BIA Separations

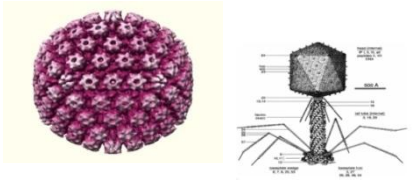
Enabling New Generation Biotherapeutics

April 2013

BIA separations

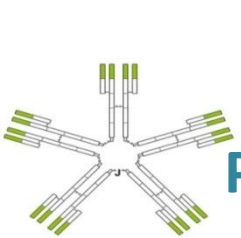
Biotechnology era

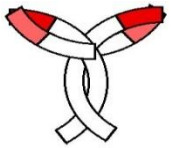
- Traditional drugs – small molecules
- Novel drugs – large, complex biomolecules



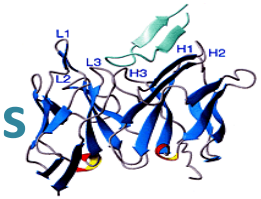
Viruses

DNA





Proteins



- Problem - purification of the substance out of the soup in the bioreactor.
- BIA has a breakthrough technology improving productivity of the biotechnological purification by an order of magnitude

BIA Separations

The business

- ***Sale of consumable CIM® products*** *based on its proprietary CIM® monolith technology to purify large biomolecules such as proteins, plasmid DNA, complex proteins (e.g. IgM), phages, viruses and viral vectors.*
- *Target market with a decisive competitive advantage is* ***about $1.2 billion*** *of the overall $2.4 billions purification/separations business growing at >15%/year.*
- *BIA at present supply CIM® products to* ***about 500 customers worldwide*** *that have about 300 projects in preclinical stage and about 50 projects in clinical phase I-III trials using CIM®.*

The company

History

- *Incorporated in September 1998 in Ljubljana, 1st financing* round *financed by Horizonte Fund*
- *2nd financing round in 2003 by Alpe Adria Venture Fund and Dr. Uwe Burkheiser*
- *3rd financing round in 2007 by "schilling" Unternehmensbeteiligung GmbH & Co V12 KG and some smaller investors*
- *In 2007 move of headquartes to Austria, BIA Separations USA established, in Feb 2011 BIA Separations China established*
- *At present 85 employees worldwide*
- *Moved to the new dedicated facility in October 2011*
- *4th financing round in 2011/2012 in amount of 10 M EUR by* ***JSR and SDK***

Strategic partnership with JSR

- JSR Corporation is **a 4 billion USD multinational company with HQ in Japan** employing over 5000 people worldwide.
- JSR is a research-oriented organization that pursues close collaborations with leading innovators in a number of industries that are a key to the present and future welfare of human society including life-sciences.
- Partnership includes:
  - joint global marketing and sales efforts
  - **collaborative R&D activities in the area of downstream purification**
- Combining BIA Separations technology with **JSR's proprietary Protein A media**, we offer the bio pharmaceutical industry a faster, more reliable downstream purification processes at a lower cost of ownership.

Strategic partnership with SDK

- Since its foundation in 1926 Showa Denko K.K. (SDK) has been contributing to the development of the chemical industry in Japan. The Group diversified into various fields, such as inorganic chemistry, organic chemistry and metallic materials providing a wide range of useful products and services that support a modern life-style, including materials and components for the electronics and automobile industries.
- Corporation is **a 9 billion USD multinational company** employing over 11.000 people worldwide.
- SDK decided to enter the purification resin market through the strategic partnership with BIA Separations, expecting to achieve good synergistic effect in terms of both technology and product mix.
- Partnership with BIA Separations includes:
  - joint global marketing and sales efforts
  - **collaborative R&D activities in the area of downstream purification**

Important milestones

- 2002: First Drug Master File (DMF) for CIM® DEAE supports.
- 2002: Pass first FDA audit for one of the projects.
- 2004: First monolith used for the industrial cGMP purification for plasmid DNA at Boehringer Ingelheim provide 15-fold increase in productivity - the 2004 Frost & Sullivan Technology Leadership Award.
- 2006: Drug Master File (DMF) for CIM® QA supports.
- 2006: First cGMP production of a vaccine (influenza) using CIM®.
- 2008: **OEM Partnership with Agilent Technologies** – develop and produce analytical monolithic columns
- 2009: Pass second FDA audit.
- 2010: Drug Master File (DMF) for CIM® SO3 supports.
- 2001 - 2012: Pass many audits by Novartis, Boehringer Ingelheim, ...

