

Genavia Therapeutics

Business plan

June 2009



Executive summary

Genavia Therapeutics aspires to reshape the global market for Factor VIII – the most commonly used treatment for haemophilia.

The cost to treat haemophilia is currently of the order NZ\$100,000 per patient each year. Although haemophilia affects only one in 5000 male births the high cost per patient means that sales of recombinant Factor VIII are approximately NZ\$6 billion dollars today. This value is growing steadily as the patient population increases. A lower cost Factor VIII would reduce the burden that current treatment regimes place on health services and make affordable treatment that isn't provided today. In particular, it would make treatment possible for many of the 75% of the world's haemophiliacs who don't receive it now.

Genavia proposes to reduce the cost to produce Factor VIII by a factor of 10x and to cut the market price by as much as 80%. The technology platform that makes this possible is manufacture using transgenic chickens. This technology has been proven for other proteins but not yet for Factor VIII. Genavia has agreed a deal to license the enabling technology from a US biotechnology company - Origen Therapeutics. Genavia will not be a research company but rather will apply the fruits of Origen's research efforts to the Factor VIII opportunity.

The key driver of success, and the key unknown at this stage, is the amount and quality of Factor VIII that will be expressed in chicken eggs using the proposed method of manufacture. The bulk of the investment that Genavia is seeking to raise at this stage will be devoted to the technical work required to find the answers around these key variables.

If the results to the initial work are positive then investors could expect very strong returns on their investment. Compared to most medical biotechnology companies, there is low risk in the expensive clinical trial stage and a high degree of certainty about the level of sales after the product is launched (Factor VIII has already been taken through clinical trials successfully by a number of firms, and the market for the product is well-established). Hence, the risk is front-loaded i.e. at the cheapest stage of development. Consequently, Genavia believes that, the risk / reward equation for investors is highly favourable.

In addition to Factor VIII, Genavia has options to use Origen's intellectual property for other potential applications including blood factors VII and IX, and monoclonal antibodies (MAbs). These options provide expansion pathways and a way to mitigate the risk of Factor VIII failing.

In order to fund the next stage of work Genavia is seeking to arrange funding commitments for NZ\$5.0m. It proposes to do this offering investors the opportunity to subscribe to shares in three tranches.

The opportunity

The company

The economics

The timetable

The detail

Genavia Therapeutics aspires to reshape the global market for Factor VIII. Factor VIII is used to treat haemophilia A – a condition caused by a genetic deficiency of Factor VIII in the blood which prevents proper blood clotting in males.

About Haemophilia

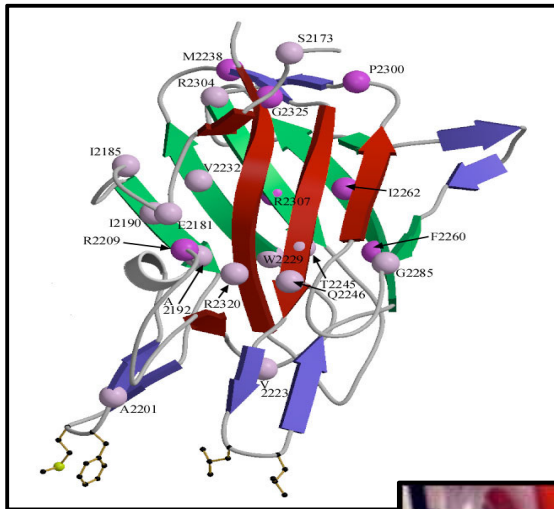


Haemophilia A

- One of two similar inherited conditions that stops blood from clotting properly
- Caused by shortage of a blood clotting factor – Factor VIII
- Affects only males - approximately 1 in 5,000 male births
- Varying degrees of severity
- Many of the world's haemophiliacs go untreated

Historically Factor VIII has been extracted from human plasma but increasingly it is made recombinantly (synthetically) using mammalian cell culture.

About Factor VIII

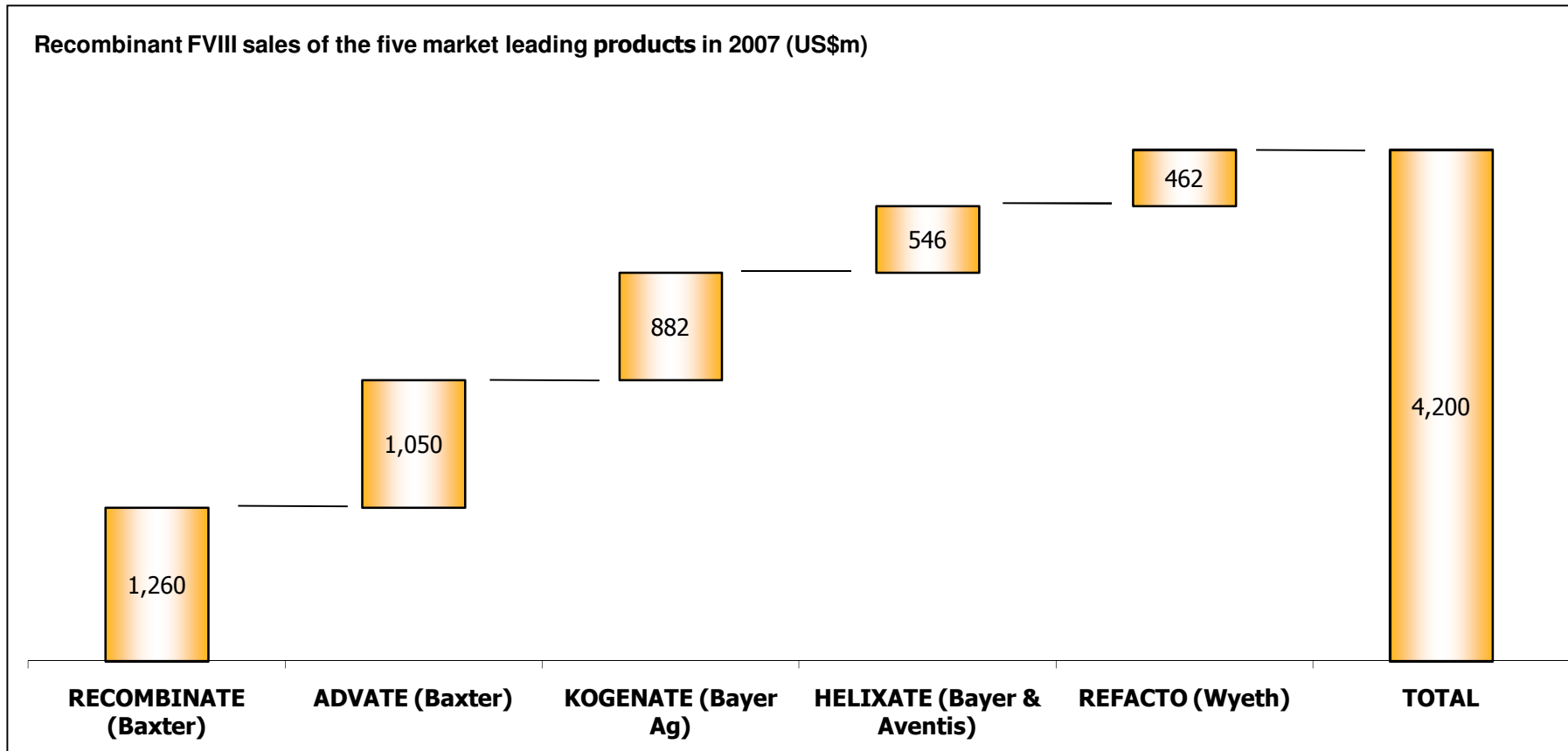


About Factor VIII

- A protein produced by the body – one of a cascade of proteins required to cause blood clotting.
- A protein used to treat haemophilia A.
- Produced in two ways
 - Derived from human plasma
 - Produced recombinantly
- Approximately 1kg of Factor VIII a year is enough to meet the entire global market today. But that 1kg is worth over NZ\$6 billion.

The global market for recombinant Factor VIII is very large. In 2007 sales of the top five brands of recombinant Factor VIII were over US\$4b. In addition, there are other brands of recombinant Factor VIII as well as still significant sales of plasma derived product.

