Development of vaccines for global use: The role of the Vaccine Industry

15th Advanced Course of Vaccinology

Fondation Merieux,

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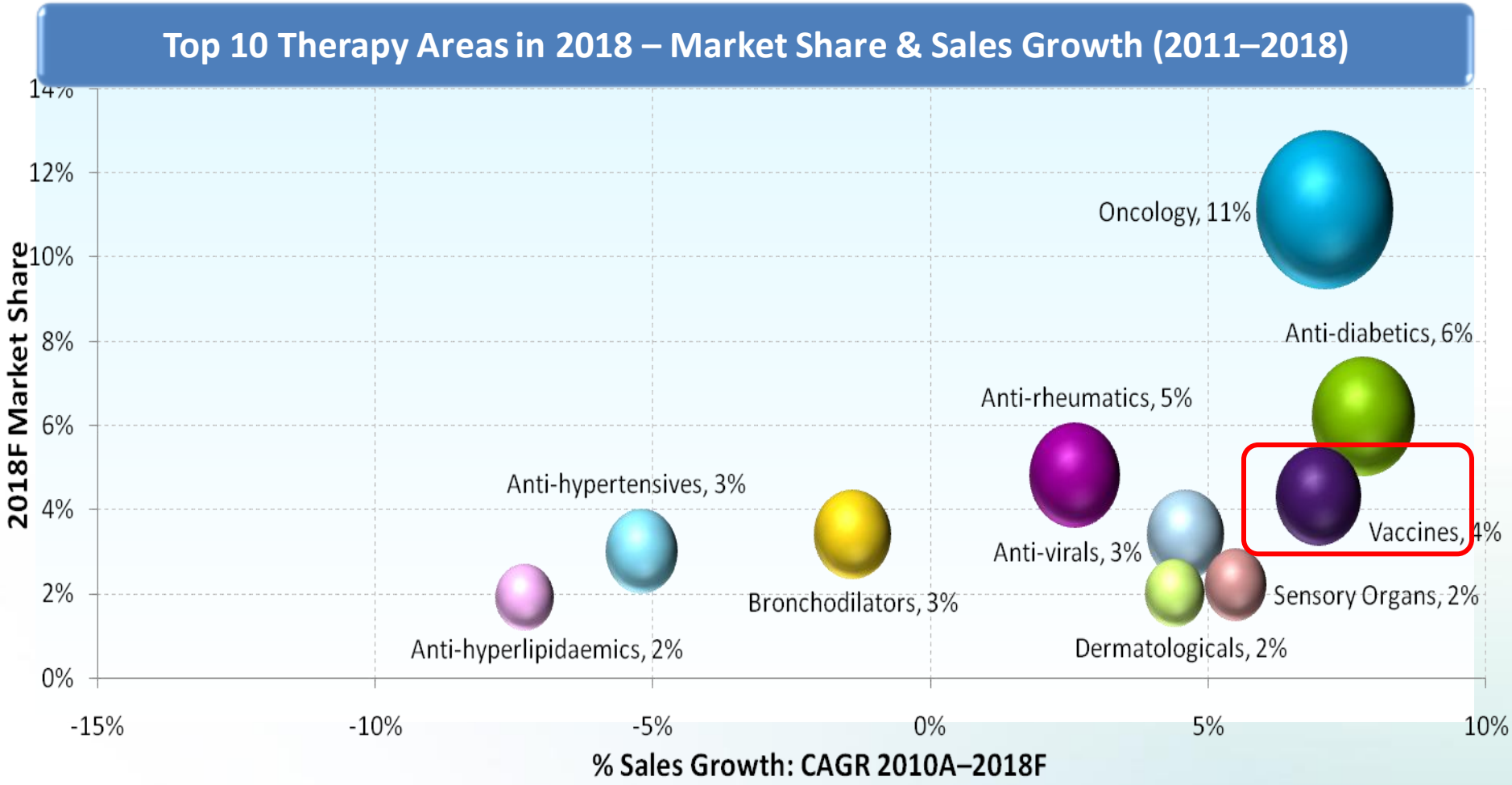
Medicines Development/Medical and Scientific Affairs

Pfizer Vaccines

Vaccines Is an Attractive Business Segment

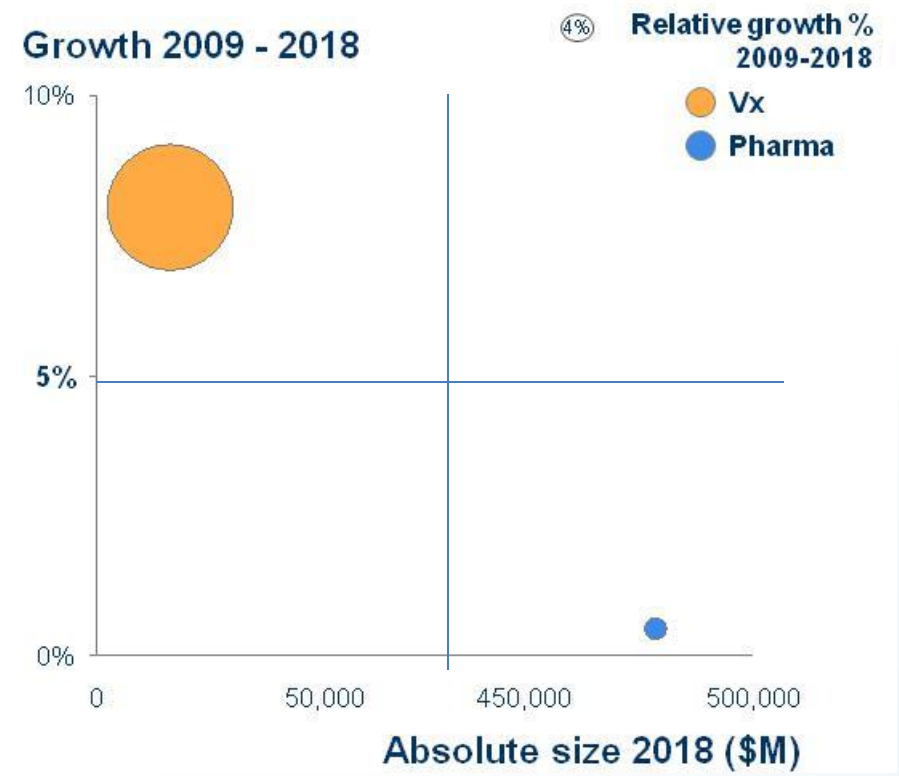
Advantaged economics (global vaccines market is projected to grow from $24B to ~$39B by 2017*)



•Indicates 2018F worldwide $ sales depicted by size of bubble.
•Vaccines include infectious disease vaccines only
Source: EvaluatePharma world Preview 2018 Embracing the Patent Cliff, June 2012.

Vaccines are growing 5X than Pharma Annually

Vaccines expected to exceed current market value by ~80% by 2018



Vaccines growth driven by changing industry trends

Vaccines developing a "Pharma – Like" business model

- Vaccines now developed / marketed like traditional pharmaceuticals
- Focus on proprietary technologies, specific at-risk demographics

In context of large wave of patent expiry, Vaccines is a growing segment with limited generic competition