The opportunity

Rapid growth of biologics

2007

Sales of biologics $ 455 B,

40% of all new drug candidates are large molecules

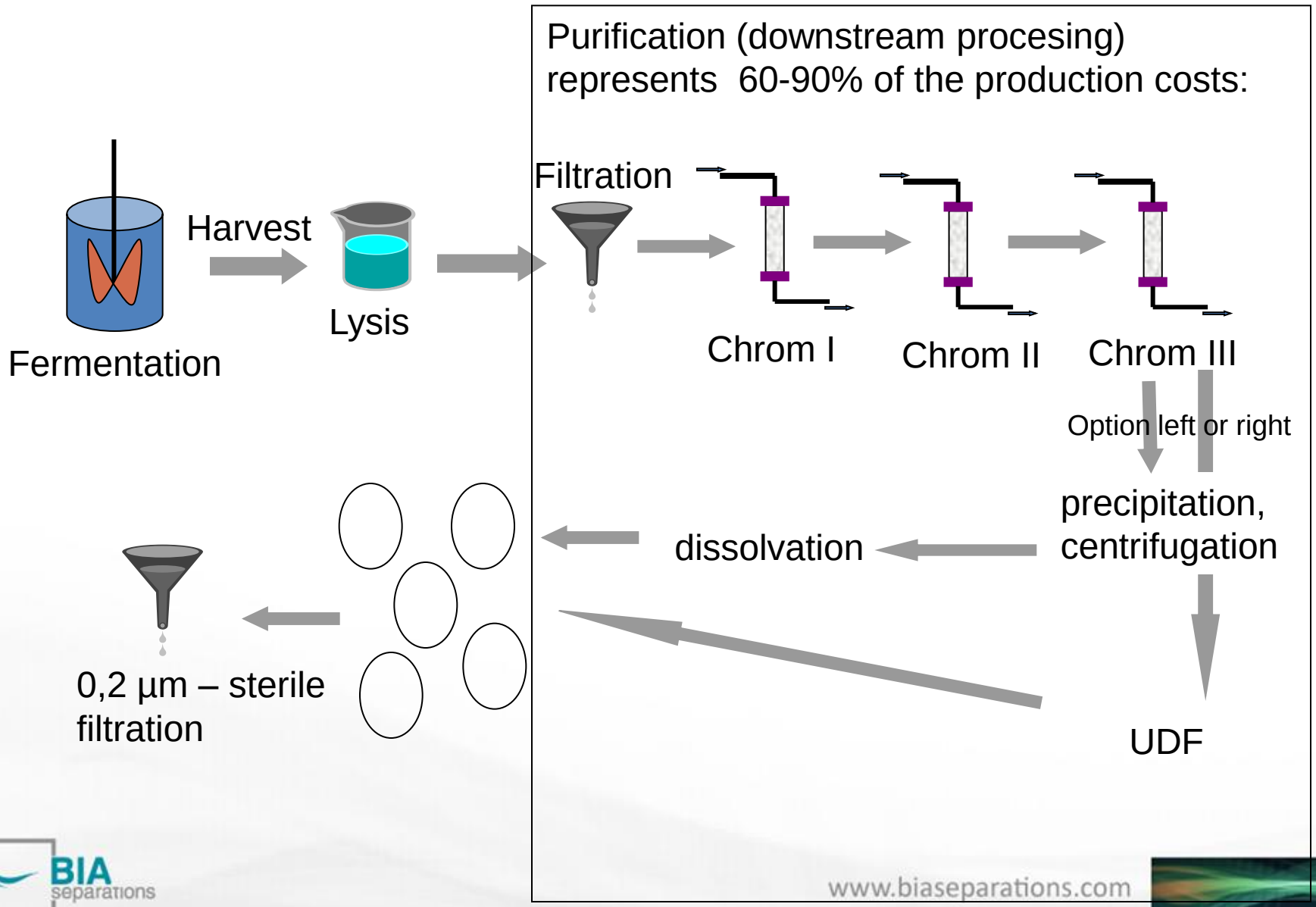
2020

Sales of biologics $ 1,000 B

By 2010

Vaccines, DNA and large proteins will dominate - face major issues in appropriate industrial scale purification