Market size - Factor VIII

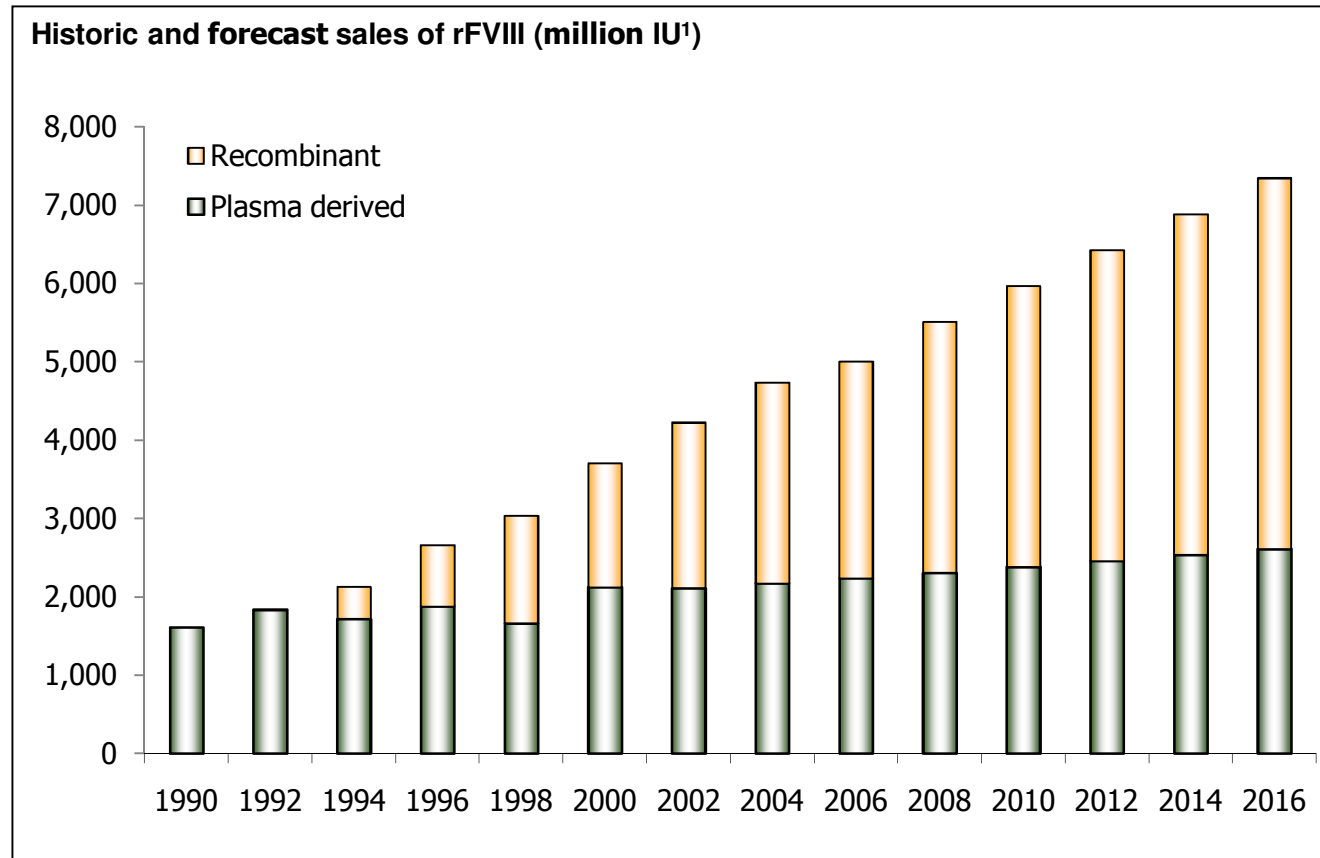


The market for recombinant Factor VIII is growing strongly. In the early 1980's contaminated blood meant that approximately 50% of all haemophiliacs, and 90% of severe haemophiliacs, contracted HIV. Approximately 95% contracted hepatitis C. Now the adult population of haemophiliacs is growing and with this demand for Factor VIII. It also means that recombinant products, with much lower risk of viral contamination, are increasingly preferred.

Sales growth – Factor VIII

Demand drivers

- Growing patient population as children born with haemophilia A since the early 1980's grow up.
- Preference to use recombinant, rather than plasma derived, product



¹. Factor VIII is measured in international units (IU). In normal human blood one litre of plasma contains 1000 IU.

Factor VIII is extremely expensive and so the cost of treating patients using Factor VIII is extremely high. In New Zealand and Australia, for example, treatment costs are funded nationally rather than through regional health boards to avoid burdening centres with a disproportionate concentration of haemophiliacs. To manage costs, treatment for less severe cases is made on-demand only (when a bleed occurs). More severe cases require prophylactic (preventative) treatment which increases the cost considerably.

The cost of treatment in New Zealand (typical of international costs)

(a) Prophylaxis			
	Patients (n)	Product use (units)	Cost (\$)
Plasma-derived products			
Adults	5	660 750	595 000
Children	1	75 000	67 500
Recombinant products			
Adults	0		
Children (8 HA, 1 HB)	9	1 137 100	1 793 000
Total	15	1 872 850	2 455 500

HA = haemophilia A; HB = haemophilia B

(b) On-demand treatment			
	Patients (n)	Product use (units)	Cost (\$)
Haemophilia A			
Plasma-derived products			
Adults	13	386 750	348 000
Children	1	2000	1800
Recombinant products			
Adults	3	56 000	90 000
Children	7	85 870	140 000
Total	24	530 620	579 800

The total amount of blood products used, and approximate cost for adults and children: (a) on prophylaxis (preventive treatment); (b) receiving on-demand treatment. Figures are for one year in New Zealand.



rFVIII can be used to treat Haemophilia using on-demand or prophylactic (preventative) treatment

- On demand treatment costs NZ\$30,000+ per year
- Prophylactic treatment costs NZ\$200,000+ per year

As well as reducing the financial burden on health systems that provide treatment today, lower cost Factor VIII would allow a number of unmet needs to be addressed. Foremost among these unmet needs is treatment of the 75% of the haemophiliac population that do not currently receive treatment. Cheaper Factor VIII would also enable better treatment regimes for patients that should be treated prophylactically but aren't, and patients that develop 'inhibitors'¹ to Factor VIII.

The need for a cheaper product

- Treat patients that can't afford any treatment today, including developing nations
- Treat development of 'inhibitors'¹ by tolerising patients (which requires large quantities for Factor VIII)
- Opportunity to treat prophylactically, not on-demand
- Close funding gap as children grow up and move out of family insurance coverage



With proper treatment, people with hemophilia can live perfectly healthy lives. Without it, many will die young or, if they survive, suffer joint damage that leaves them with permanent disabilities. Tragically, only about 25 percent of the estimated 400,000 people with hemophilia receive adequate treatment.

World Federation of Hemophilia website

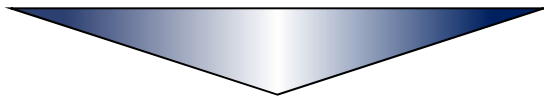
¹ Because Factor VIII is not produced naturally by their bodies, some haemophiliacs suffer an immune reaction to injected Factor VIII. Their immune system creates antibodies against Factor VIII which are often call inhibitors.

The very high cost of recombinant Factor VIII is a result of its very high manufacturing costs. Factor VIII is a large, unstable protein. It is difficult to express and difficult to purify from cell culture.

Why Factor VIII is so expensive

Expression

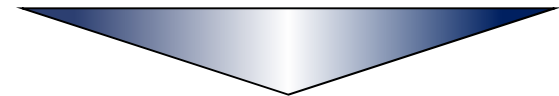
- Recombinant Factor VIII is produced in Chinese Hamster Ovary (CHO) or Baby Hamster Kidney (BHK) cells. The capital and operating costs of these production systems are large
- Factor VIII is very unstable and is subject to degradation from proteases (enzymes) in the cell culture mixture
- The expression rate (productivity) of Factor VIII is very low compared to other proteins produced in CHO & BHK cells



Very costly to express each gram of protein

Purification

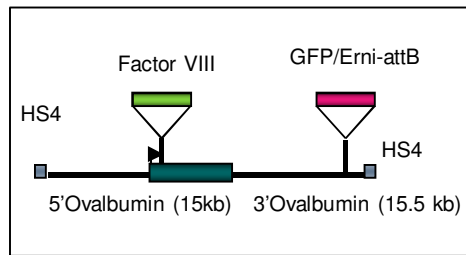
- Protein needs to be extracted using affinity columns rather than cheaper purification methods
- Because expression rate is low, a lot of affinity columns are required



Very costly to purify protein from the CHO media

The manufacturing process proposed by Genavia replaces cell culture with egg production. Genavia believes that the purification process will also be simpler as affinity columns should not be required - this will be tested in the planned work.

Factor VIII production using transgenic chickens



Create bioengineered chickens that express human Factor VIII in their oviducts



Develop a flock of chickens that produce Factor VIII in egg white



Purify Factor VIII from egg white using low-cost protein purification methods.



Formulated and put into an injectable dosage form.

Expression of Factor VIII in eggs offers an opportunity to dramatically reduce the cost of manufacture. If the technology works as envisaged it will allow Genavia to reshape the global market for Factor VIII.

Advantages of the chicken transgenic platform

- The cost to express the protein in eggs is expected to be much lower than the cost to produce in CHO cells
 - Potential for much better expression rates
 - Lower capital and operating costs
 - Easy to scale up
- The cost to purify Factor VIII from egg white should be much lower than the cost to purify from CHO cells
 - Remove the need for expensive affinity columns
 - Eliminate aggregate products



Genavia is targeting:

- A **10x** reduction in the cost to manufacture Factor VIII
- The ability to drop Average Wholesale Price by **5x**

If early results for Factor VIII appear promising there are a number of other potential target proteins that could be considered. Factors VII and IX are sold in similar markets although they pose different technical challenges.

Other blood factors

Blood factor	Market attractiveness	Technical feasibility
Factor VII	<ul style="list-style-type: none"> • Used to treat patients that develop antibodies (inhibitors) to Factor VIII • Even more valuable than Factor VIII on a mg basis • Sales of approximately US\$1.4b • NovoNordisk has had a production monopoly but patent due to end shortly 	<ul style="list-style-type: none"> • Key issue will be gamma carboxylation – a secondary modification of the protein sequence.
Factor IX	<ul style="list-style-type: none"> • Used to treat haemophilia B • Sales of order ~US\$1.0b 	<ul style="list-style-type: none"> • Key issue will be gamma carboxylation – a secondary modification of the protein sequence.