High barriers to entry given scientific and technical regulatory requirements

Ability to win share with strong Government/VTC recommendations

Future growth driven by specialty and therapeutic segments

Source: EvalutePharma January 2010; BCG Analysis

Eight Distinct Vaccine Market Segments

Segment		Description	Example Diseases/Vaccines
Pediatric <6 yrs	Traditional Pediatric	Commodity-based vaccines based on older technologies with strongly regulated pricing	• DTP, HepB/Hib, Polio (Pediarix, PentAct-HIB) • MMR (Proquad, MMR II)
	Specialty pediatric	Newly targeted pediatric diseases based on more innovative technologies	• Pneumococcal (Prevnar13, Synflorix) • Rotavirus (RotaTeq, Rotarix) • Mening C (Menactra, Menjugate, Menomune)
Adult	Adult Booster	Vaccines targeting adolescents and adults to refresh and strengthen protection by primary childhood vaccination Immunocompromised individuals	• DTP (Repevax, Decavac, Boostrix, Adacel) • TdaP • PPV23
	Specialty adolescent/ adult	Newly targeted infectious diseases with high unmet need	• HPV (Cervarix, Gardasil) • Pneumococcal (PPV23, Prevnar 13) • Herpes zoster (Zostavax)
Across Ages	Travelers / Endemic	Infectious diseases with low/no prevalence in mature countries, but needed by military, travelers, etc. Disease prevalent exclusively in the developing world	• HepB (Recombivax, HB-Vax, Hepavax) • MenigA (MenfriVac) • Yellow fever (Flavimun, Arilvax)
	Seasonal / Pandemic	Vaccines requiring fast scale-up due to cyclical or urgent demand	• Influenza (Fluzone, Fluvirin, FluLaval, Fluvax) • Anthrax (BioThrax) • Smallpox (ACAM2000, Lancy-Vaxina)
	Therapeutic	Vaccine technology leveraged to treat diseases, such as cancer	• Oncology (lung, breast, prostate) • CNS (Alzheimer's, drug addiction) • Allergy (pollen, dust)
	Special populations	Vaccines for surgical populations , long-term care facilities	• *Staph aureus* • *C.difficile*

Welcome to the vaccine Company “Vacurion”
You are now a senior executive in industry

Vacurion vaccine portfolio

Segment		Description
Pediatric <6 yrs	Traditional Pediatric	Commodity-based vaccines based on older technologies with strongly regulated pricing
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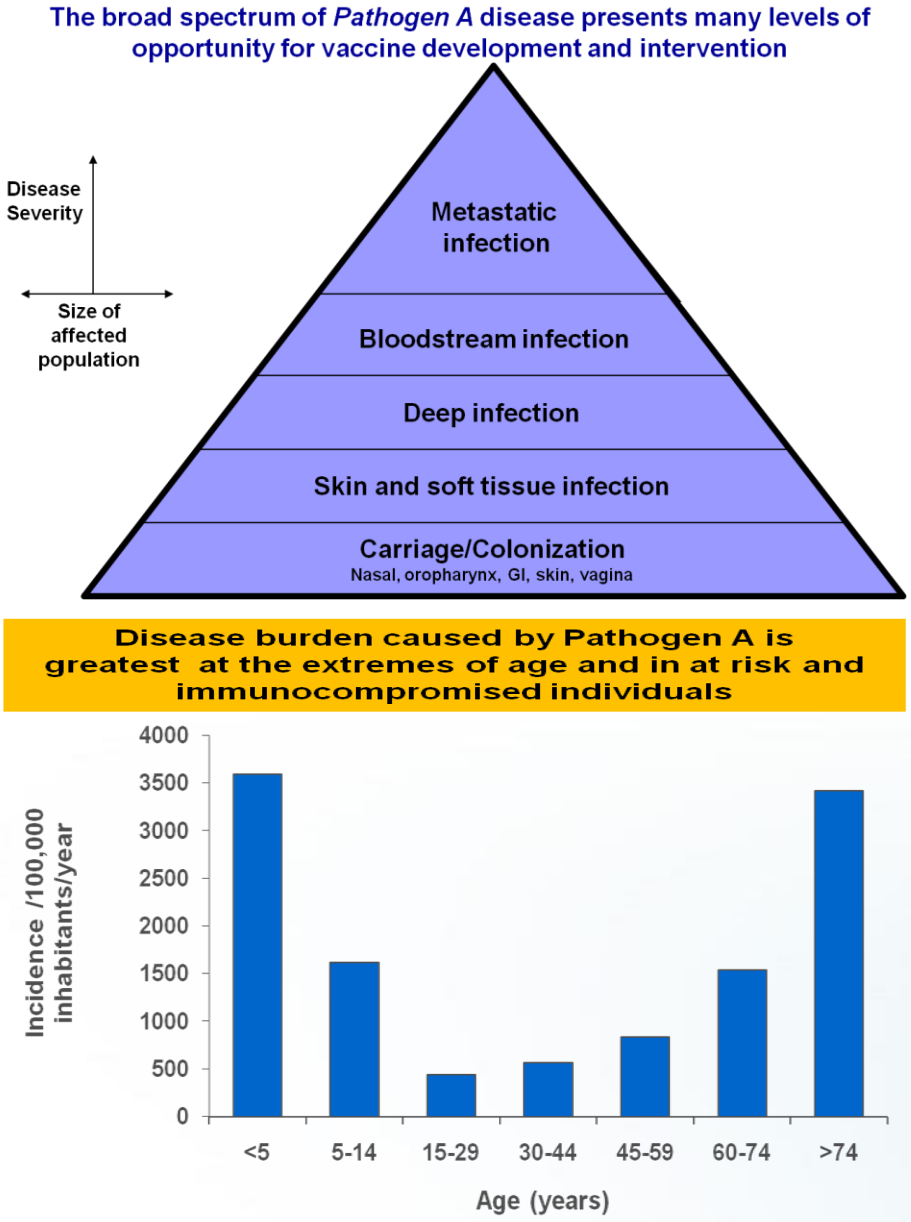
New Vaccine against *Microbium terribilis*

Microbium terribilis: the unmet medical need



- A range of populations are at-risk for infection, both in community and healthcare settings both in industrialized and the developing world
- The number of multi drug resistant strains is increasing rendering treatment more difficult and associated costs to increase
- There is a need for a vaccine able to confer broad protection against the most virulent strains of *M.terribilis*

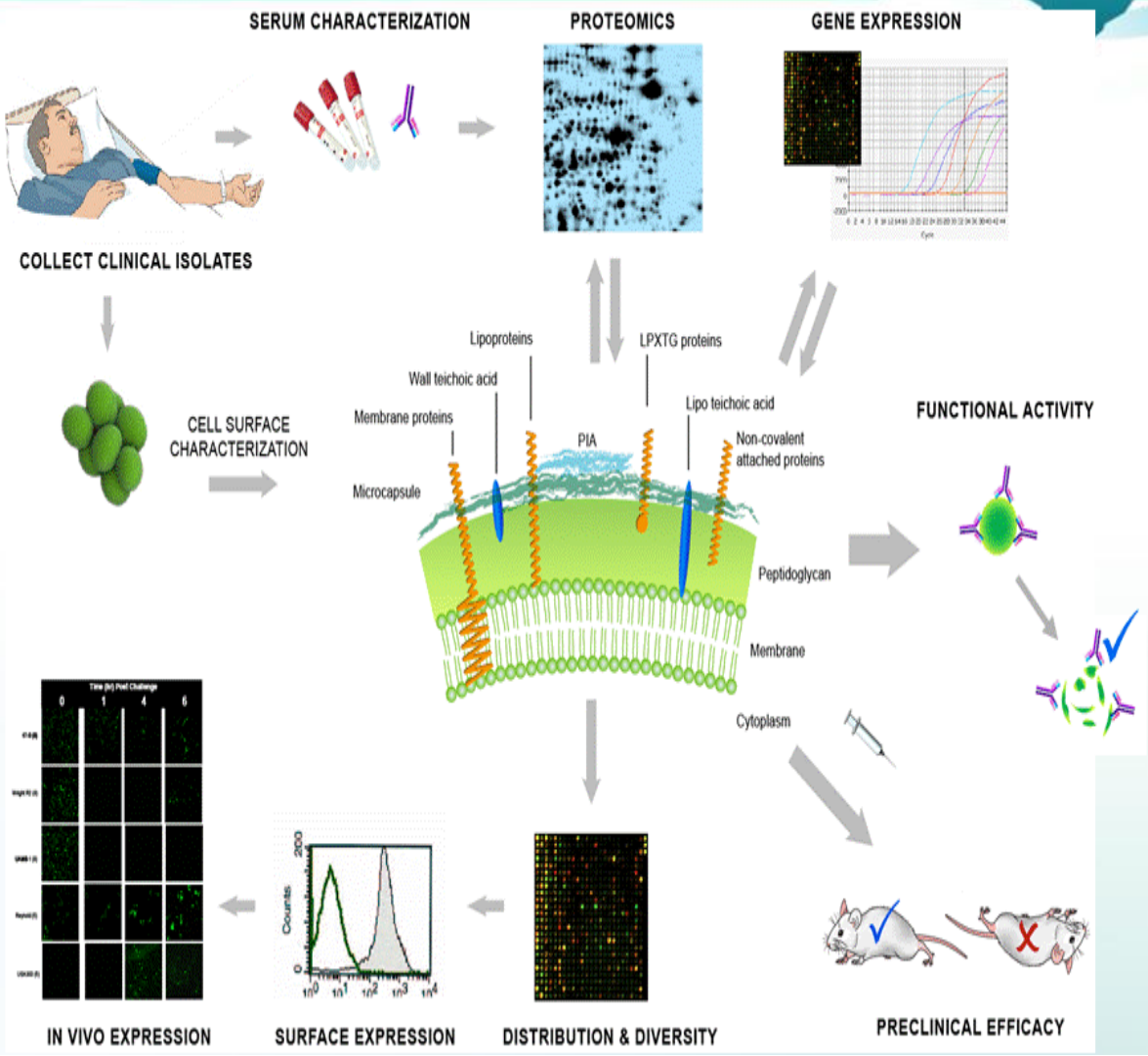
M. terribilis :
Vaccine Discovery

Antigens are:

- Surface expressed by majority of *M.terribilis* disease causing isolates
- Conserved
- Important in pathogenesis mechanisms
- Effective in pre-clinical animal models
- Capable of generating antibodies with specific functional activity

Vaccine should be

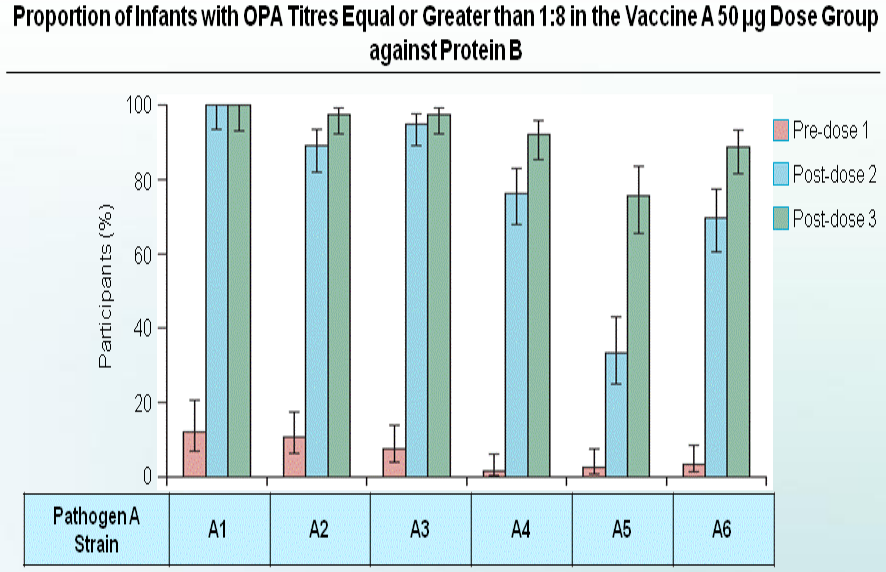
- Capable of providing coverage for multiple strains
- Be effective for different disease states
- Effective in diverse geographies



M. terribilis
Vaccine development and Proof of Concept

Antigen	Virulence Factor	Functional Immunoaasay
Capsular PS (X and Y)	Phagocytic activity	OPA
Protein A	Mediates adhesion and invasion of host cells	Luminex competitive Immunoassay (CLIA)
Protein B	Participates in transport into and out of the cell membrane	CLIA, OPA

- **Phase II clinical results**
  - •Acceptable safety and tolerability after a three dose regimen
  - • Substantial increases in CLIA and OPA titers post 2 and 3 doses and each antigen
  - • Antibody responses maintained over 12 months



First Decision that you have to make is:
Should we invest to launch a vaccine against *M.terribilis?*

Segment		Description
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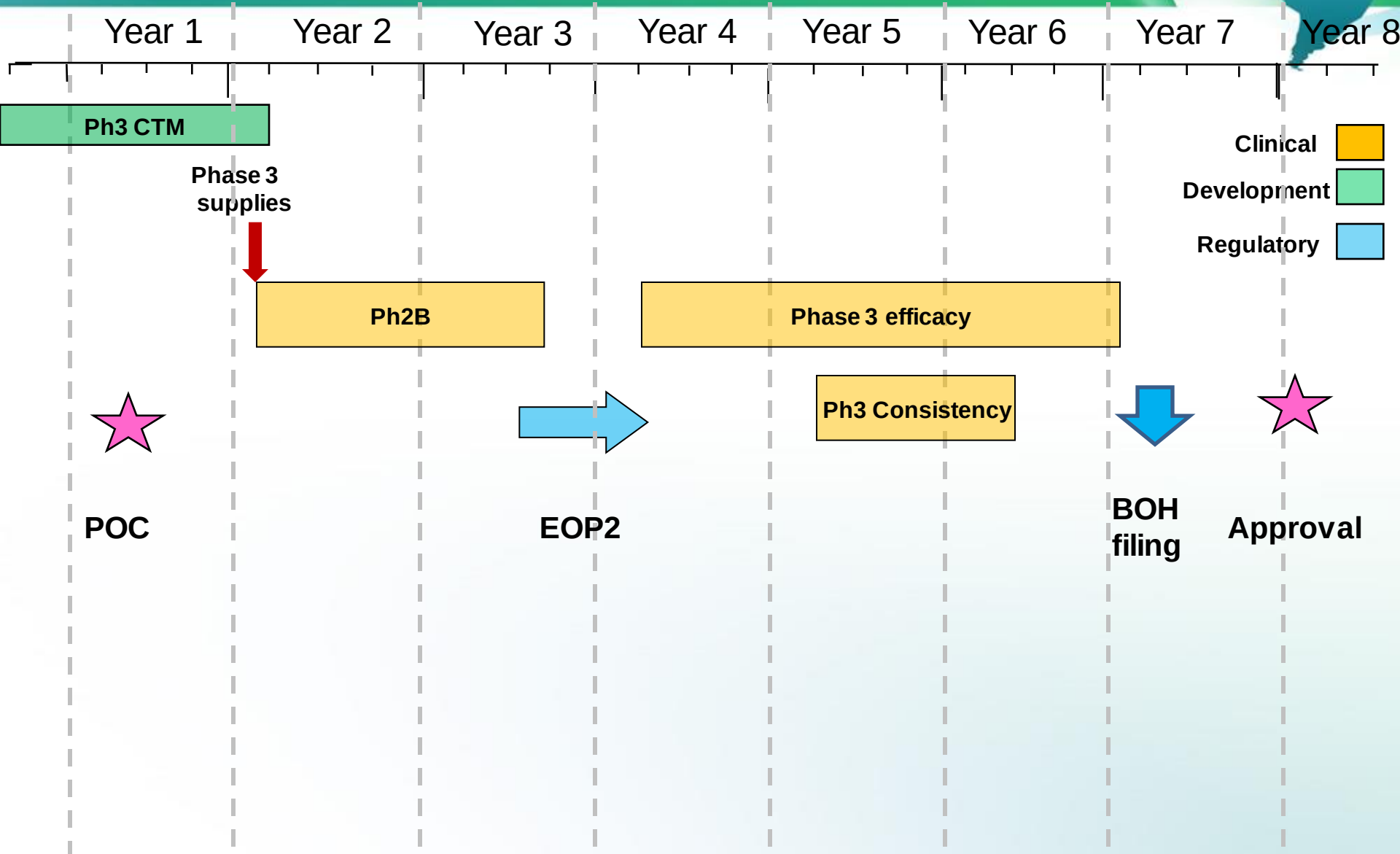
Vacurion vaccine portfolio

