BIOPROCESS FOR THE PRODUCTION OF GENE THERAPY FOR HAEMOPHILIA A:

Bioprocess Dessign Part II

FINAL PROJECT BIOTECHNOLOGY 2015

AUTHORS: Ana Marrodan and **Beatriz García**

TUTOR: Carles Solà Ferrando

ACKNOWLEDGEMENTS

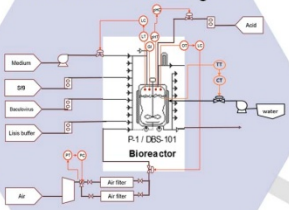
This work would have been impossible without the contributions of the former members of the team. A special thanks to Josh Callan, Clara Fernando and Lluís Revilla

1. QUALITY BY DESIGN

Critical Quality Attributes

- Sterility
- Purity
- 80% capside fullness
- Dose: 10^{15} AAV

Piping & Instrumentation Diagram



Critical Process Elements

- Bioreactor
- BV production
- Affinity Chromatography
- Filters and compressors

2. PLANT LAYOUT

Plant Location: Catalonia

- Strength of biotechnological and pharmaceutical sector in Catalunya.
- Ensuring operate with European standards of safety and quality.
- Existence of qualified personnel.
- Enhance synergies between big-players in the same bio-region and continent.
- The catalan constitutional framework,framed within the European Union guarantees the social coverage of workers.

Plant Layout

Clean Room design to minimize cross contamination:

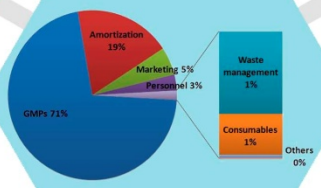
- People and material flow
- Allowable number and size of particles per m3 of air according room classification.
- Maintaining a positive pressure.
- Facilities adapted to clean room conditions.
- Clean Room Standards : ISO-14644

3. ECONOMIC ANALYSIS

Investment	43.085.900,00 €
Production cost of a dose	31.269,24 €
Price dose	150.000,00 €
ROI	228%
VAN	1.885.331.367,19 €

VAN vs price dose

Break-up Operational Cost



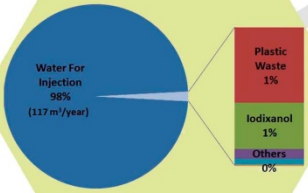
4. SOCIAL ANALYSIS

- ~50,000 patients cured for life
- Innovation
- Job creation
- Workers rights. Net earnings: 2100 -4800 €
- Public perception:Information campaign (3% costs)

(to 5)

5. ENVIRONMENTAL ANALYSIS

Main Mass Indexes



Waste management

- **Incineration: plastic waste and others biohazardous solids like cake from centrifugues or filters: cell debris, empty capsids from AAVs, baculovirus**
- **Chemical stabilization: corrosive material solutions (Tris-HCl)**
- **Filtered/Autoclaved of biohazardous liquids, wastewater of any process units. Conditioning for use it as process water.**

6. FUTURE IMPROVEMENTS

Clone the whole AAV genome inside the cell. Inducible expression system.

- New cell would contain the full genome of the virus in addition to the gene of interest under the control of an inducible promoter like polyhedrine promoter. This allows:
  -Working with wt-baculovirus.
  -Avoiding royalties
- Other means of induction (antibiotics, pH, T..)

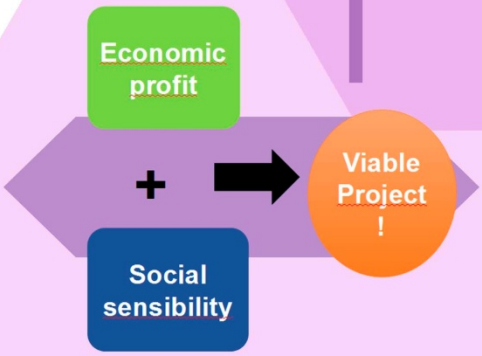
Focus towards a new target disease.

Replacing the gene of interest and mantaining the expression vector.

Expand the market.

Asia, USA

7. CONCLUSIONS



Bibliography:

Aguirre R. et al. (2014) Recomanacions per a l'aplicació de sistemes de gestió de la qualitat pel disseny (QbD) en la fabricació industrial de medicaments comercialitzats. Direcció General d'Ordenació i Regulació Sanitàries,p. 1–67.

International Conference of Harmonisation . ICH Harmonised Tripartite Guideline: Q8(R2), Q9 & Q10. Retrieved from: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

España. "Real Decreto Legislativo 1/1995, de 24 de marzo, por el que se aprueba eltexto refundido de la Ley del Estatuto de los Trabajadores". BOE, no. 75, p.9654-9688. 29 de marzo de 1995.

Graham, B., Gahan, D., & Thomas, K. (2007). The application of Knowledge Management practices in the procurement and construction of cleanroom projects.

Petrides, D. (2000). Bioprocess design and economics. Bioseparations Science and Engineering.