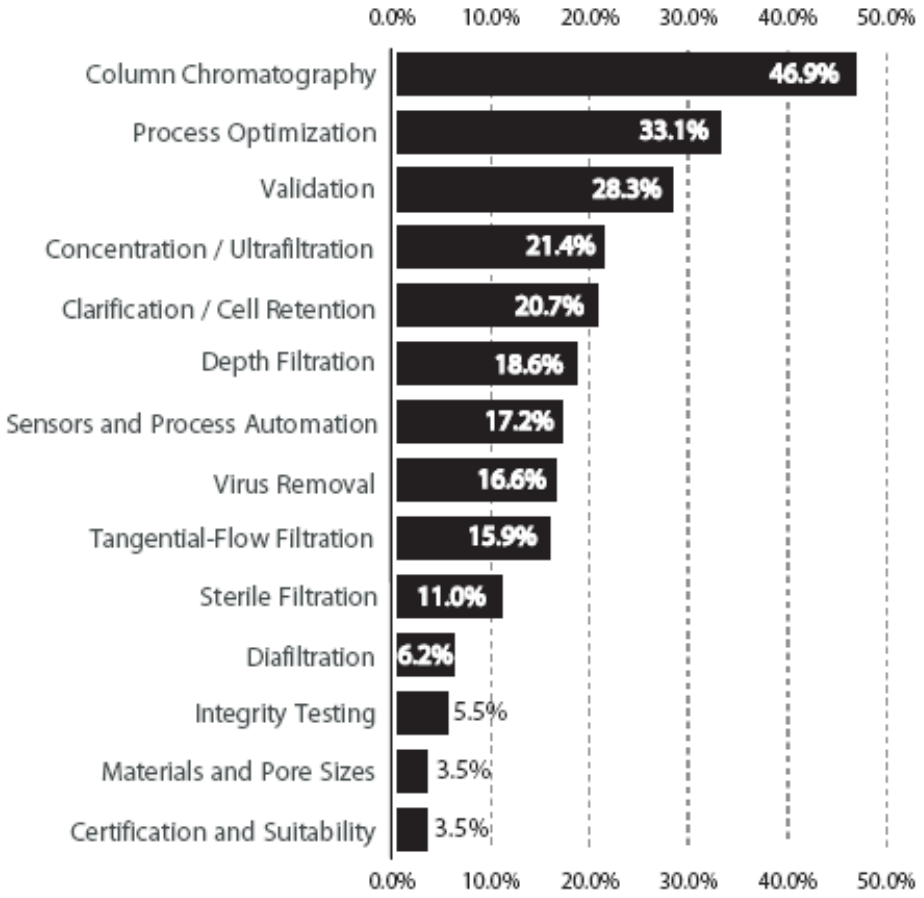
Biomolecule production chart



Crucial bottleneck

"If this Industry is to avoid significant capacity constraints, the most important areas to be addressed are."

"Which downstream operations do you believe will cause your facility significant problems in 2008?"



"Report and Survey of Biopharmaceutical Manufacturing Capacity and Production" published by BioPlan Associates, Inc, 2008

Many novel drug targets are large and complex, and in some cases used live

- These include different viral particles, pDNA, protein complex, IgM.

- ”Whilst highly effective for the purification of proteins and smaller molecules, chromatographic techniques are not necessarily well suited to purification of these newer, larger targets.“ (N. Willoughby, J Chem Tech & Biotech, 84, 2008, 145).

