Biodefense : Considerations for the manufacture of vaccines and therapeutic agents

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Safe harbor statement

Today's presentation and discussion will contain forward-looking statements including statements regarding future operating performance, financial or revenue growth targets, or client project pipelines. These statements may be identified by words such as "expects", "anticipates", "intends", "estimates", "believes" or similar expressions.

These statements are based on Cambrex's current plans and expectations and involve risks and uncertainties that could cause actual outcomes and results to materially differ from those set forth in the forward-looking statements. For discussion of these and other risks and uncertainties, see the "Forward-Looking Statements" and "Risk Factors That May Affect Future Results" sections in the Annual Report Form 10-K for the period ending December 31, 2004.

The Company undertakes no obligation to update forward-looking statements. For further information, please refer to Cambrex's reports and filings with the Securities and Exchange Commission.

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Introduction

- Production and maintenance of stockpile of protein preparations to meet potential bioterrorism threats
- Vaccines and therapeutics
- Requirements for manufacturing are not unique but require some considerations with respect to intended applications and end-users
- Data abstracted from biodefense development and manufacturing programs outsourced to Cambrex Biopharma

Biopharmaceuticals : Biological expression

- Products which may never be used
- Diversity
- Mechanism for risk management

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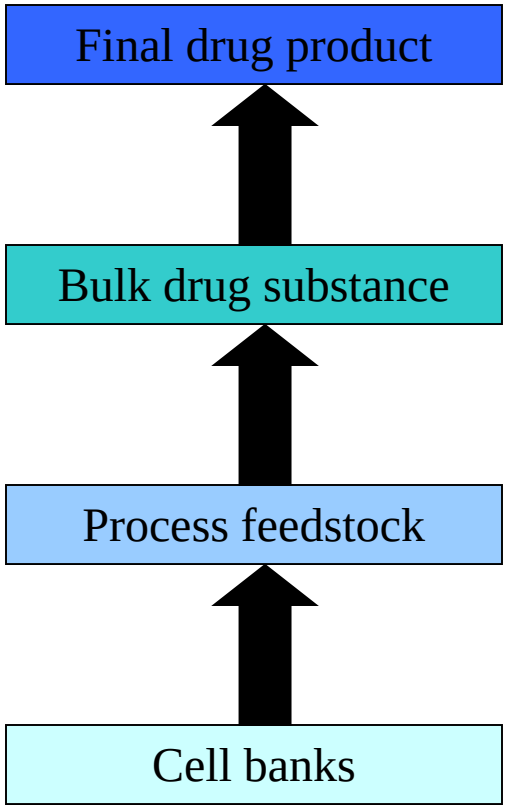
Diversity and risk management



Ready to administer, stockpile

Stability, formulate in response to demand

Storage of process intermediate or feedstream (example = transgenic milk)

Ease of storage, distribution, multiple repositories

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Model for stockpile

- Inventory of final drug product or bulk drug substance
- Location and strategy for inventory management
- Size of repository (risk)
- Local repositories to serve large urban areas
- Stability of final drug product or bulk drug substance determines replenishment rate / frequency

- Scenarios for inventory design and management
- Prioritisation of end-users ?
- First responders
- Vulnerable section of population
- Radius of response : Localised response

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- Portability of manufacturing processes
- Requirement for efficient, cost-effective manufacturing process
- Rational design of biopharmaceutical manufacturing processes
- Cost of goods (COG) considerations
- Stability of bulk drug substance or final drug product

Portability : “Ease of transfer of a manufacturing process to a new site”

Key factors to address :

- Site limitations
- Scale of operations
- Equipment limitations
- Fill/finish, logistics
- Process intensification

- 100L-1000L scale of operations is portable, matches current projected requirements for TED, localised response for civilian use and maintenance of biodefense stockpiles.