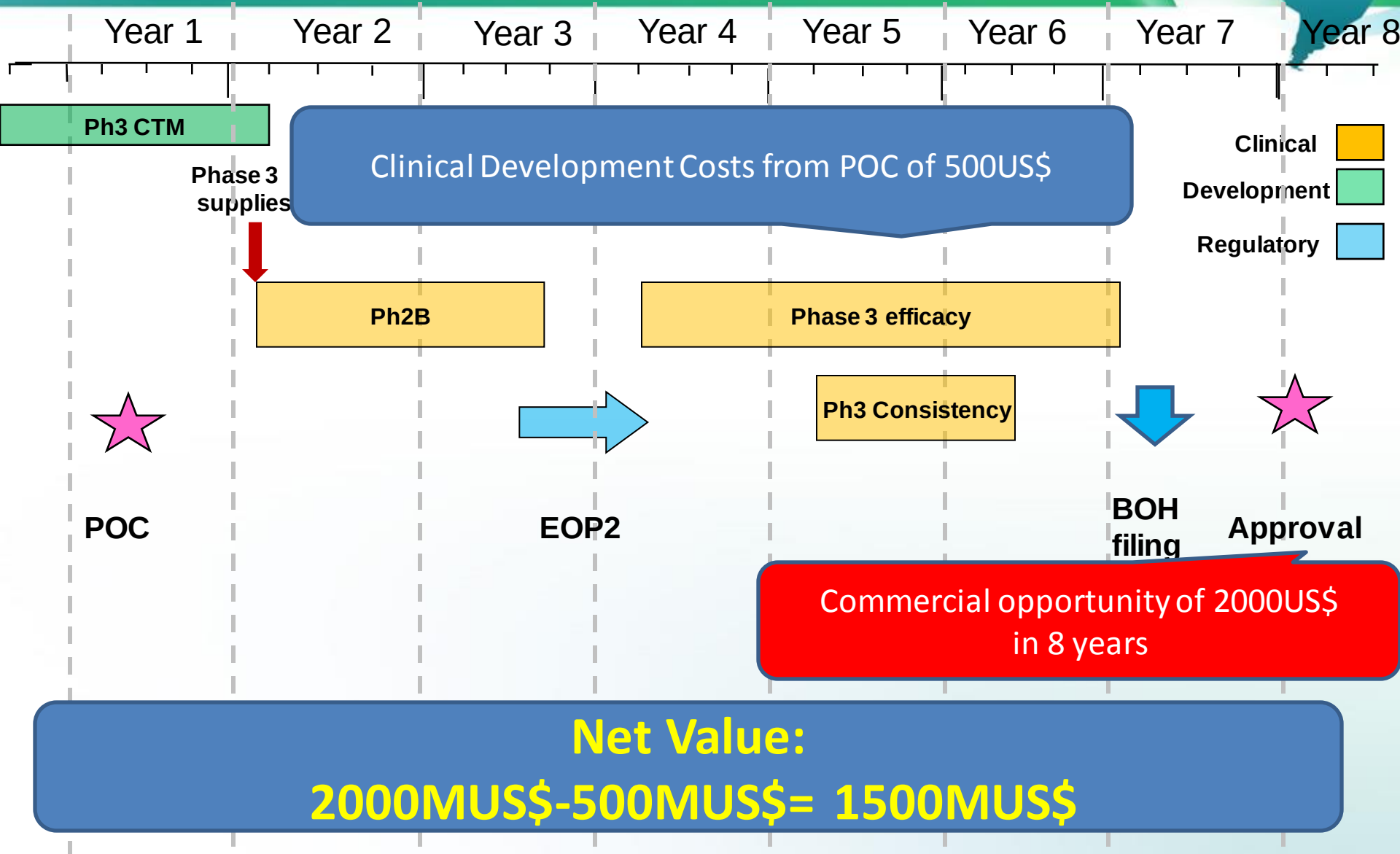
New Vaccine against *M. terribilis*

What is the expected Net Present Value of Vaccine against M. terribilis?

M.terribilis
Vaccine Clinical Development Program

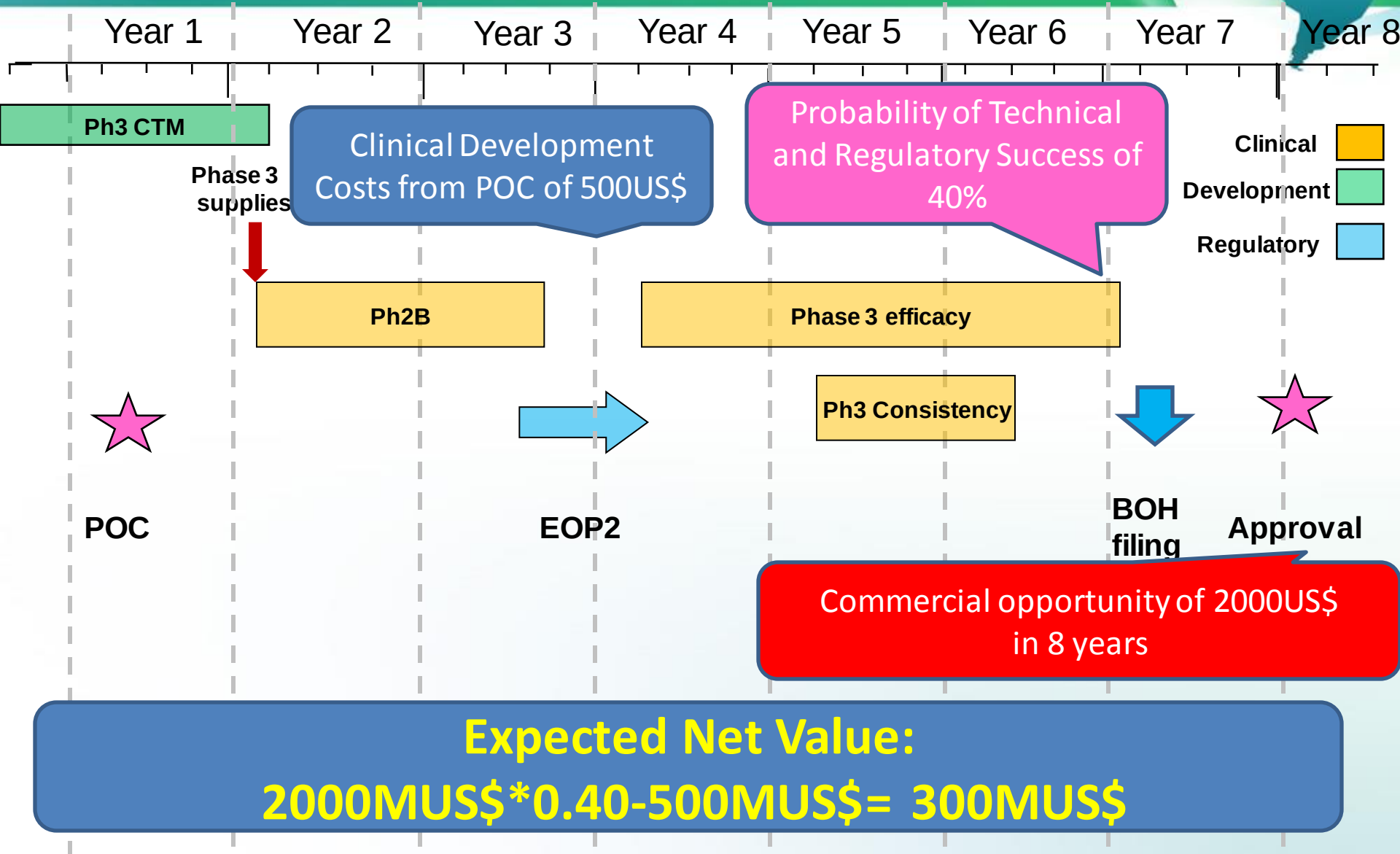


What is the net value of the program?