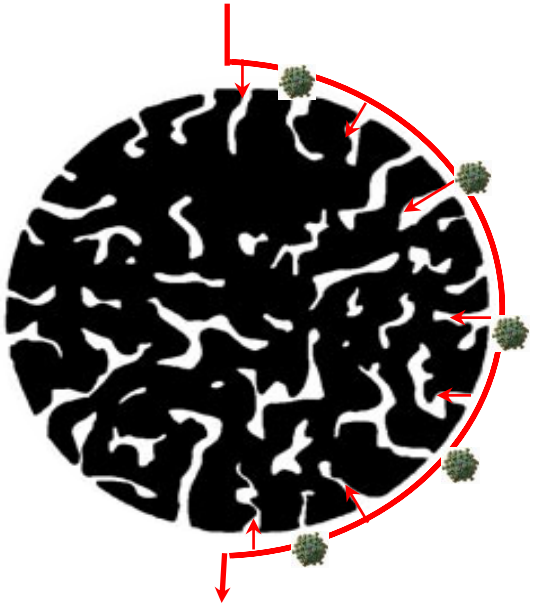
The solution

Monoliths

- *to Pete Gagnon, a member of GEN's editorial advisory board on process chromatography, are "Seen to Revitalize Bioseparations"*
- *"the first original breakthrough to have occurred in this area since Twsett invented chromatography a century ago" by G. Guiochon, Prof. at University of Tennessee*
- *BIA Separations technology is already "getting centre stage as the newest invention" by R. Majors, editor of LC-GC, Business development manager at Agilent Technologies*

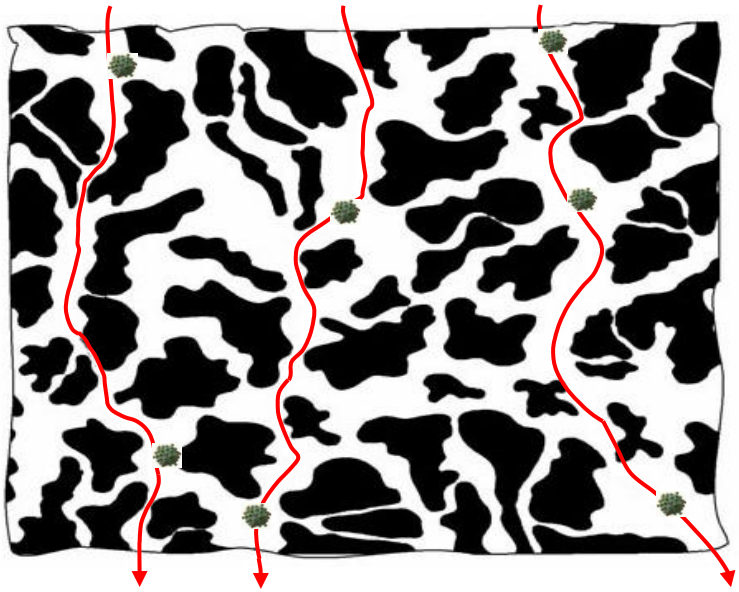
BIA Separations is positioned to become the lead company in complex biomolecule purification.

Sum up: CIM® Monolithic Columns are purpose designed for the chromatography of big biomolecules



Traditional approach - Porous particle:

1. Diffusive mass transport – slow process or **lower resolution**
2. Pores too small – very **low capacity**
3. Countercurrent flow - shear forces – **lower yields**

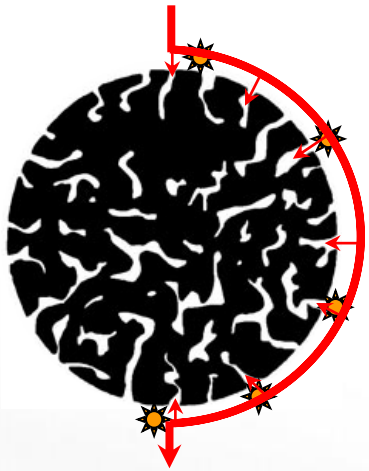


Novel approach – CIM monoliths:

1. Convective mass transport – **flow independent resolution and capacity,** very fast process
2. Big channels – **high capacity**
3. Laminar flow - No shear forces – **better yields**