- Scale of operations (Microbial expression systems) / Available capacity

Scale of operations	Available capacity	Notes
100L	High	CMO Biopharma companies All regions (US)
1000L	Medium	CMO (East/West coast) Biopharma companies
10 000L	Low	1 x CMO (West coast)

- Process intensification to enable exploitation of low volume assets

- Scale of operations (Transgenic milk expression system)
  1 x CMO with experience of large scale processing

Good design practices

- Design for GMP / Compliance as key driver
- Defined raw materials and procurement plan
- Balance between conventional (established) technologies and innovation
- Maximise volumetric productivity
- Minimum # unit operations
- Minimise cycle time
- Seamless transition between unit operations
- Good understanding of selectivity, capacity and robustness
- Process intensification to minimise COG elements

(Real) Examples from process development

Technologies to avoid	Substitute technologies
Filter press	Centrifugation, depth filtration
Precipitation unit operations	(Selectivity)
HPLC	Low/medium pressure chromatographic techniques
Unit operations requiring large volumes of organic solvents	Aqueous chemistries, water soluble modifiers
Refold	Soluble expression
Affinity chromatography	(Resin screening) Orthogonal chromatographic chemistries
Multiple UF/DF unit operations for buffer exchange/conditioning	(Rational design) Seamless integration of unit operations

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$$\textbf{Cost of goods (COG)} = \frac{\textbf{\$ operational}}{\textbf{Yield (mass)}} = \textbf{\$/g}$$

Operational cost elements :

- Duration of process (cycle time, # unit operations, technology)
- Labor
- Raw materials
- Facility overhead

Yield elements

- Productivity
- Unit operation yield
- Compound yield

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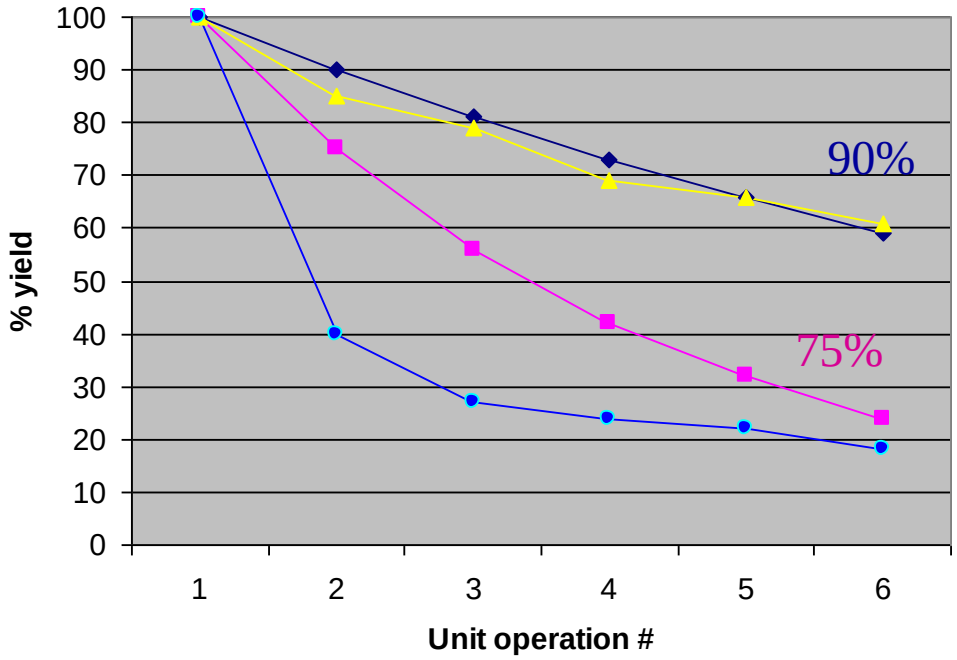
Process design : Mass balance sheet



Expression = Product formation

Purification = Product loss

Yield ~ # unit operations

Yield ~ Unit operation efficiency

Impact of technology on expression :

Molecular biology = 10 fold

Fermentation development = 3-5 fold

Concepts : Volumetric productivity, specific productivity

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- COG bulk drug substance (biopharmaceutical) ~ $100-1000/g
- Traditional vaccines require relatively high sales volume
- Biodefense vaccines considered high risk by established large pharma

Why COG is important in biodefense manufacturing processes

• Establish and maintain stockpile of products that may never be used

• Focus of threat may change

• If stockpile replenishment rate is low due to high stability ~ low annual demand ?