Net Value:
2000MUS$-500MUS$= 1500MUS$

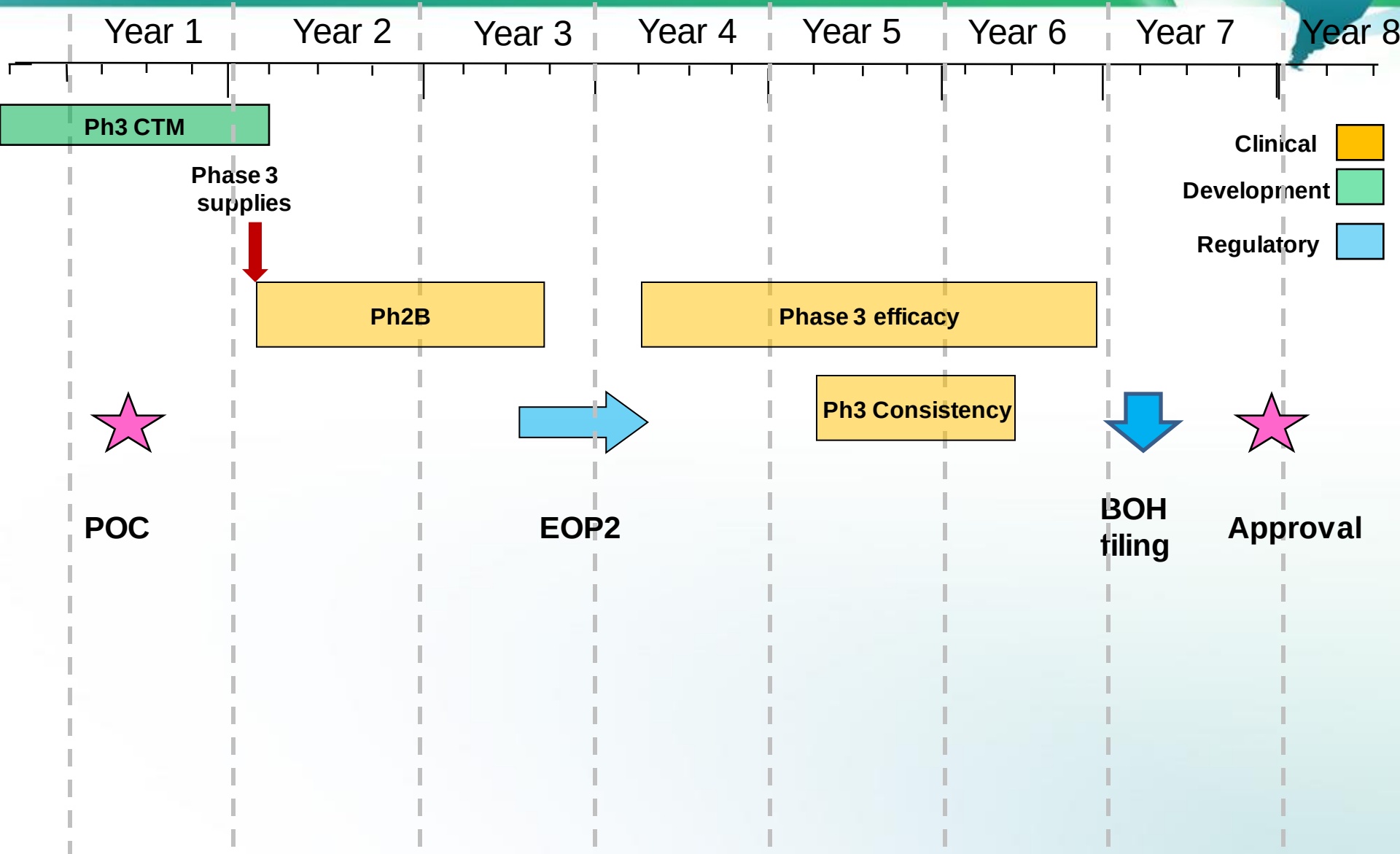
What is the expected net value of the program?



Expected Net Value:

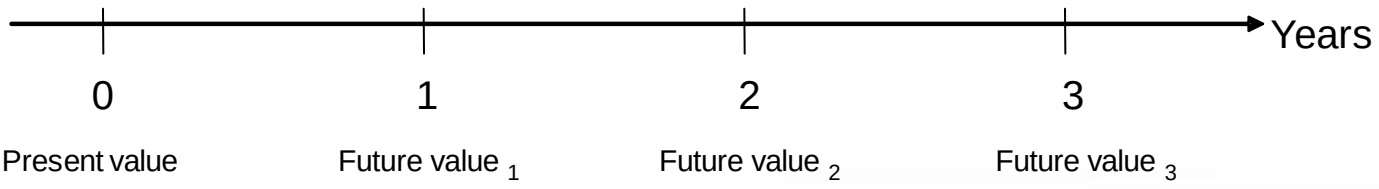
2000MUS$*0.40-500MUS$= 300MUS$

What is the expected net present value of the program?



Time is money: a dollar today is worth more than a dollar in the future

- Because Vacurion can deposit money in savings account, earn interests and end up with more $ in the future
- For example:
  - Deposit $100 today in savings account
  - Interest rate = 5%
  - Have $105 in Year 1, $110 in Year 2, $116 in Year 3 …



$100 @5% $100 → $105 → $110 → $116

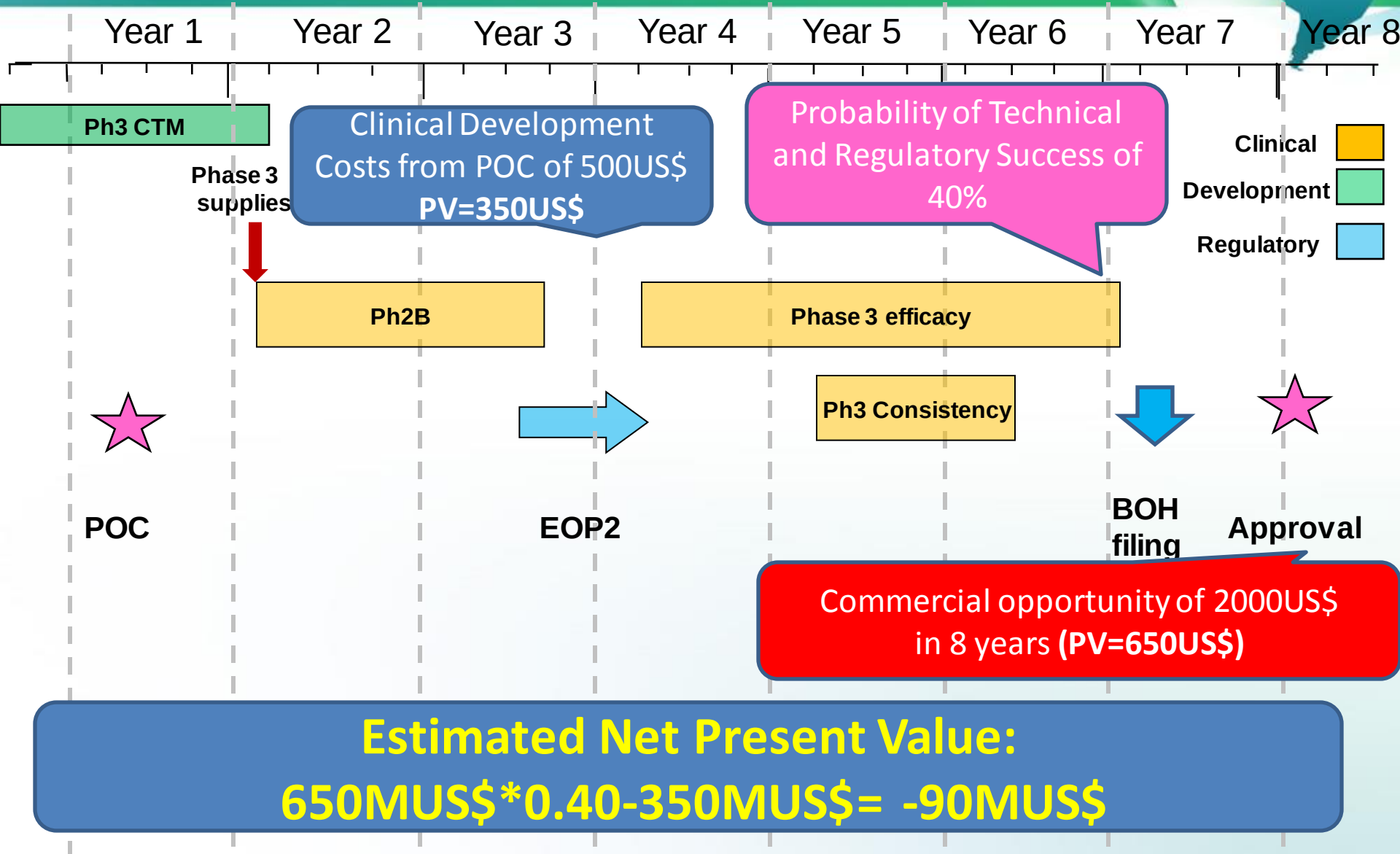
What is $100 in one year worth today? ? = $95 ← $100