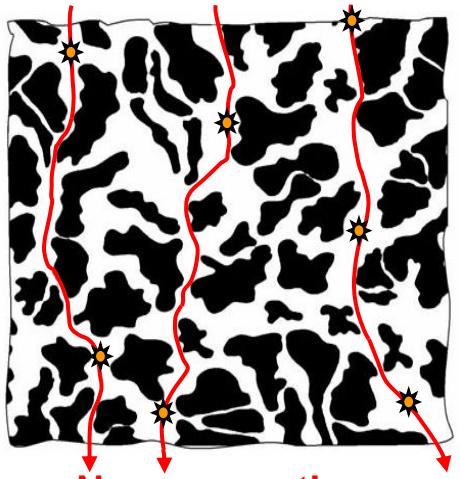
CIM® monolith competitive advantages

- Boost productivity
- Cost efficiency
- Enable purification of very big unstable products



Traditional approach - Porous particle

Filter technology approach - Membrane absorbers

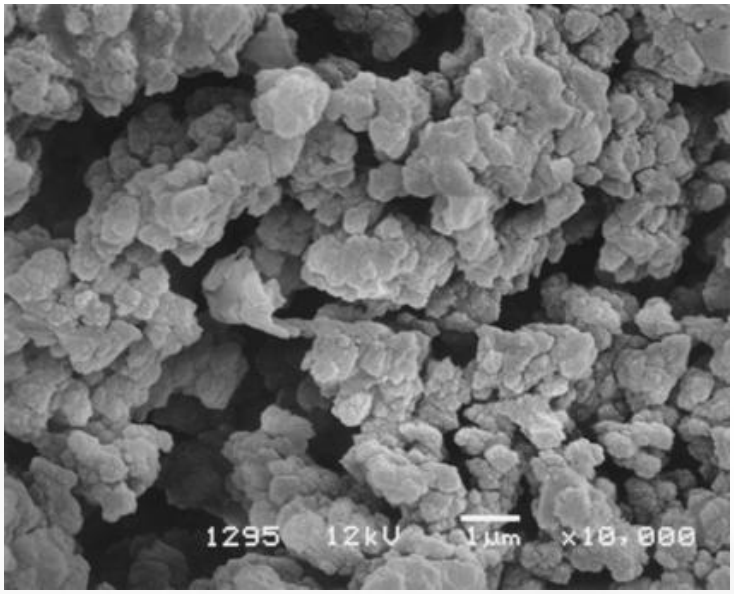


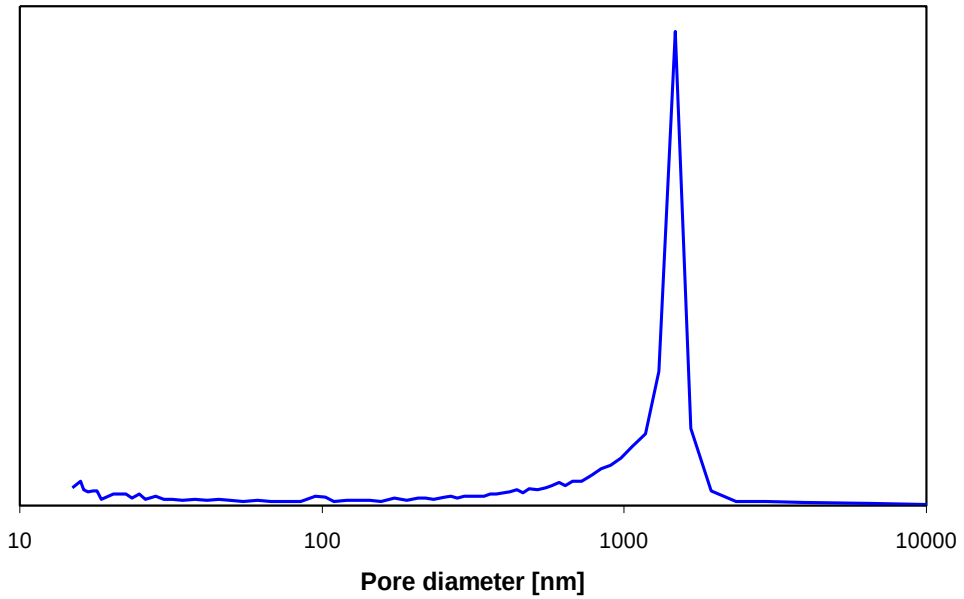
New generation – CIM® Monoliths – BIA's proprietary technology