• Stockpile may be subject to global political change and priorities

• Rational design of GMP manufacturing processes for the production of vaccines and therapeutic proteins

• Case study : *RiVax*

Complete development of a manufacturing process for production of bulk drug substance (antigen)

- Dor Biopharma awarded grant from NIH
- Design of integrated vaccine development program
- Assembly of specialist teams at multiple sites
- Cambrex Biopharma to provide process development and GMP manufacturing

<u>Challenges</u>

Management of multiple teams

Management of diverse disciplines

Multiple locations

Fast-track timeline

Sustained progress to report to grant awarding body

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Background

- Initial process developed in academic laboratory
- *Escherichia coli* expression system
- Low productivity and yield
- Unsuitable for GMP production

Scope of work

Molecular biology

Fermentation development

Purification development

Formulation

Requirements

- Product quality attributes (purity, antigenicity, HCP, DNA)
- Product stability
- COG

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RiVax : Molecular biology

Academic process

pET plasmid

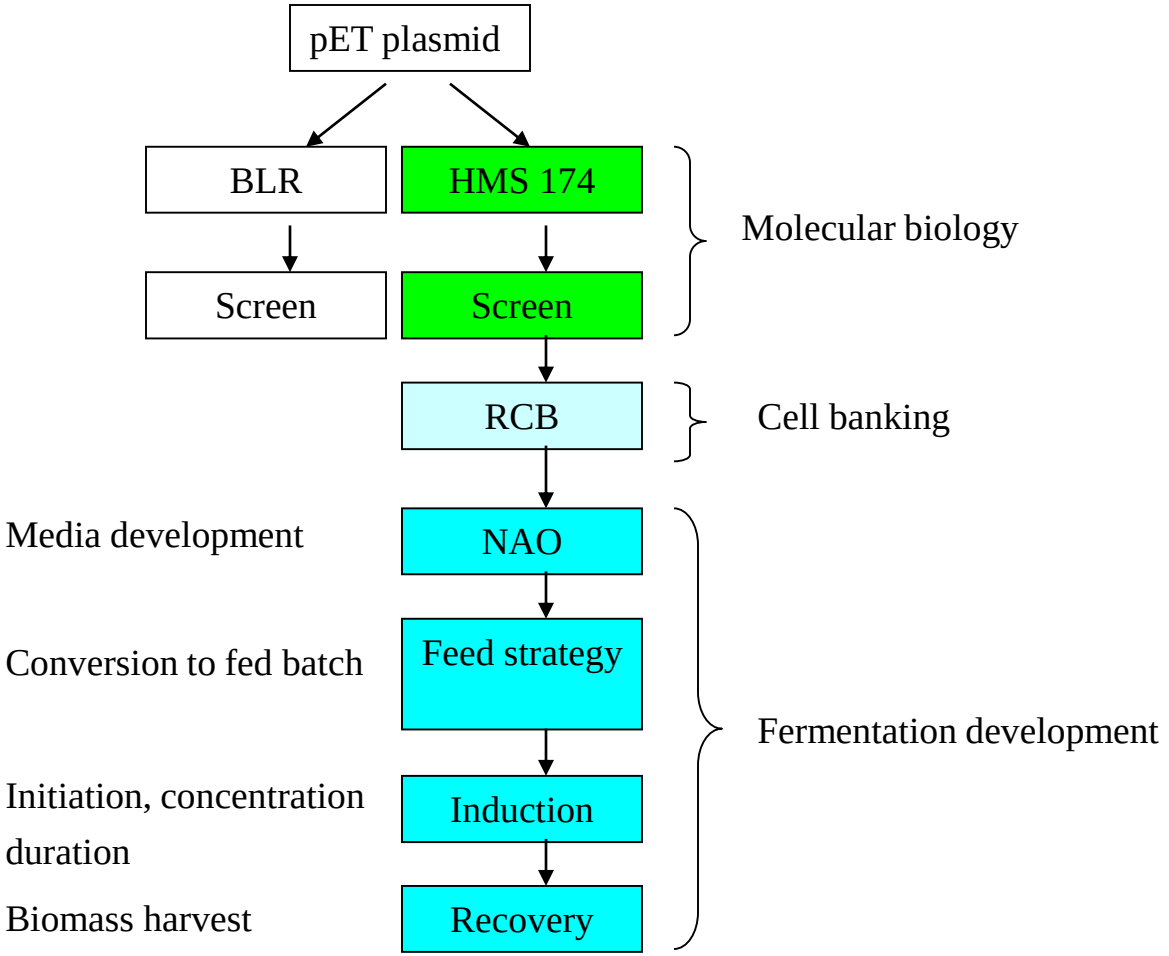
↓

BL21(DE3)

↓

Not suitable for GMP production

New scope of work



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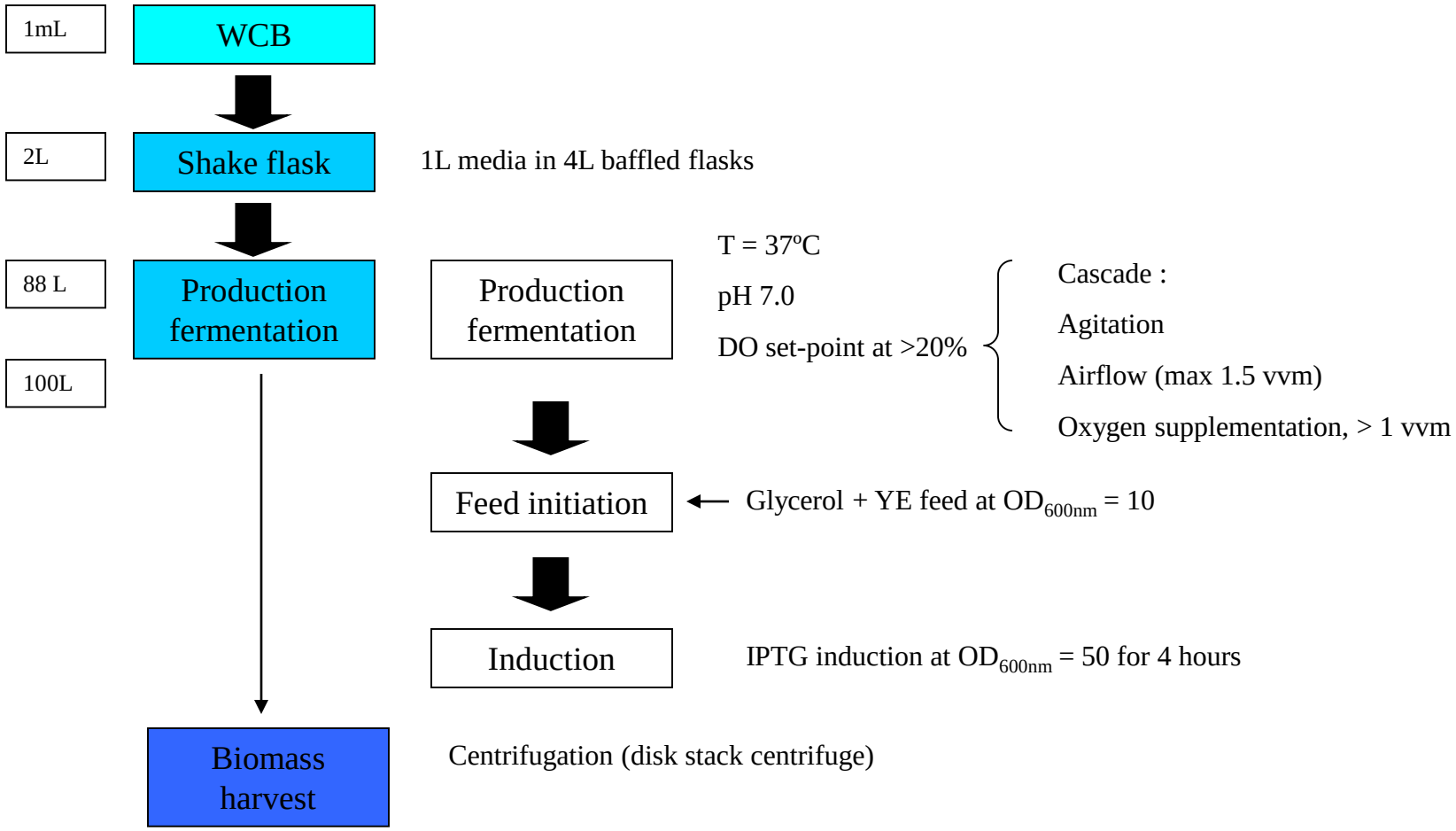
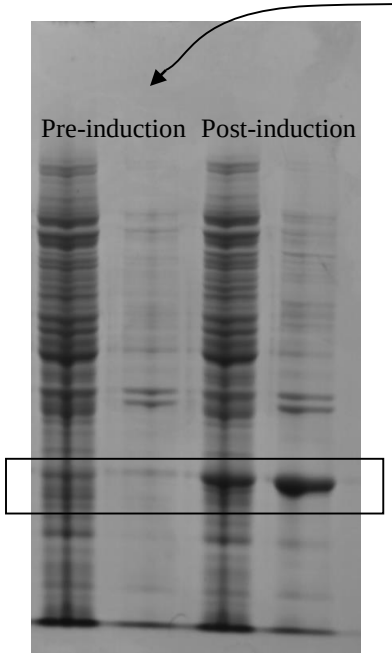
RiVax : Fermentation development



