, while rules & regulations and societal arguments are more ambiguously defined, thus more intangible. Moreover, the rules & regulations and the societal potential arguments are straightforward. While in technical and commercial potential many variables play a role including stakeholders' involvement, influence of various factors at different levels, high interest to be gained by different parties. The stakes are high, both literally and figuratively.

Interpreting the results, some restrictions apply to this study. A methodological difficulty was the inability to measure success due to the novelty of GM vaccines. Consequently, future research makes it possible to compare successful and un-successful market entries of GM vaccines, and back trace what CSFs were of influence, and when these factors played what role on the market.

Although CSFs are generally used to identify key areas of one product or company, the unique customized methodology for CSFs created for this study made it possible to generate a clear overview of the GM vaccine market potential. Moreover, application of multiple methods during data gathering reinforced the results. Interdisciplinary approach of this study through the involvement of diverse international experts and KOLs forms another strength.

In conclusion, when it comes to the technical potential GM vaccines offer the possibility to target previously untargeted diseases. GM vaccines are the next step in vaccine development and once proven their added value they could replace conventional vaccines. Nevertheless, barriers still exist, mostly in the categories rules & regulations and societal potential. The societal barriers could be overcome by emphasizing the current successful applications of GM technology in other fields. Furthermore, general public needs to become aware of the added value of GM and the necessity of vaccination. People tend to forget that it is a matter of life and death. The most profound concerns are rules & regulations, which require immediate attention and intervention. Future research needs to focus on how these regulatory hurdles could be overcome, as many yet untargeted diseases are about to get targeted by emerging GM vaccines. This paper forms a quantitative stepping-stone that shows the immediate attention and intervention required in societal and regulatory parts of GM vaccines development.

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### Conflicts of interest

The authors declare that they have no conflict of interest.

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