CIM® Monoliths - Properties

CIM® monolithic supports are highly porous rigid polymers with:

- High porosity (over 60 %)
- Flow-through channels ("pores") having large diameter (1.5 µm), for Vaccinia special monolith (3-4 µm)
- Biocompatible with uniform channel connectivity in 3D (homogeneous structure)
- Ligands (active groups) for **AEX, CEX, HIC, RPC, Affinity, Activated, Bioreactor.**





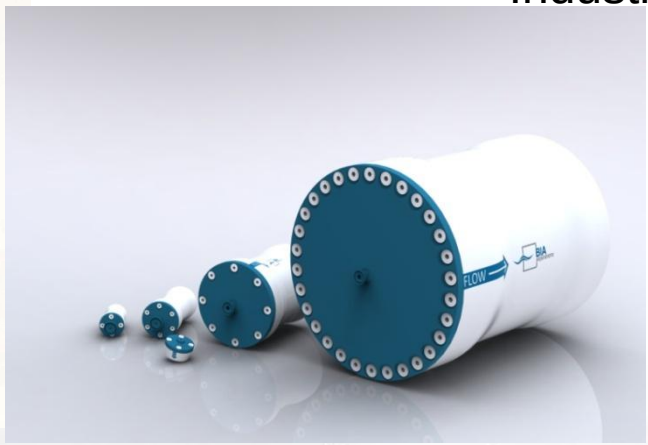
CIM® technology: Consumable Products

The company has achieved full industrial scale-up and for very large molecules today covers the whole range from laboratory to industrial scale.

0.34 ml disk → *8 ml tube* → *80 ml tube* → *800 ml tube* → *8.000 ml tube*

Lab scale

Industrial scale



Disposable and Continuous Liquid Chromatography Systems Fit to "Single use" Vaccine Production Facility

Courtesy of Xcellerex

IPR position

BIA Sep has implemented a comprehensive patent strategy to protect the monolith platform technology in all major markets

4 US patents and > 50 their foreign equivalents granted, more pending:

- *CIM® technology and manufacturing*
- *Different geometries including scale-up*

Certifications & Approvals

The operations of BIA Separations have been certified and audited by

- *ISO 9001: 2000*
- *FDA*
- *Partners (Novartis, Boehringer Ingelheim, Octapharma,..)*

DMF for DEAE, QA and SO3 CIM® monoliths have been filed

Status of company development

Over the past years BIA Separations has achieved

- *Development of CIM® technology*
- *Industrial scale-up*
- *Comprehensive IPR position, certifications*
- *Key industrial reference customers*

NOW: Broad international roll-out

Company business strategy

CIM® – broad technology platform and product range

4 strategic business units (SBU's)

SBU 1: Virus & DNA kits – OEM partners

SBU 2: Analytical CIM® columns – own sales network/OEM

SBU 3: Preparative CIM® columns for viruses, DNA & larger proteins – establish own sales network