Genavia has shared this business plan with three major participants in the blood factors market.

Market feedback

Background



- Major player in plasma-derived Factor VIII.
- Currently working to develop recombinant product

Key points

- Interested when we have proof-of-principle
- Believe the key opportunity for our product is China, Russia, Brazil, India first, then developed country markets
- Advise Genavia not to underestimate purification issues



- World number 2 in recombinant Factor VIII

- Confirmed cost of goods is a major issue for them
- Primary interest would be Factors VII and IX



- Producer of recombinant Factor VIIa (coming off-patent 2010)

- Actively prospecting for new partnerships in the blood products arena
- Interested when we have proof-of-principle

Monoclonal antibodies present a somewhat different market opportunity. Genavia could provide a contract manufacturing service to biotechnology companies with monoclonal antibodies in their product pipeline.

Monoclonal antibodies

- Economics of MAb production (on an mg basis) are highly competitive (capital and operating cost)
- MAb's produced using chickens would be fucose free¹ – this increases the efficacy of the therapeutic produced by 10 to 100 times.



Genavia could target niche opportunities – potentially in partnership with drug originators

¹ Fucose is a sugar produced by rodent cell but not avian cells. Fucose interferes with antibody binding reducing the efficacy of MAbs.

In the medium term Origen's core business could create further opportunities for Genavia.

Polyclonal antibodies

- Origen Therapeutics is developing polyclonal antibodies as their key commercial platform
- Origen do not currently have a manufacturing plan.



Genavia could become a contract manufacturer for Origen and / or Origen's partners

The opportunity

The company

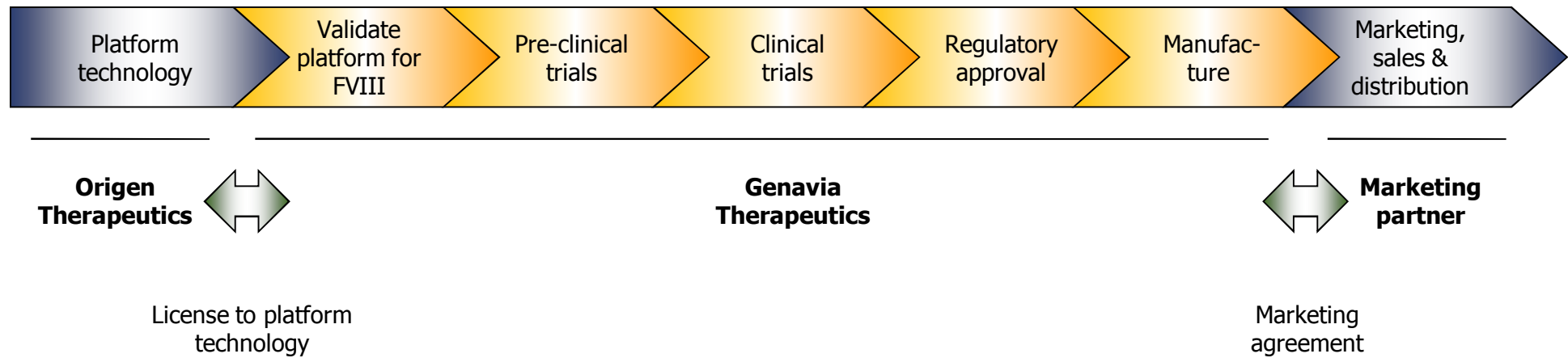
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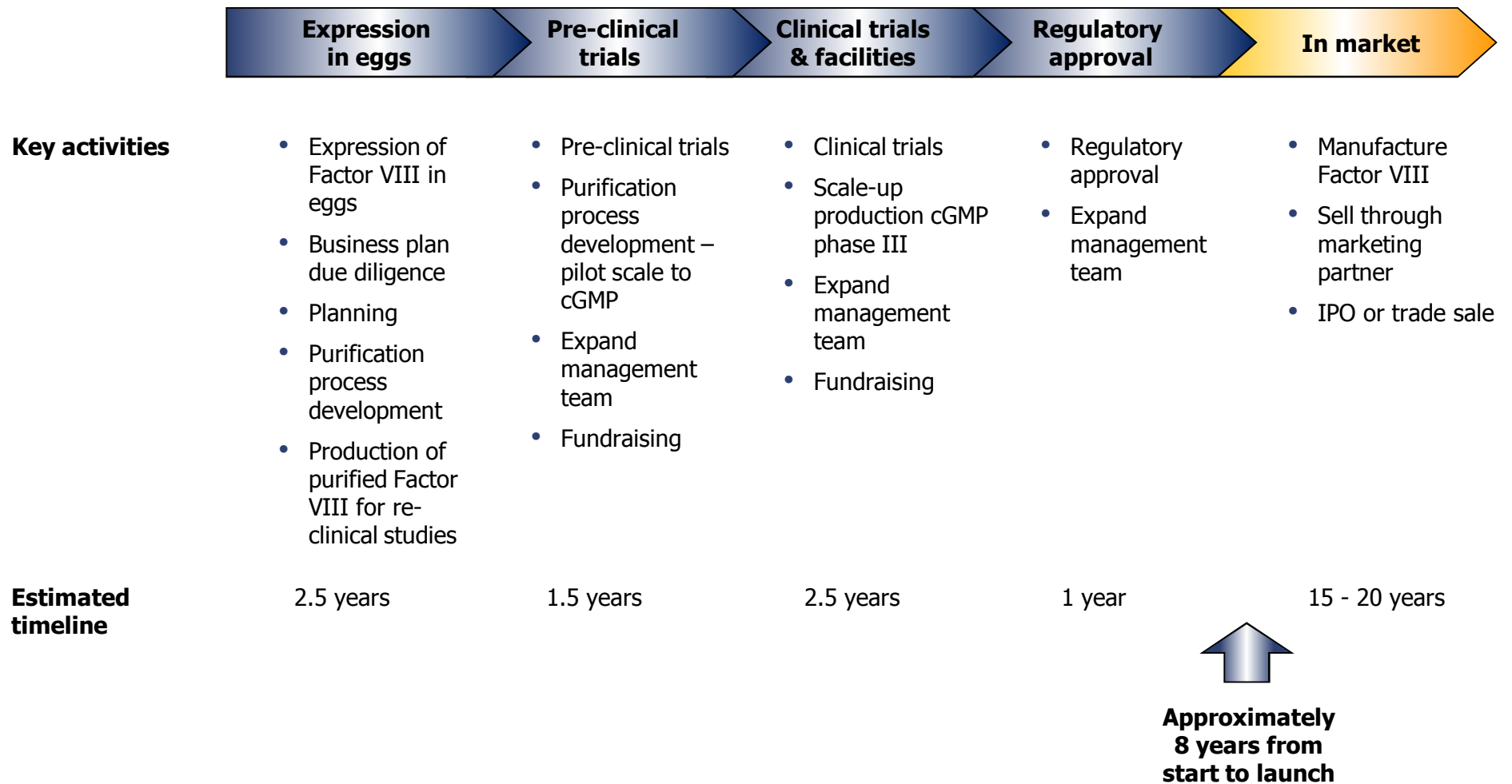
Genavia proposes to license technology from Origen Therapeutics to allow it to produce Factor VIII in chicken. Genavia envisages that it will prove Factor VIII can be produced by chickens, then take it through pre-clinical and clinical trials. Genavia will own manufacturing operations but will seek one or more marketing partners to sell the product internationally.