What is $100 in two year worth today? ? = $91 ← ? = $95 ← $100

What is $100 in three year worth today? ? = $86 ← ? = $91 ← ? = $95 ← $100

Present value = future cash flow stream expressed in today s terms

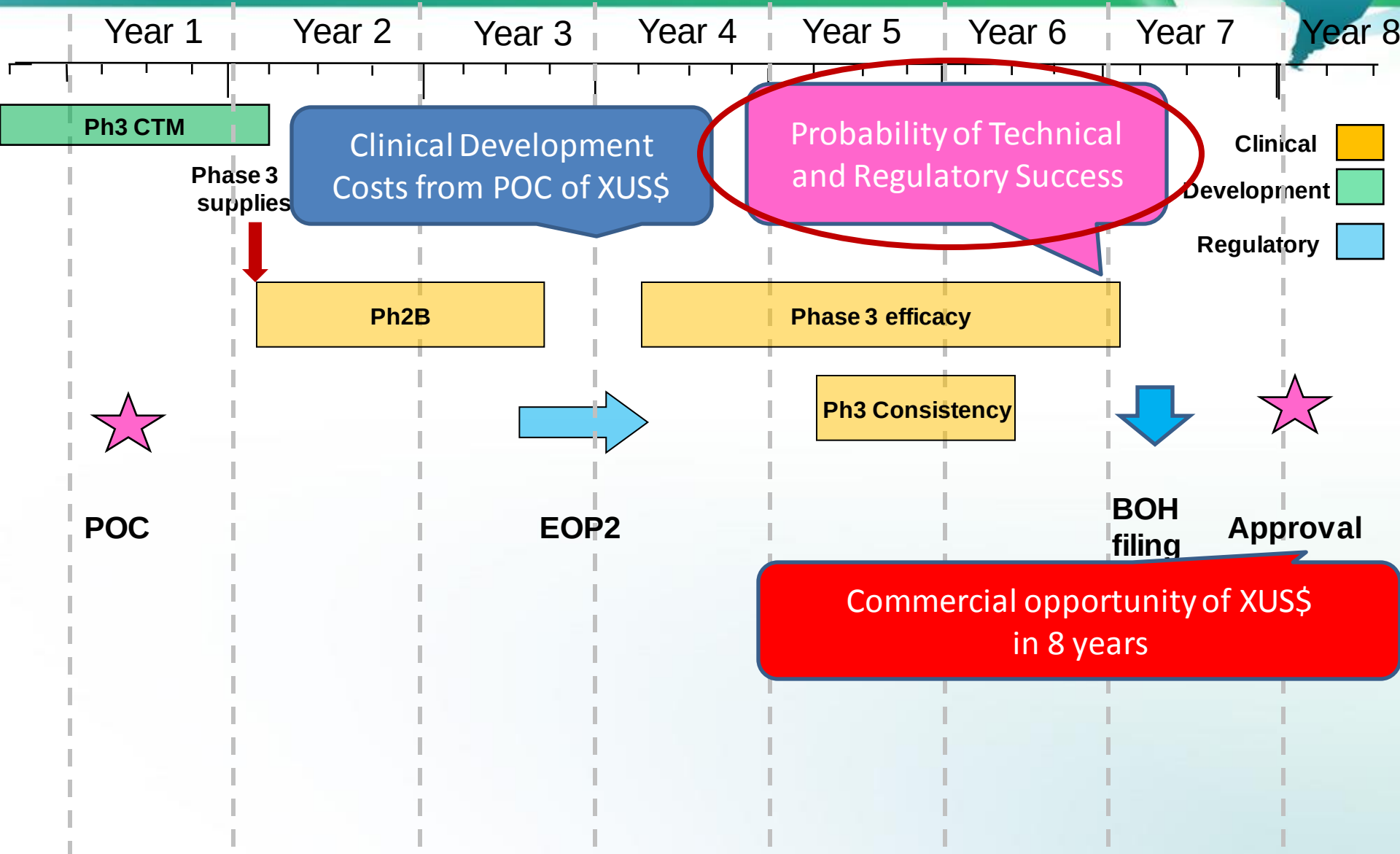
What is the expected net present value of the program?



Estimated Net Present Value:

650MUS$*0.40-350MUS$= -90MUS$

How each of these elements affect the eNPV of the program?



Probability of Technical and Regulatory Success (PTRS)

Clinical Program for *M. terribilis*

- **There is a threshold level of immune responses that correlates with protection**
- **Phase 2B measures safety and immunogenicity in a targeted population**
- **Phase 3 is a non-inferiority comparison with an existing vaccine in a targeted and known population**

PTRS assumptions

PTS			PRS	PTRS
Phase 2b	Phase III	Overall		

85%

Phase II trials have shown this vaccine to be safe and immunogenic

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PTRS assumptions

PTS			PRS	PTRS
Phase 2b	Phase III	Overall		
85%	80%	72%		

Immune responses in previous trials have elicited several fold higher titers than existing vaccine

Probability of Technical and Regulatory Success (PTRS)

Clinical Program for *M. terribilis*

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- **Phase 2B measures safety and immunogenicity in a targeted population**
- **Phase 3 is a non-inferiority comparison with an existing vaccine in a targeted and known population**

PTRS assumptions

PTS			PRS	PTRS
Phase 2b	Phase III	Overall		
85%	85%	72%	90%	65%

Immunogenicity accepted as endpoint for licensure and non-inferiority criteria agreed with regulators

Expected Net Present Value:
650MUS$*0.65-350MUS$= 72MUS$

Probability of Technical and Regulatory Success (PTRS)

Clinical Program for *M. terribilis*

- **There is not established correlate of protection**
- **Phase 2B measures safety and immunogenicity in a targeted population**
- **Phase 3 is a randomized double blind placebo controlled efficacy trial in an highly heterogeneous population (e.g. multiple at risk subgroups)**

PTRS assumptions

PTS			PRS	PTRS
Phase 2b	Phase III	Overall		

85%

Phase II trials have shown this vaccine to be safe and immunogenic

Probability of Technical and Regulatory Success (PTRS)

Clinical Program for *M. terribilis*

- **There is not established correlate of protection and no existing vaccine**
- **Phase 2B measures safety and immunogenicity in a targeted population**
- **Phase 3 is a randomized double blind placebo controlled efficacy trial in an highly heterogeneous population (e.g. multiple at risk populations)**

PTRS assumptions

PTS			PRS	PTRS
Phase 2b	Phase III	Overall		
85%	50%	42%		

Immune responses shown in earlier trials may not predict efficacy in humans and heterogeneity of at risk sub-groups may render different efficacy

Probability of Technical and Regulatory Success (PTRS)

Clinical Program for *M. terribilis*

- **There is not established correlate of protection and no existing vaccine**
- **Phase 2B measures safety and immunogenicity in a targeted population**
- **Phase 3 is a randomized double blind placebo controlled efficacy trial in an highly heterogeneous population (e.g. multiple at risk populations)**