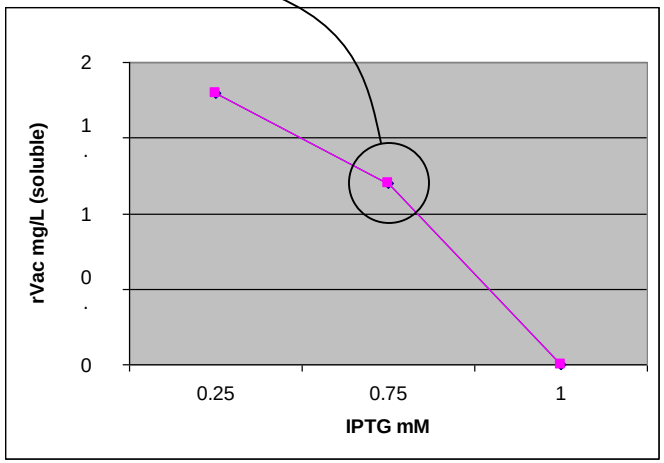
Fermentation : Localization of expression

- Localization of expression
- IB as convenient process hold and inventory stockpile
- Soluble expression to circumvent refold, minimize # unit operations
- Strategies for directing product localization

[IPTG] : Solubility and expression level / Bias to soluble intracellular expression