Genavia Therapeutics' business model for Factor VIII



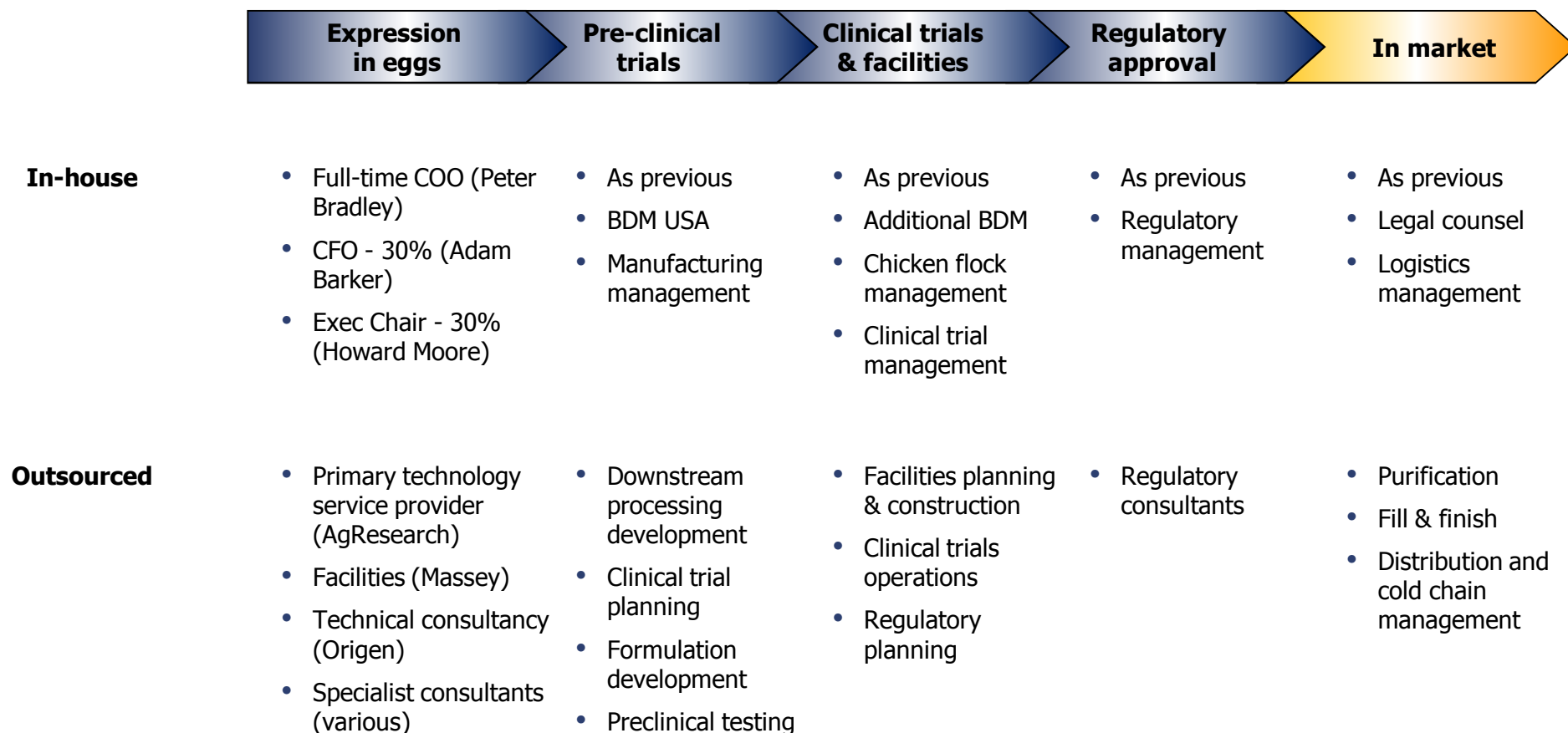
While the primary risks involved in producing a viable Factor VIII are in the first 2.5 years of development, the timeline for drug development and approval is such that the time to market is estimated at 8 years.

Business phases – Factor VIII development



Genavia will avoid building in-house operations that could become redundant further down the development process and become a burden on the company. Initially it will outsource almost all of its activities. As the company progresses Genavia will build in-house manufacturing capability and this will become the companies' core business in the long-term.

Proposed operations model



Origen Therapeutics is a US-based biotech company focussed on technology to produce proteins in chicken eggs. They are one of two surviving companies that sought to develop this technology and they have advanced further than the other (Avigenics) technically. Origen's commercial focus is on polyclonal antibodies (a next generation class of therapeutics). This creates an opportunity for a partner to apply their technology to current products such as blood factors and monoclonal antibodies.

About Origen Therapeutics

About Origen Therapeutics

Company

- Founded 1997
- Located in San Francisco, USA
- Fully equipped laboratories and animal facility
- Currently 12 employees (10 in research)

Platform

- Proprietary transgenic chicken production

Focus

- Developing therapeutic monoclonal antibodies and polyclonal antibodies with enhanced potency via ADCC¹
- Efforts directed towards platform technology rather than products

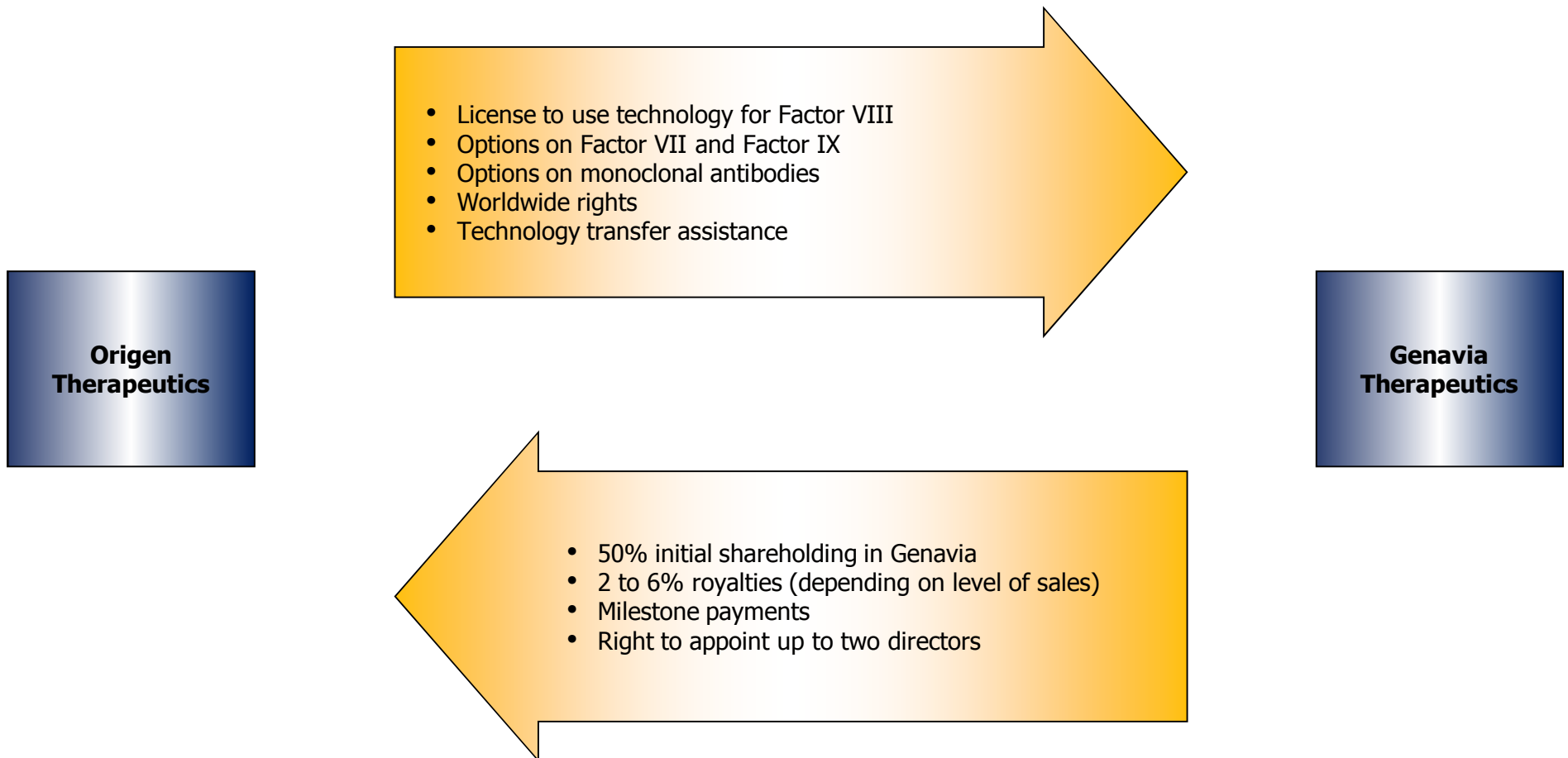
Technology Transfer to Genavia

- Dr Phil Leighton; Origen Research Director to lead technology transfer from Origen to Genavia
- Dr Christine Mather-Love; Former Director of Embryology and Animal Services at Origen is willing to join Genavia in similar role. The world's leading expert in the primordial germ cells – the enabling technology (Recommended by Origen CEO, Bob Kay)
- Dr Babette Heyer; Molecular biologist ex-Origen (Recommended by Origen CEO, Bob Kay)

¹ antibody dependent cellular cytotoxicity

The license agreement with Origen will give Genavia unrestricted rights to commercialise Factor VIII using Origen’s technology as well as options of Factors VII and IX. In return receive Origen will equity, milestone payments and royalties. There are no upfront payments to be made and the first milestone payment is only due when an application is made to the FDA to start clinical trials.

Key terms of the license agreement



The founding team have considerable experience of biotechnology businesses from start-up to public offering. The team's functional experience encompasses managing science teams, managing clinical trials, fundraising – including fundraising in North America, and international business development. The team has specific field experience in both blood products and transgenics.

People – company founders

Howard Moore – Executive chair



Howard Moore is one of a handful of New Zealanders who have achieved success as a biotechnology entrepreneur. He is also an experienced dairy industry executive with 25 years in the business. He entered the venture capital industry when he joined BioPacificVentures in March 2004 as executive director.

Prior to joining BioPacificVentures, Howard was executive vice president of Tercica Inc., a U.S.-based corporation he co-founded in Auckland before moving the business to San Francisco. In March 2004, Tercica listed on the NASDAQ, only the second New Zealand-founded company to achieve a listing on the world's leading technology stock market. Tercica's drug, Increlex (IGF-1) was approved on Aug 30, 2005 by the FDA for marketing.

Howard has a Bachelor of Food Technology from Massey University.

Peter Bradley – Chief Operating Officer



Peter is a director of Qatalyst Bioconsulting Limited, a business consultancy focused on commercialisation of biotechnology innovations. Peter has 25 years experience in all aspects of medical science and business. He is a highly skilled, scientifically trained leader with a wide knowledge of the health, pharmaceutical and laboratory based businesses. He has extensive knowledge and experience in commercialisation of science with hands on experience in developing and marketing technology based products. Most recently as MD of a privately held biotechnology company he has had experience within the biotechnology and medical device industries but most relevantly 13 years at CSL Limited the world's largest fractionator of human plasma.