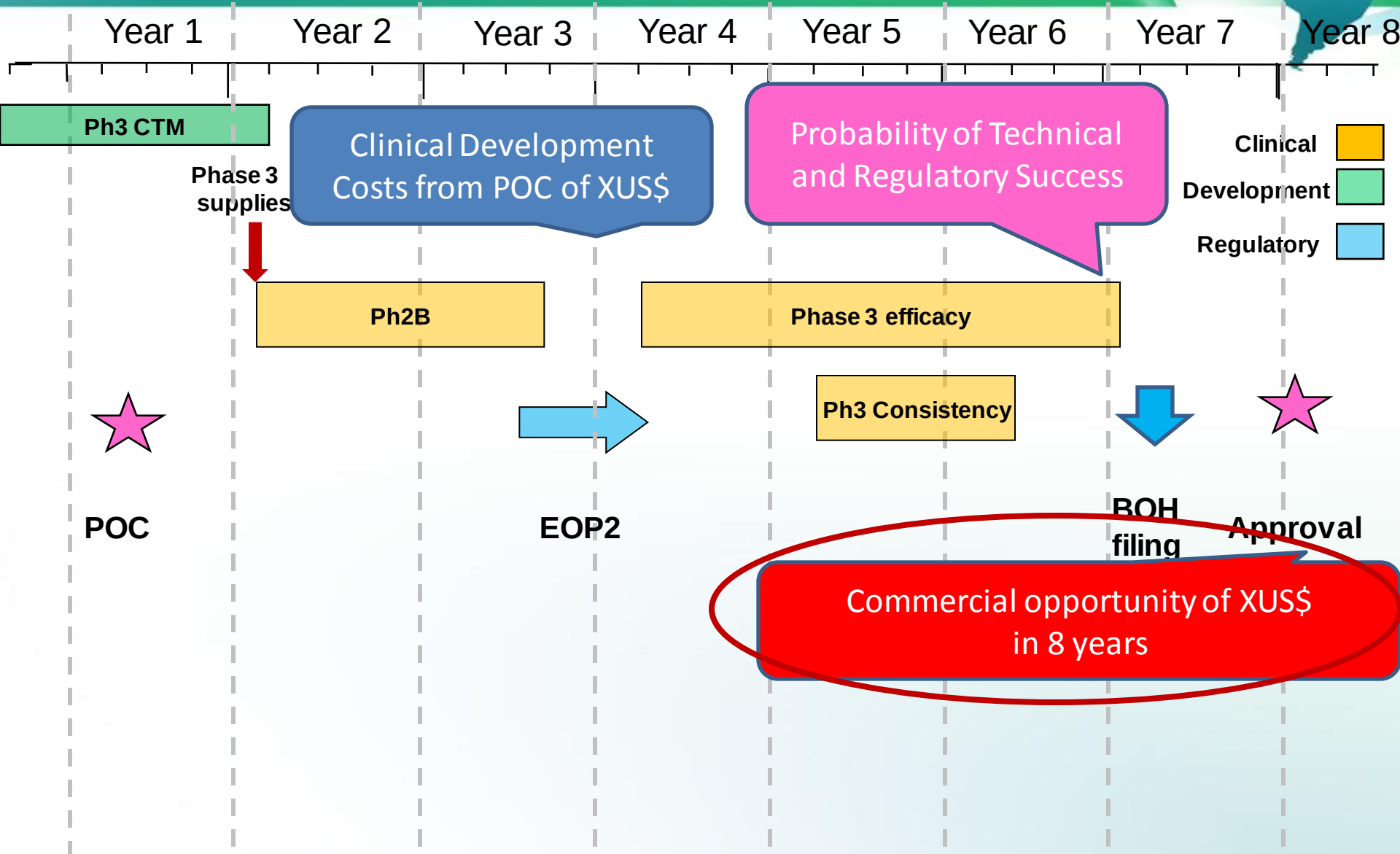
PTRS assumptions

PTS			PRS	PTRS
Phase 2b	Phase III	Overall		
85%	50%	42%	55%	23%

Regulators may challenge the concept of a single trial for all at risk populations and request different trials

Expected Net Present Value:
650MUS$*0.23 -350MUS$= -200 MUS$

How each of these elements affect the eNPV of the program?



If the vaccine against M.terribilis is licensed is it likely that will be recommended for inclusion into a National Immunization Program?

Disease Burden considerations

- **Epidemiological data at a global or local level (e.g.US) is well known (morbidity, mortality, sequelae, serotype/strain distribution)**
- **Disease awareness (e.g. epidem**
- **Availab treatm**
- **Vaccine effectiveness**

Program & economic considerations

- **Existence of an established program for vaccination (e.g adolescents, surgical populations) and No. doses**
- **Price/dose and Budgetary implications for the Government**

ost of illness

ess

uation (permissive, compulsory)

The Answer is YES
Commercial opportunity of 1 Billion/year or 8 Billion US$ in 8 years

Expected Net Present Value:
3400MUS$*0.40-350MUS$= 1010MUS$

But what about if the vaccine against M. terribilis is targeted to specific at-risk rather than age-based populations and competition is looming?

Disease Burden/SOC considerations

- Epidemiological data is confusing gathered only in some at-risk populations and difficult to extrapolate
- Incidence of disease is higher in some at risk groups vs others
- Perception of the disease burden is mixed and the unmet medical need is not well recognized
- A competitive vaccin
threatens to launch 2
vaccine and accordin
appears to be well di

Program & economic considerations

- No distribution channels available and the treatment paradigm for physicians has to change – high educational demand
- Health Outcomes argument is increasingly difficult with a perceived low unmet need and missing epidemiological data as well as competing interests
- Recommending Bodies will review the vaccine but
r a certain
leemed at a
an overall
andidate

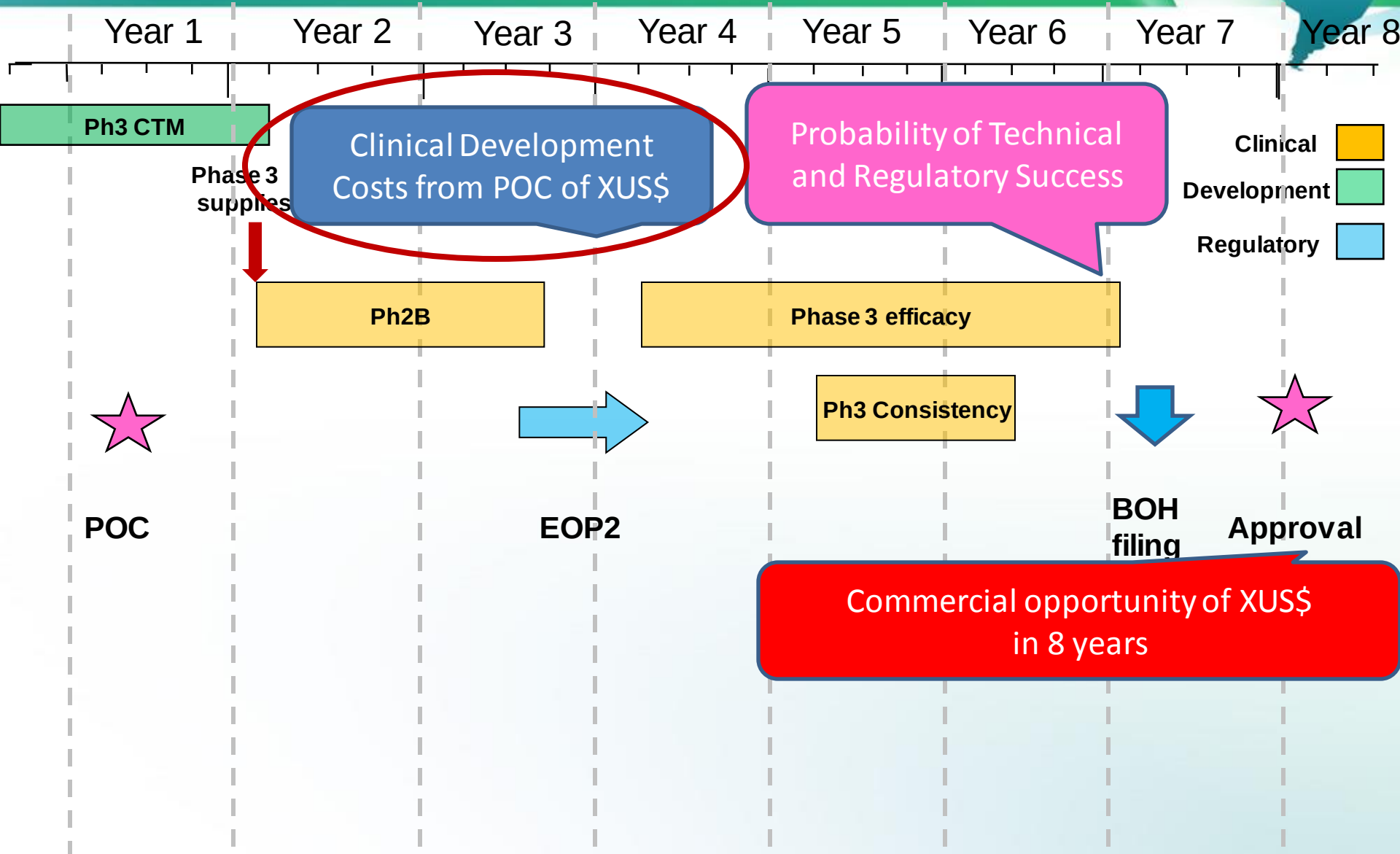
Commercial opportunity is of 1 billion US$ in 8 years

Market share post
erode over time

Early pricing & access negotiations
in key markets difficult

Expected Net Present Value:
325MUS$*0.40-350MUS$= -220MUS$

How each of these elements affect the eNPV of the program?