RiVax



S = Soluble fraction

I = Insoluble fraction

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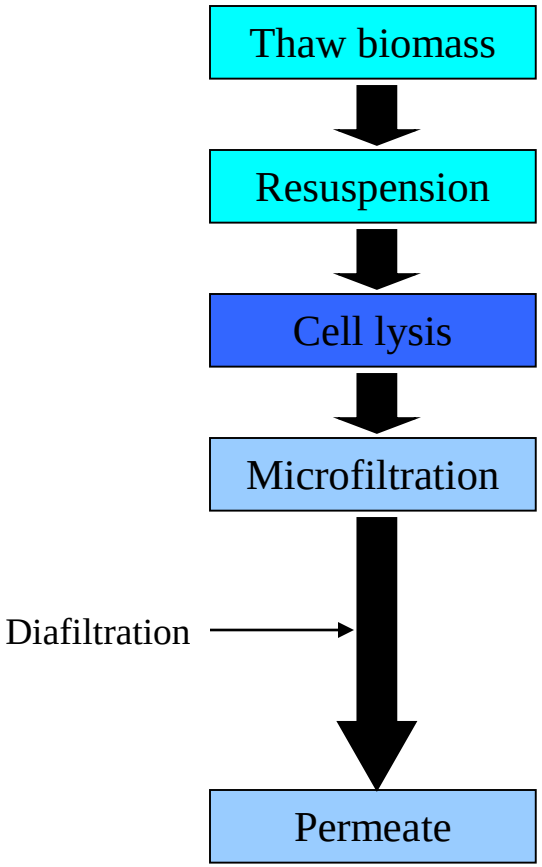
RiVax : Recovery



	Conditions	Function
Thaw biomass	2-8ºC for 48-60 hours	
Resuspension	25mM sodium phosphate pH 6.5	Lysis buffer
Cell lysis	10 000 psig , T < 20ºC	Release of intracellular soluble product
Microfiltration	0.2µm Hollow fiber	Clarification : Removal of particulate material
Diafiltration	25mM sodium phosphate pH 6.5, 3-4 DV	Increased efficiency of *RiVax* recovery
Permeate		

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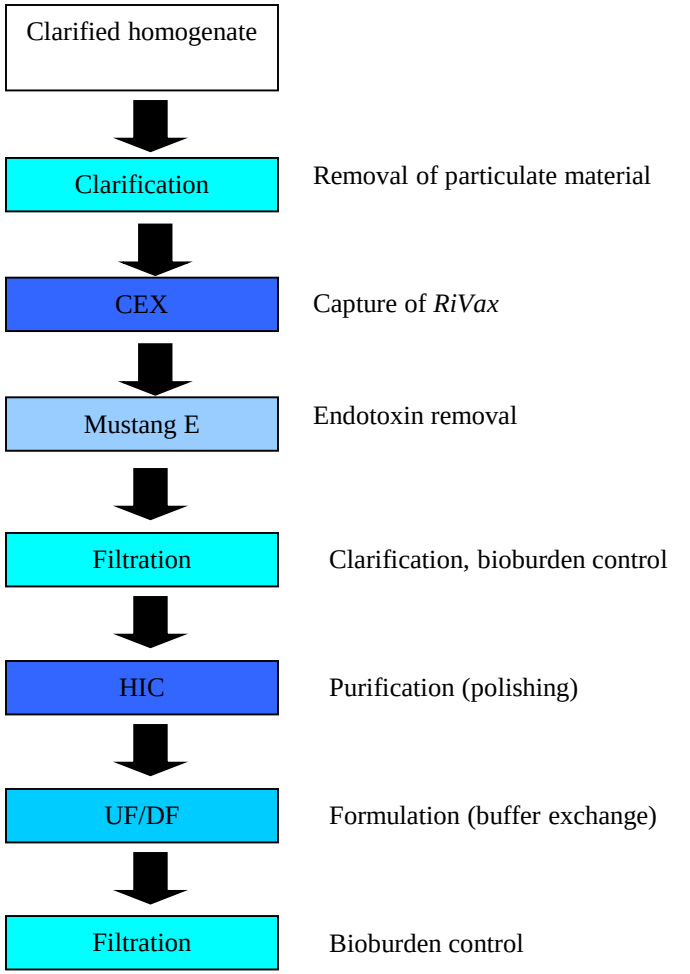
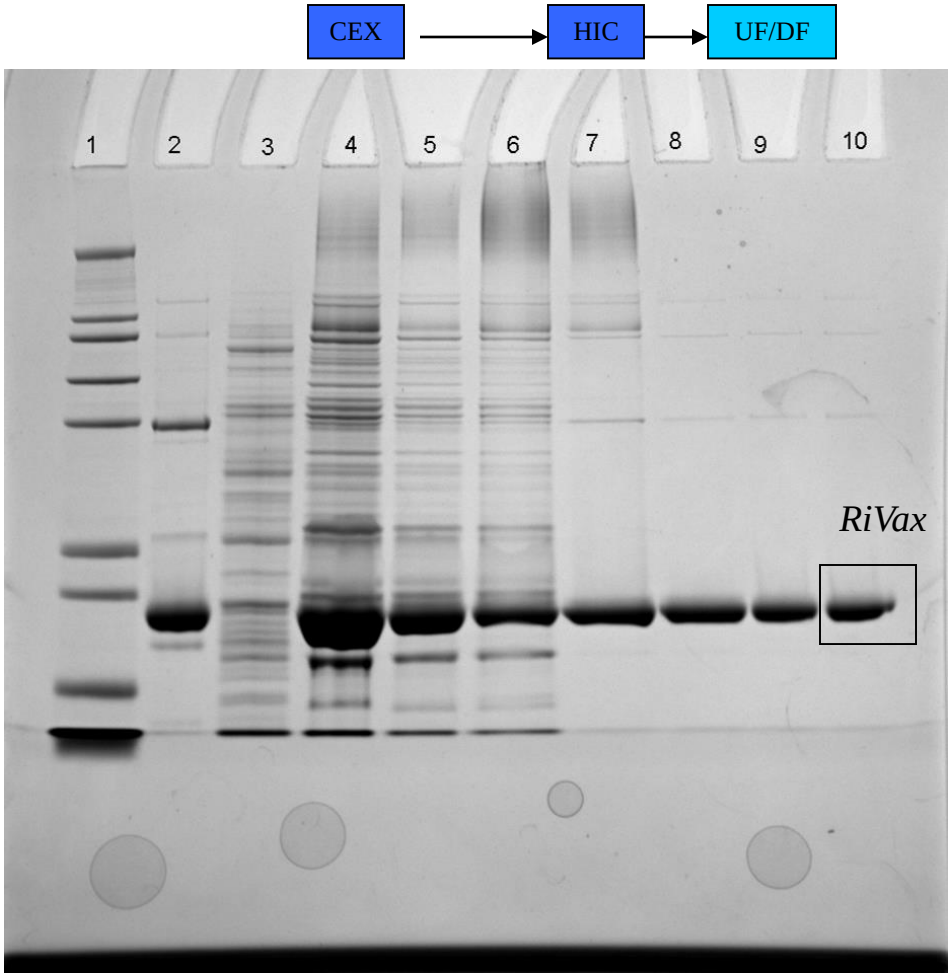
RiVax : Purification