Peter holds a Bachelor of Applied Science (Medical Science) from the University of South Australia, a Masters of Technology Management from the Melbourne Business School and is a Fellow of the Australian Institute of Medical Science.

Dr. Adam Barker – Chief Financial Officer



Adam Barker is a director of Scarlatti Limited, a business consultancy with a focus on early stage technology businesses, particularly in the life sciences. His work has spanned business strategy and project management but a particular emphasis has been development and analysis of business models for early stage ventures.

Adam was previously Chief Operating Officer of Celentis, a commercial science company owned by AgResearch, and before that was a consultant for leading strategy consultancy McKinsey & Company, based in London. While working with AgResearch he led a project to investigate the feasibility of commercialising their transgenic technology.

Adam holds a Bachelor of Engineering (First Class Honours) from Auckland University and a Doctorate in Engineering from the University of Cambridge, United Kingdom.

Genavia has discussed its plans with a range of New Zealand organisations and partnerships are being put in place.

Partnerships in New Zealand



Massey University

- Poultry science expertise
- Facilities at Palmerston North campus



AgResearch

- Molecular biology



Aviagen

- Supply of SPF¹ eggs / breeding stock
- Expertise for managing SPF poultry facilities

¹. Specific Pathogen Free – a term used for laboratory animals that are guaranteed free of particular pathogens

Genavia has built a network of experts across all areas of the business. The people listed below are a representative sample and not a complete list.

Genavia: examples of project experts and resources.

Factor VIII fundamental science

- **Randy Kauffman:** Developed '3rd generation' rFVIII products
- **Dionysis Pantazatos:** Post doc at Harvard working on Factor VIII and von Willebrand factor.

Recombinant Factor VIII manufacture

- **Juan Davagnino:** Formulation specialist. Factor VIII experience from Baxter.
- **Mike Parker:** Previously quality manager at Bayer
- **Bruce Gardner:** Process scientist with primarily fill/finish experience. Factor VIII experience from Bayer.
- **Christophe Grimm:** Engineer with Sartorius. Former Project Engineer with Baxter for Factor VIII.
- **Kathleen Harris:** Spent 16 years at Bayer as a Process Scientist.
- **Don Gerson:** Previous head of Wyeth Vaccines

Other bio-pharmaceutical manufacture

- **Ed Calamai** – PM&C Inc.
- **Michael Morey** – ex CSL Bioplasma Head of Technology Transfer

Clinical Development

- **Stuart McLachlan** – Director Clinical Research at NYCOMED AMERSHAM

Markets for Factor VIII

- **Anthony Russell:** Medical Marketing and Comms. Recombinate (Baxter) Factor VIII marketing experience.
- **Dr Neil Goss** former Director of R&D CSL Bioplasma a division of CSL Limited
- **Dr Albert Farrugia,** Senior Vice President, Plasma Protein Therapeutics Association and Blood Safety Adviser, World Federation of Hemophilia

Regulatory (New Zealand)

- **Kieran Elborough,** Chairperson for the Environmental Risk Management Authority GMO standing committee
- **Shaun Slattery:** Ex-ERMA – advised AgResearch Transgenic program

Poultry science

- **Alan Alexander** (Massey),
- **Rob Etches** (ex CSO of Origen)

Transgenic company links

- GTC Biotherapeutics
- AgResearch

Genavia would establish an advisory board during its first year. Genavia would particularly seek to find individuals with knowledge of the clinical market for Factor VIII

Advisory board

Key skills / experience

- Understand clinical market for Factor VIII (e.g. a haematologist)
- Knowledge of clinical trial design (e.g. ex-executive from Bayer, Baxter, Wyeth)

Size

- 3-4 members

Meetings

- 2-3 meetings per year (probably mixture of US and NZ locations)

The opportunity

The company

The economics

The timetable

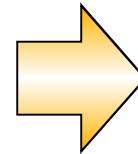
The detail

Genavia have built a comprehensive economic model of the business. This estimates the value of the company at the time of product launch and then works backwards to determine the value uplift over time.

An economic model of Genavia – overall approach

Step 1 – model the company value at launch

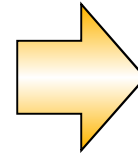
- Forecast sales (a function of price)
- Estimate COGS (a function of expression rate)
- Apply a discount factor
- Choose the price that maximises value



Valuation at launch

Step 2 – model how value grows over time

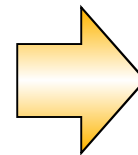
- Estimate the cost of each stage before launch
- Estimate the risk (probability of success) of each stage before launch
- Apply a discount factor



Value growth

Step 3 – model investment and share values

- Input initial shareholding (founders and Genavia)
- Model investment & dilution
- Model impact of stock options



Investor returns

A wide range of variable play a role in determining the company's value.

Major determinants of company value



Revenues from the marketed product

- Market size & growth
- Impact of lower pricing
- Market share (final)
- Sales growth
- Value sharing agreements with partners



Time to complete key development activities

- Proof-of-concept
- Pre-clinical
- Clinical trials
- FDA / EMEA approval



Cost to manufacture

- Expression in eggs
- Purification



Stage by stage risks

- Proof-of-concept
- Preclinical
- Clinical trials
- FDA / EMEA approval



Cost to complete key development activities

- Proof-of-concept
- Pre-clinical
- Clinical trials
- Manufacturing (including regulatory requirements)

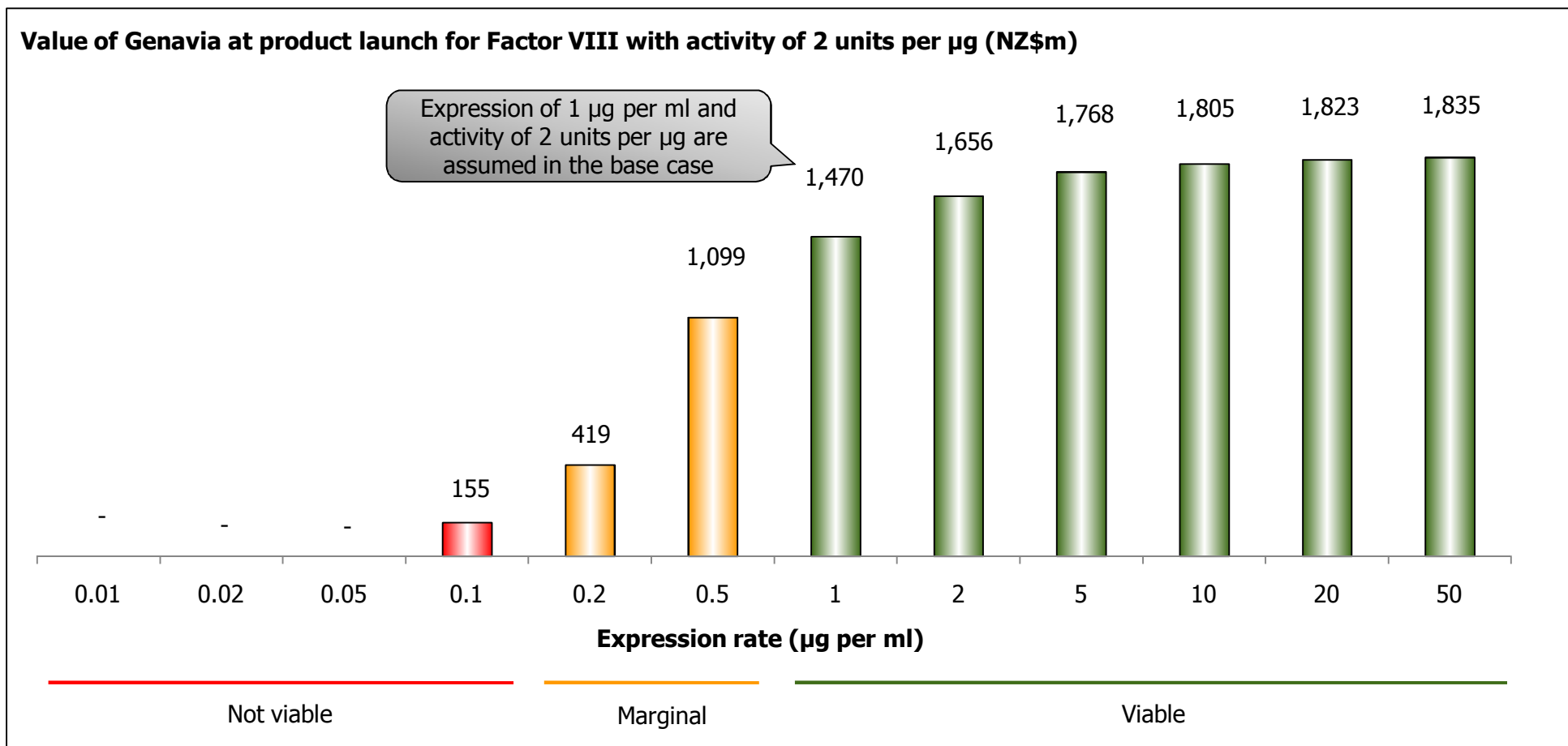


Overall business risks

- Attitudes towards animal derived proteins
- Transgenic competition
- Pegylated Factor VIII
- Gene therapy
- Other novel manufacturing processes
- Intellectual property

The single most important factor in determining Genavia’s value at launch is the amount of Factor VIII produced in each egg. There are two variables to be considered – the *expression rate* (μg of FVIII per ml egg white) and *the activity* (units per μg of Factor VIII). With activity of 2 units per μg and expression of $1\mu\text{g}$ per ml Genavia will be viable. Although expression of $0.1\mu\text{g}$ per ml would be good enough to manufacture and sell profitably, the value of the company at launch wouldn’t be enough to justify investment in preclinical work and clinical trials. With expression above $5\mu\text{g}$ per ml cost of goods become negligible and further improvements don’t add value.