Please welcome:
The Productivity Index Measure

- **Let's take into consideration making an eNPV = $150m from one of either projects:**
  - **Vaccine A against *M. terribilis* Costs $200m in today's dollars (Present Value)**
  - **Vaccine B costs $40m in today's dollars (Present Value)**
- **Both would seem equal using eNPV, but we would rather make $150m with a lower investment so we can have money**
- **We div** **ected develop** **(PI):**
  - **Vaccine A: PI = 150 / 200 = $0.75 of eNPV / dollar of investment**
  - **Vaccine B: PI = 150 / 40 = $3.75 of eNPV / dollar of investment**

Vaccine B uses money more efficiently !!!

The Good News:
You have been promoted CEO of Vacurion
You have a wonderful portfolio across all Vaccine segments

	Segment	Description
Pediatric <6 yrs	Traditional Pediatric	Commodity-based vaccines based on older technologies with strongly regulated pricing
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	Therapeutic	Vaccine technology leveraged to treat diseases, such as cancer
	Special populations	Vaccines for surgical populations , long-term care facilities

Vacurion vaccine portfolio

- Vaccine against *M.terribilis*
- Vaccine against Pathogen B
- Vaccine against Pathogen C
- Vaccine against Pathogen D
- Vaccine against Pathogen E
- Vaccine against Pathogen F
- Vaccine against Pathogen G
- Vaccine against Pathogen F

The Bad News:
You ONLY have 200USM$ to invest

Segment

- Pediatric <6 yrs
  - Traditional Pediatric
  - Specialty pediatric
- Adult
  - Adult Booster
  - Specialty adolescent/adult
- Across Ages
  - Travelers / Endemic
  - Seasonal / Pandemic
  - Therapeutic
  - Special populations

Vacurion vaccine portfolio

Vaccine	Cost	NPV	PI	Cumulative Cost
M				$68m
				$78m
				$124m
				$216m
				$238m
				$250m
				$343m
H	$37m	$203m	5.5	$380m

Every team wishes its vaccine to be funded- often there are many years of R&D efforts

The solution:
Order vaccine candidates by decreasing PI

Segment

- Pediatric <6 yrs
  - Traditional Pediatric
  - Specialty pediatric
- Adult
  - Adult Booster
  - Specialty adolescent/adult
- Across Ages
  - Travelers / Endemic
  - Seasonal / Pandemic
  - Therapeutic
  - Special populations

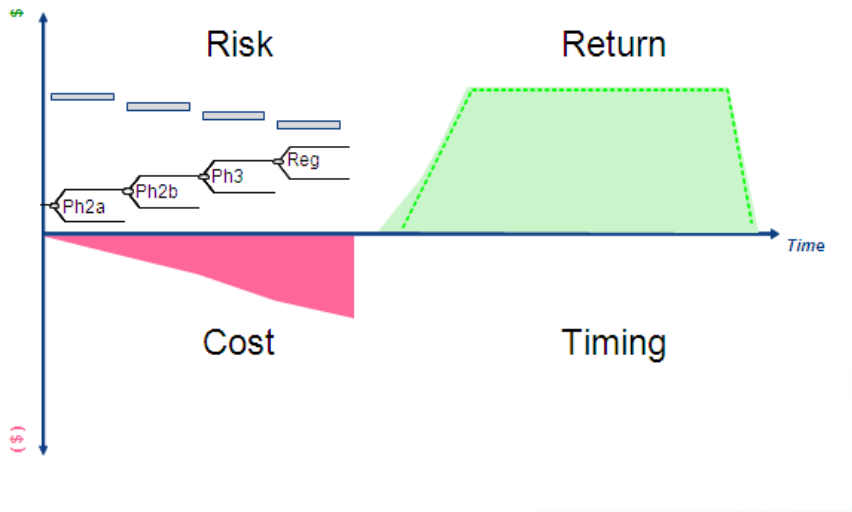
Vacurion vaccine portfolio

Vaccine	Cost	NPV	PI	Cumulative Cost	Cumulative NPV
F	$12m	$108m	8.7	$12m	$108m
H	$37m	$203m	5.5	$173m	$1,189m
G	$93m	$388m	4.2	$266m	$1,577m
M.terribilis	$68m	$253m	3.7	$334m	$1,830m
C	$46m	$134m	2.9	$380m	$1,964m

Cut off according to my cumulative cost- Vaccines G,*M.terribilis*,C are unaffordable

Nevertheless…This is not the end of the story

Key inputs are gathered to construct a set of valuation metrics for each potential Vaccine candidate



Vaccine candidate-specific analysis are incorporated into a portfolio level view to determine which candidates to fund

Management judgment is also incorporated into the strategic analysis

Management Judgment

- **Maximize Value**
  Shareholder value: eNPV
- **Maintain Portfolio Balance**
  Cash flow timing, risk, diseases, technologies, targets, geographic areas, etc.
- **Maintain Alignment with Corporate Strategy**
  R&D investments are aligned with the stated business strategy
- **Support the Right Number of Projects**
  R&D investments are capable of being operationalized by resources available to avoid pipeline gridlock and omission of key project activities.

In summary…

- Vaccines are growing at a faster pace than small molecules and their business model represents an attractive area for investment in the Pharmaceutical industry
- There are multiple vaccine candidates targeting a variety of population and geographies that have potentially a great value
- Because of high development costs and financial constraints, industry is forced to assign a value to each candidate in development
- For an organization that wants to grow in value, expected Net Present Value (eNPV) is the measure to use
- Expected Productivity Index (ePI) is the measure to use to help prioritize projects when we have more projects than capital
- Whereas value analysis are important for prioritization and sound investment, management judgment is ultimately essential

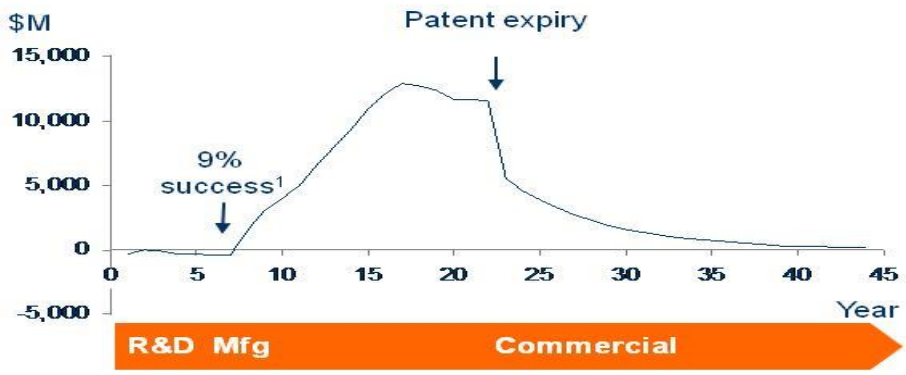
Thank you for your attention
Questions?

BACK UP

Vaccines versus Small Molecules

Development/ clinical	Manufacturing	Distribution and sales
Expensive late stage development ▪ Zero tolerance for side-effects ▪ Very large clinical trials (tens of thousands of people) required to prove adequate safety	Complex biologic manufacturing process, making operational excellence critical Long lead times in capacity building and production	Pediatric Vx sold through national immunization programs (NIPs) Adult Vx sold through PCPs, and require DTC marketing

Small molecule sales dependent on exclusivity



- Shorter development cycle (7-9 years), but lower probability of success
- Subscription model with high lifetime value
- Loss of revenue due to patent expiry and follow-on generic competition

Specialty Prophylactic vaccine sales dependent on population coverage

- Longer development cycle (9-14 years) but higher probability of success
- Single purchase model with some potential for booster market
- Step-changes possible from new gov't recommendations (e.g. increase age group)

Source: Reuters; Bear Stearns; BCG analysis, Credit Suisse, Evaluate Pharma