RiVax manufacturing process : Summary of productivity, yield and cost effectiveness

Expression = 1.5 -2.0 g/L in fermentation
Compound yield = 50-60% in extraction – purification
CEX = >90%
Mustang E = 100%
HIC = 50-60%
UF/DF = 100%

Quality attributes
Purity = >95%
Endotoxin = <10 EU/mg
Residual DNA = <15 pg/mg

$ indicators (full analysis pending completion of clinical campaigns)
Cycle time (Fermentation – purification) = 7 days
Material requirements : Low
Longevity of multi-use components : Medium
Process risk : Low

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RiVax manufacturing process

- *E.coli* based expression
- 100L w/v scale of operations
- Simple fed-batch fermentation strategy
- Well defined and readily available fermentation media components
- Soluble expression
- Conventional biomass extraction and lysate clarification regime
- Purification comprises 3 unit operations that impact product mass balance and 4 unit operations essential to maintaining product quality attributes
- Conventional column chromatography media and membrane technologies
- Highly efficient capture chromatography unit operation
- Bulk drug substance/intermediate formulation for stability

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Conclusions

- Limited number of organisations are developing biodefense products (vaccines, therapeutics).
- Some products may never be deployed
- Cost of goods critical to product economics
- Rational design to maximise productivity and yield
- Portability of manufacturing processes desirable to offset risk
- Potential of diverse expression platforms for biodefense products

Acknowledgements

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Cambrex Corporation

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