Sensitivity of launch value to expression rate



The other major determinant of launch value (along with expression rate) is forecast sales. Assumptions are made about the market share capture from existing products on the market and about sales into new markets created by a lower price point. There is expected to be a trade-off between sales volume and gross margin. The model both characterises this trade-off (i.e. how much do sales go up as the price drops?) and calculates an optimal price. Like any long range sales forecast the projection shown below must be considered indicative. However, it illustrates that Genavia can reasonably expect to become a billion dollar company if it executes its business plan successfully.

Sales assumptions and projections

Displacement of product sold currently

- If price was free, market share would be 50%
- Market share reduces as price goes up, dropping to zero when the Average Wholesale Price (AWP) of Genavia's product is 50% AWP today
- 8 years to reach ultimate market share

Additional use for existing patients

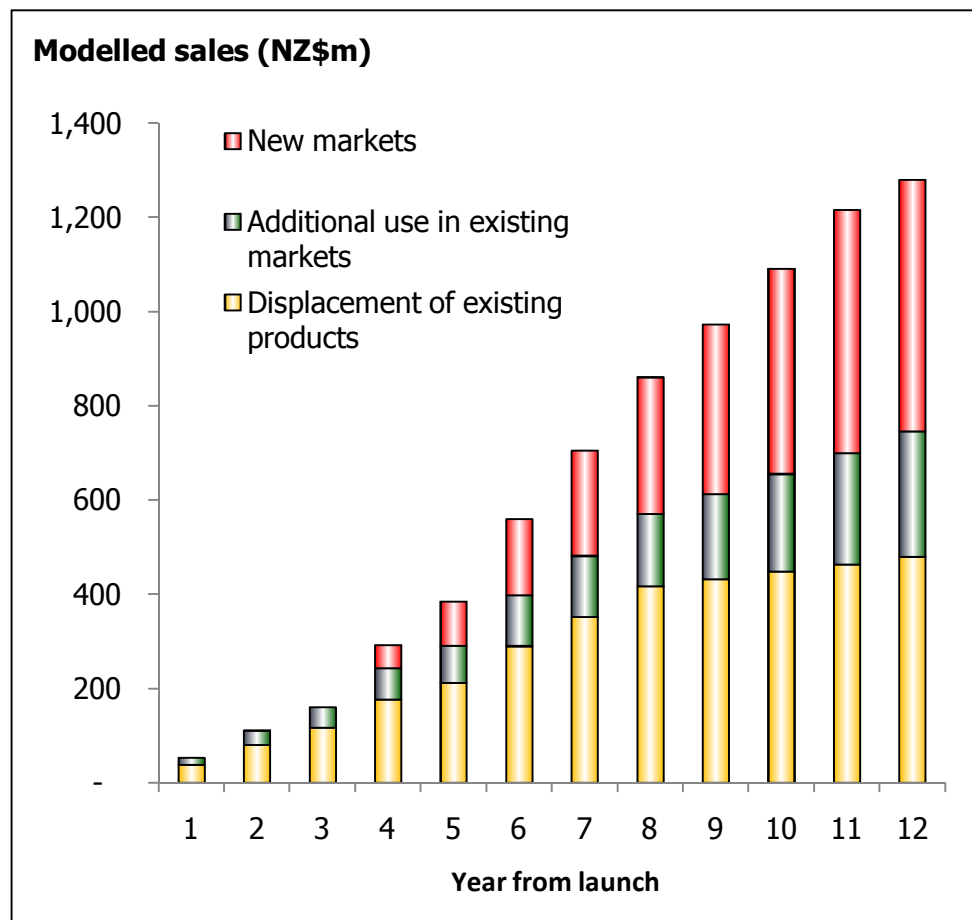
- Volume used would increase by 50% if free product was available
- Volume used reduces linearly as price goes up, dropping to zero if the Average Wholesale Price (AWP) of Genavia's product is 30% AWP today
- 12 years to reach full potential

Sales to patients not currently treated

- Total volume sold would double if free product was available
- Volume used reduces linearly as price goes up, dropping to zero if the Average Wholesale Price (AWP) of Genavia's product is 30% AWP today
- 3 year lag until sales start
- Then 8 years to reach full potential

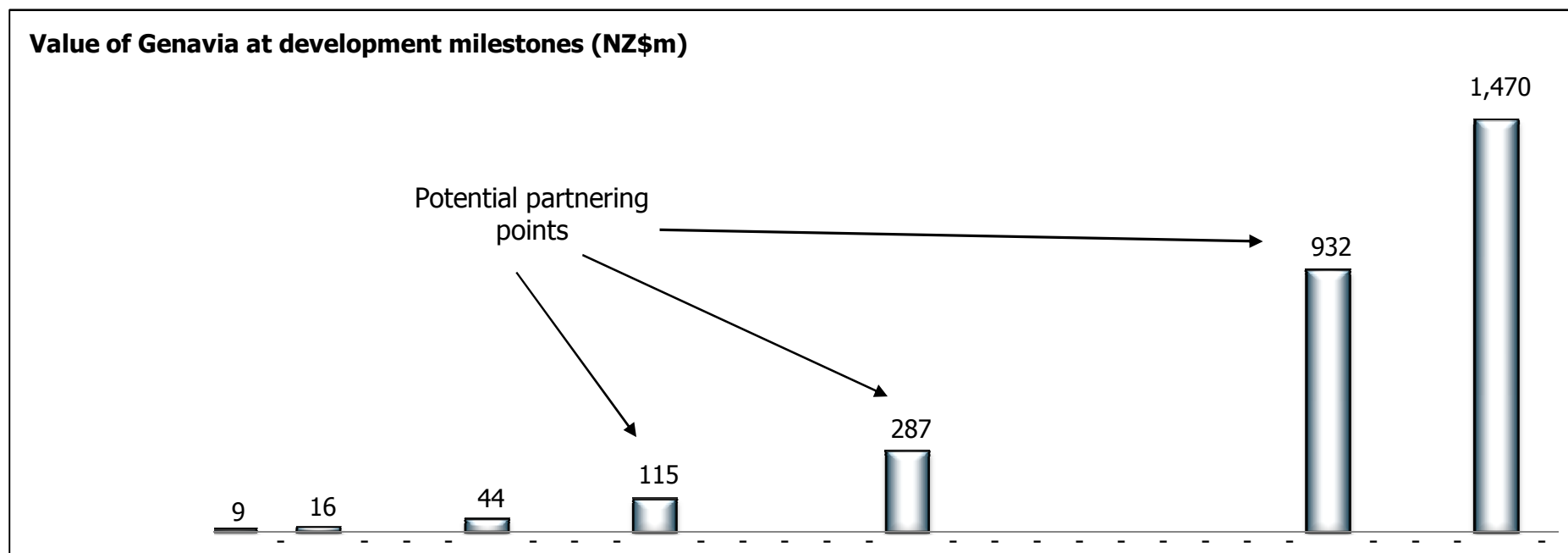
Optimal price

- AWP of Genavia's product is 22% of existing AWP (i.e. US\$0.22)



Genavia’s value at different points over the development timetable has been projected by working back from the launch value. At each milestone the value is determined by working back from the previous milestone and discounting based on Genavia’s estimates of the probability of success at each stage and the investment requirement. The valuations are then further discounted using an annual discount rate of 40%.

Projected value uplift



	Year 1				Year 2				Year 3				Year 4				Year 5				Year 6				Year 7				Year 8			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Milestone	◇				◇				◇				◇				◇				◇				◇							
	Due diligence & purification OK				Expression - gland cells				Expression - eggs				IND submission								Submission to regulator				Product launch							
Probability of success	70%		55%		55%				70%						80%						90%											
Investment requirement (NZ\$m)	~0.7		~1.5		~1.5				~12						~80						~20											

Genavia's value at different points over the development timetable has been defined by specific milestones. Each milestone sees a step change in the value of the company based on addition of significant value or elimination of a particular risk.

Key milestones - value uplift

Expression of FVIII in eggs

- The initial phase of this project bears the greatest risk. Whilst the protein expression system has been demonstrated it has not been done with FVIII.

IND submission

- Once the FVIII has been produced a process for purification must be developed. Subsequently the product must undergo a well established suite of preclinical testing to ensure safety and potential efficacy. These results will form the basis for an Investigational New Drug submission that will allow clinical trials to commence

Submission to Regulator

- The clinical trials for this product will follow a well established and proven format. Assuming these are successful the regulatory dossier for approval will be submitted. Once approval is granted the product can be marketed

Product Launch

The opportunity

The company

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The detail

An intensive programme of commercial and technical work is proposed for the next six months. This work is intended to identify any as yet unidentified risks at an early stage, and to address any risks that can be investigated comparatively cheaply at an early stage. This includes work to uncover and address any unknown flaws in the business plan and work to demonstrate that purification of Factor VIII from egg white is straightforward compared to purification from cell culture.

Immediate next steps

Finalise license deal with Origen Therapeutics

- Convert existing option agreement into full license

Further validate the business plan

- Develop deeper understanding of the cost of manufacture of Factor VIII in cell culture
- Undertake IP due diligence
- Refine economic model

- Test business plan on a wide network of experts

Develop purification process at bench scale

- Demonstrate ability to purify FVIII from egg white using scaleable and robust methods.

Kick-off the science programme

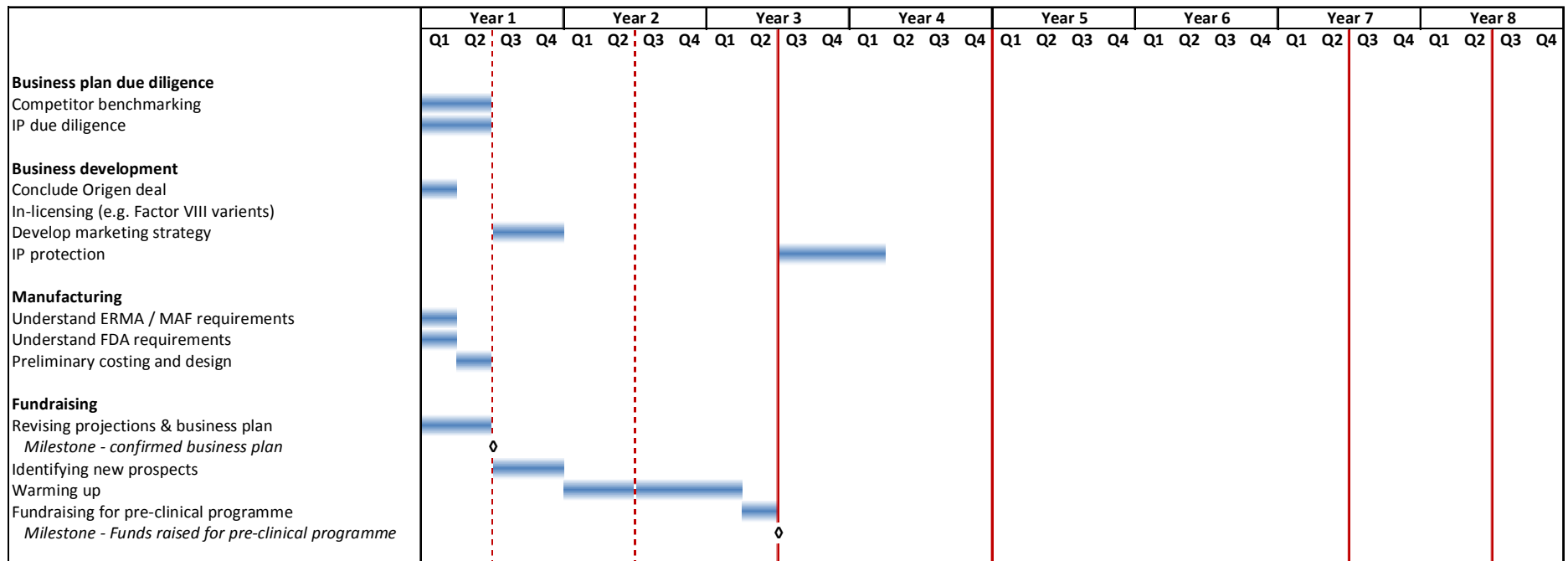
- Begin early stage work with Origen and AgResearch

Plan for future stages

- Identify requirements for pre-clinical, clinical and regulatory stages

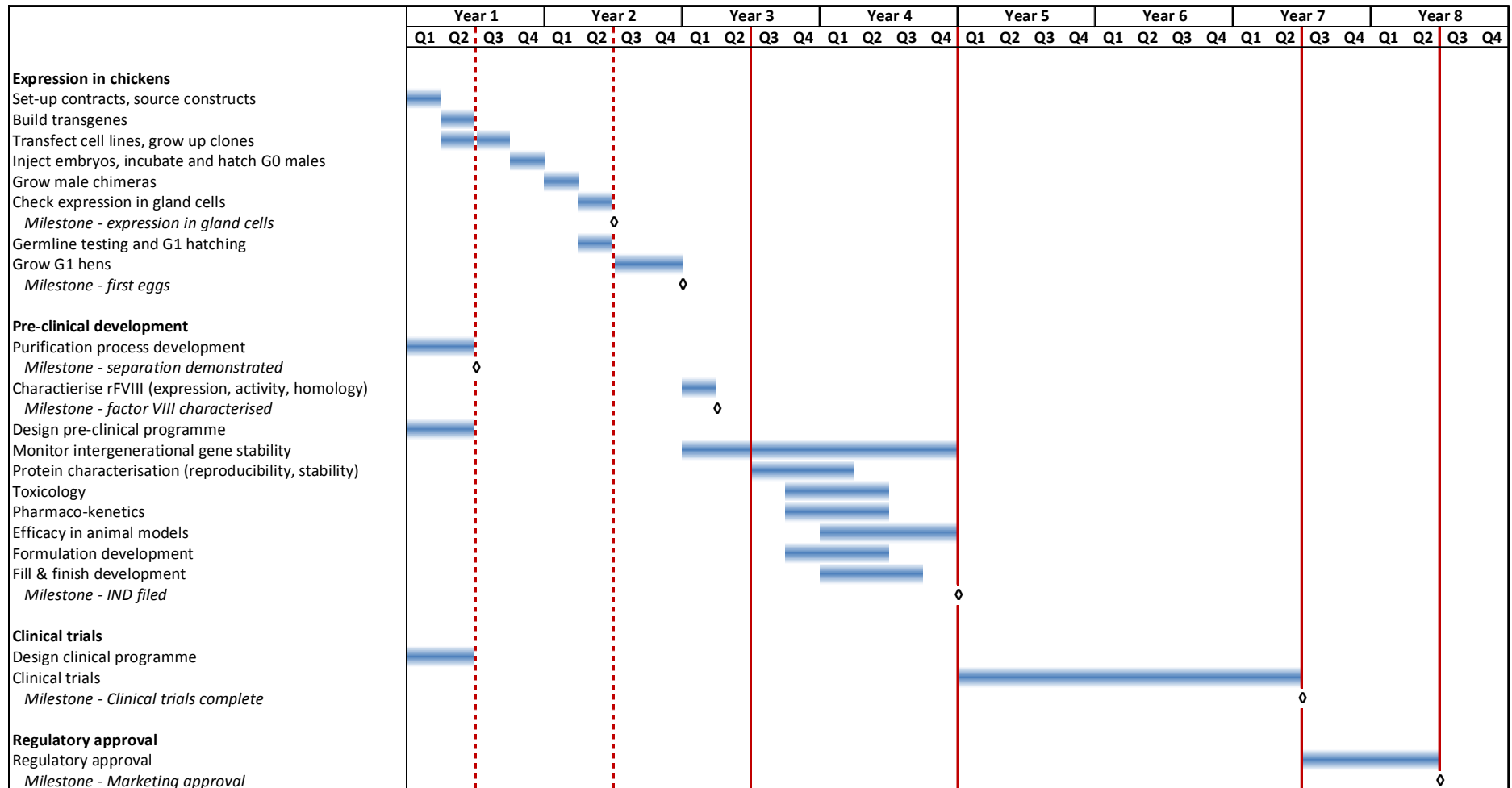
The first stage of work (expression in eggs) can be broken into three sub-stages with intermediate milestones. Commercial due diligence and planning will go through a six month burst upfront concluding with business plan and purification development milestones. The science work will reach a milestone at approximately 18 months when it will be possible to check whether Factor VIII is produced in the birds' tubular gland cells. The first stage is not completed until funding has been raised for preclinical work.

Gantt chart – commercial



It will take a little over two years to reach the point of having shown proof of concept that Factor VIII can be successfully expressed, recovered, and purified from eggs. A further 3-6 months are required to test the protein and to complete the next round of fundraising.

Gantt chart – science



The opportunity

The company

The economics

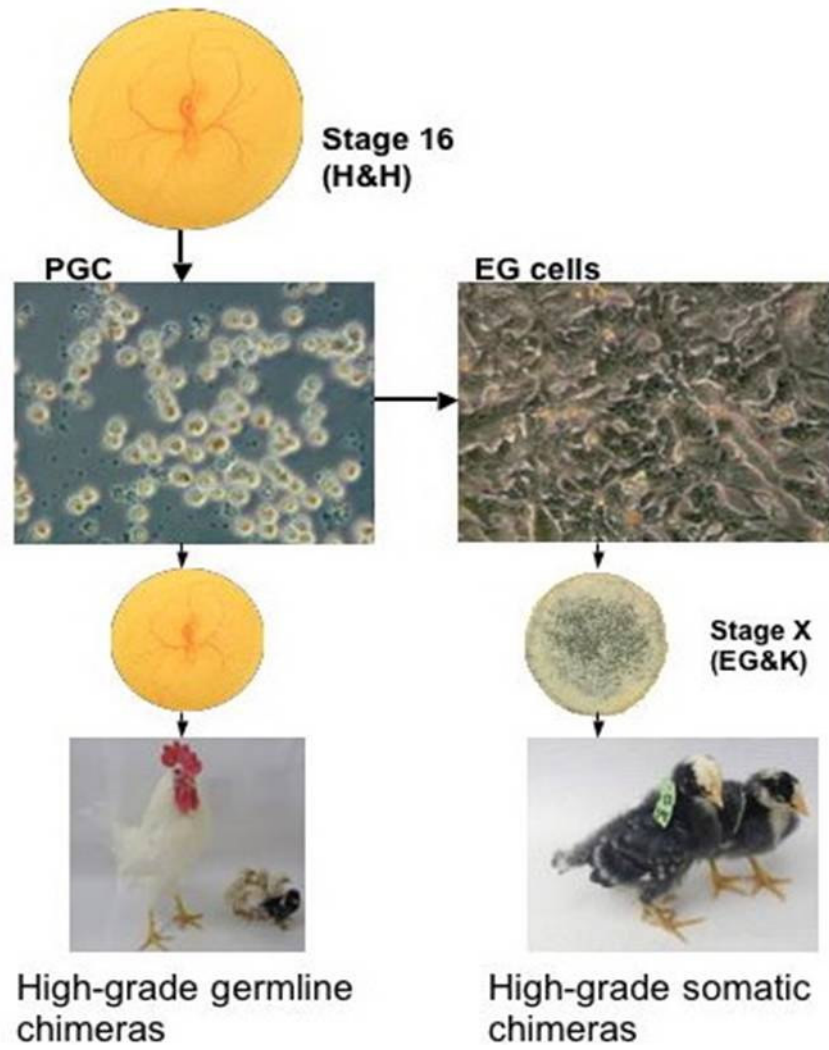
The timetable

The detail

- Science

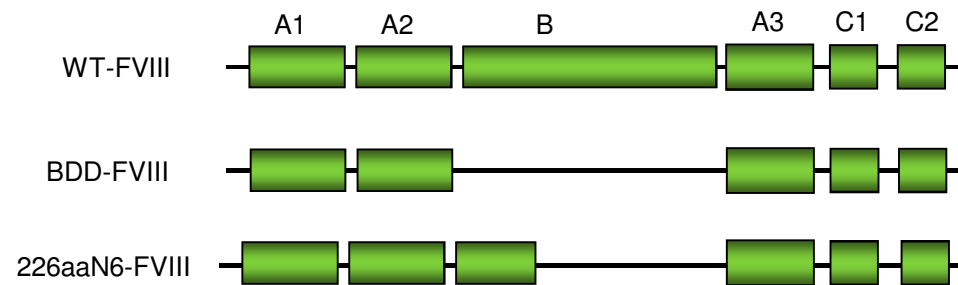
Avian transgenic process

PGCs derived from Stage 16 chicken embryos can contribute to the germline and can be converted into EG cells that contribute to somatic tissues.

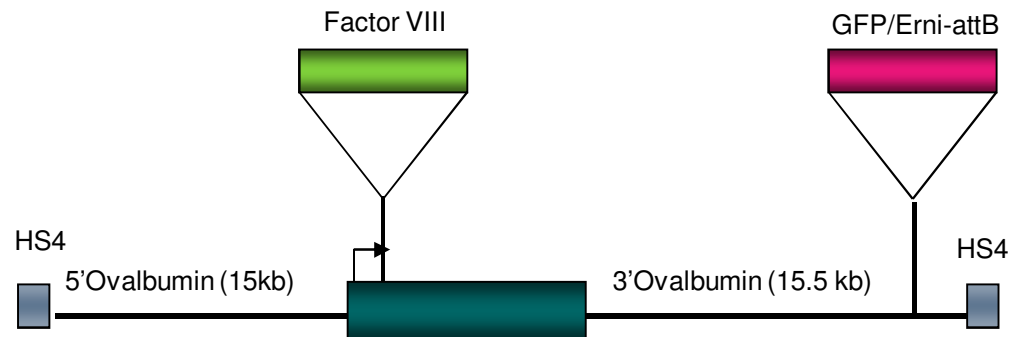


Design of a transgene expressing for Factor VIII

A: human Factor VIII cDNA variants



B: OV - Factor VIII expression vector



Technology platform

Origen's transgenic chicken platform

Eggs as a method of protein production

- Sterile packaging
- Easily handled on a large scale
- Significant knowledge from the vaccine industry
- Each hen lays about 300 eggs per year -> 15 grams of product (MAbs)

Origen's technology position

- Origen has established a proprietary, unified transgenesis system for chickens
- Embryonic Stem Cells for developing transgenes ("cESC")
- Primordial Germ Cells for germline transmission ("cPGC")

Operations

- GMP operations established
- Chickens breed rapidly and efficiently

Risk factors associated with expressing Factor VIII in chicken eggs

1. Building a transgene encoding Factor VIII

- Transgenes capable of tissue specific expression of proteins in the tubular gland cells of the chicken oviduct have been built and tested.
- Construction of transgenes encoding human Factor VIII has been widely accomplished for mammalian cell expression.
- Combining the two above technologies to generate a transgene capable of expressing human Factor VIII in the chicken oviduct should pose little risk.

2. Creating a transgenic chicken carrying the Factor VIII transgene

- Fully transgenic chickens have been produced at Origen using primordial germ cells (PGCs).
- The PGC technology allows for the introduction of large transgenes as will be needed for Factor VIII expression.
- No major risk factors are associated with applying PGC technology to introducing Factor VIII transgenes into the chicken germline

3. Expressing Factor VIII in the egg

There are four aspects to expression of Factor VIII in the chicken oviduct:

- i) Transcription of the transgene in the tubular gland cells driven by the ovalbumin promoter and correct processing of the primary transcript.
While we have seen minor issues with post-transcriptional processing in the design of transgenes expressing monoclonal antibodies, these design issues are readily addressable. Of note has been incorrect intron excision or exon skipping. This can be corrected with removal of the intron or using the Factor VIII cDNA.
- ii) Translation of the Factor VIII mRNA in tubular gland cells.
We see no obvious issues associated with the translation of Factor VIII mRNA in the tubular gland cells. By comparison, human sequence monoclonal antibody mRNA was efficiently translated in these cells.
- iii) Post-translational processing of the Factor VIII protein in the tubular gland cells.
Factor VIII protein is large and complex and requires both proteolytic cleavage and glycosylation before becoming fully functional. We have no experience expressing this protein in these cells and this does represent a significant risk factor.
- iv) Secretion of the Factor VIII from the cells into the lumen and accumulation in egg white.
Secretion of Factor VIII from mammalian cells is not efficient and considerable work has been done by others to improve secretion including removing the B domain and modifying the protein sequence to remove a site associated with binding to certain cellular proteins. Co-expression with other stabilizing proteins has also been investigated although expert advice suggests this will not be necessary. We have no experience with secretion of human Factor VIII from chicken cells and particularly tubular gland cells. This does represent a significant risk factor.

The opportunity

The company

The economics

The timetable

The detail

- Planning

Commercial due diligence – areas to be addressed

Validate rFVIII as a target

- Refine understanding of rFVIII manufacture in mammalian cell culture (particularly economics)
- Understand history of rFVIII research / development by other transgenic groups
- Identify and establish interest from potential marketing partners
- Forecast selling volumes and margins

Prioritise other targets

- Identify other targets that fit in the transgenic niche

Prepare detailed costings

- Pre-clinical requirements and costs
- Facilities costs
- New Zealand regulatory costs (ERMA)
- Clinical trials
- EMEA and FDA requirements and costs (follow-on biologics regulations?)

Establish required timelines through benchmarking

- Pre-clinical trials
- Facilities build programme
- New Zealand regulatory delays
- Clinical trials
- EMEA and FDA approvals

Reality checks

- Why did Viragen drop transgenics?

Partners

- What assets exist at potential partners in New Zealand (Massey, AgResearch, NZP, ICPBio)?

Intellectual property

- What FTO does Origen have?
- What IP barriers can Origen put up?

Financial modelling

- Full financial model with sensitivity analysis
- Probability of success by milestone
- Go – no go conditions at defined milestones

Further investment

- Identify investors with a reason to invest in this (e.g. funds linked to haemophilia research, reducing cost of drugs in developing markets)

Planning – areas to be addressed

Licenses (including Origen)

Human Resources

- Recruit clinical advisory board
- Recruit appropriate management team

Facilities

- ERMA approvals
- cGMP approvals
- Life of facility
- Eventual home of egg production facilities

Marketing

- Distribution of final product by territory (see reg affairs)
- Peer reviewed publications
- Prospective marketing partners

ERMA approvals

- Chickens
- Eggs
- Final product

Manufacturing partners

- Purification
- Fill & finish

Location

- People (New Zealand vs USA)
- Operations (New Zealand vs USA)

Clinical trials -refer clinical advisory board

- Phase I – Territory
- Phase II – Patient cohorts – classifications?
- Phase III – Which competitor – recombinant or plasma derived. Do we need a trial to address inhibitor levels between products (more importantly do we need to address this?)
- Establishment of clinical advisory board

Regulatory Affairs

- Preclinical programme
- Bioequivalence testing
- Documented development history and compliance with cGLP
- Regulatory Dossier
 - Manufacturing validation
 - Egg harvesting and initial recovery
 - Purification of bulk drug substance IFVIII protein
 - Preparation of final dosage form
 - Assay Validation
 - In place cleaning validation
 - Stability trial
 - Animal Ethics documentation and approvals