SBU 4: Contract services - own sales network

SBU 1: Virus & DNA kits –

OEM partners

Only in development

SBU 1: Kit business

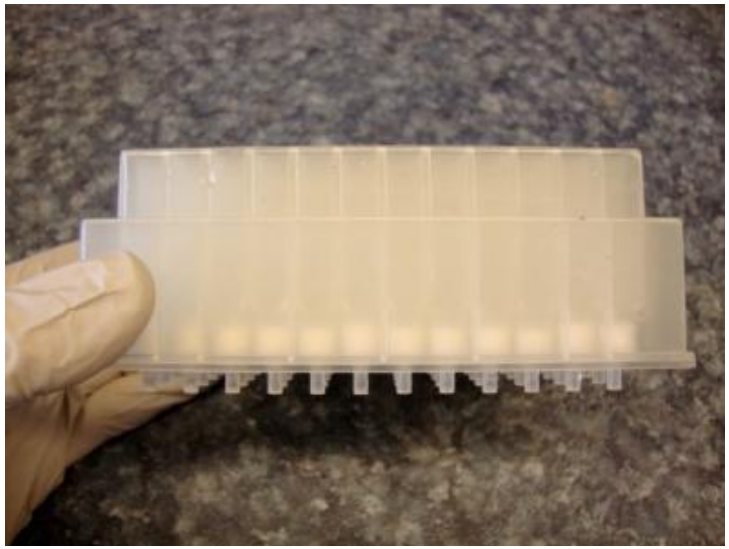
- Research in progress

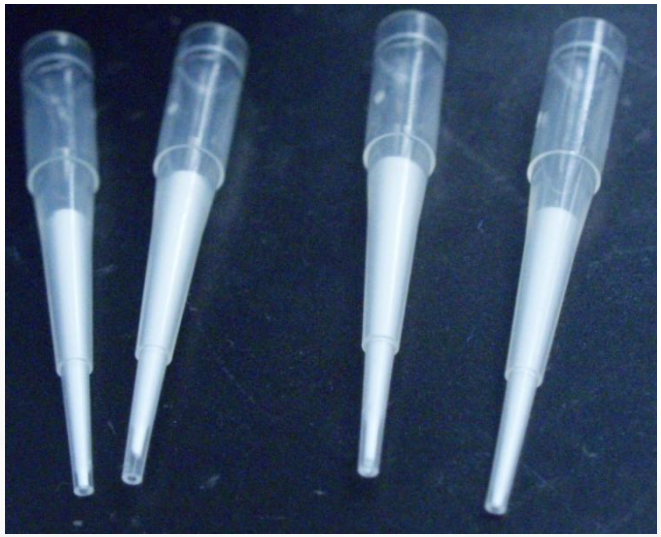
- Searching for OEM partners

- Development activities will start when additional investment is secured

- Will be set-up in Austria

Kits in development



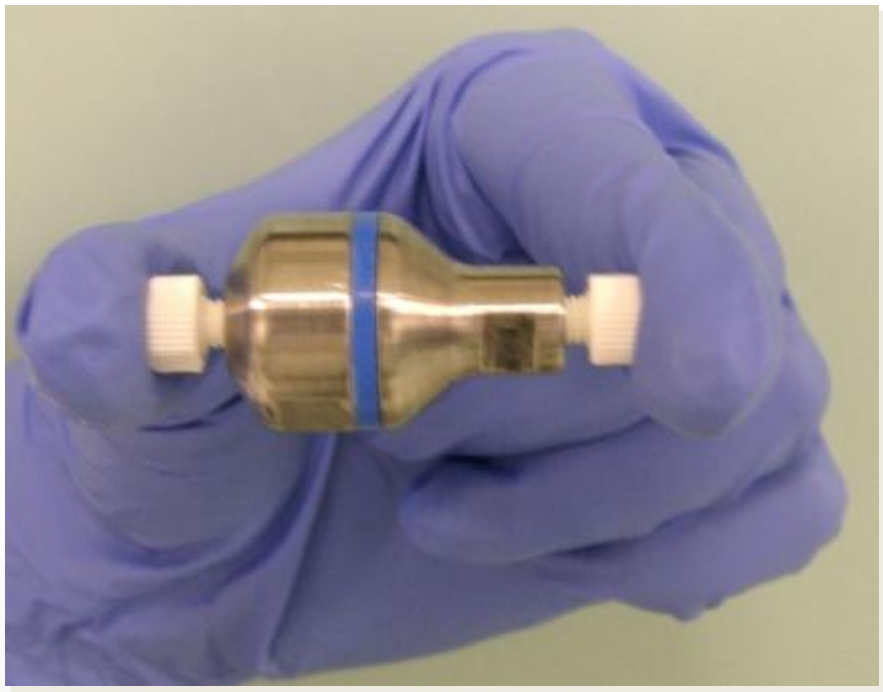


SBU 2: Analytical CIM® columns –

own sales network/OEM

OEM with Agilent in-place

OEM with Agilent Technologies



SBU 3: Preparative CIM® columns for viruses, DNA & larger proteins –

establish own sales network,

partnership with JSR and SDK

Example 1: Gene Therapy

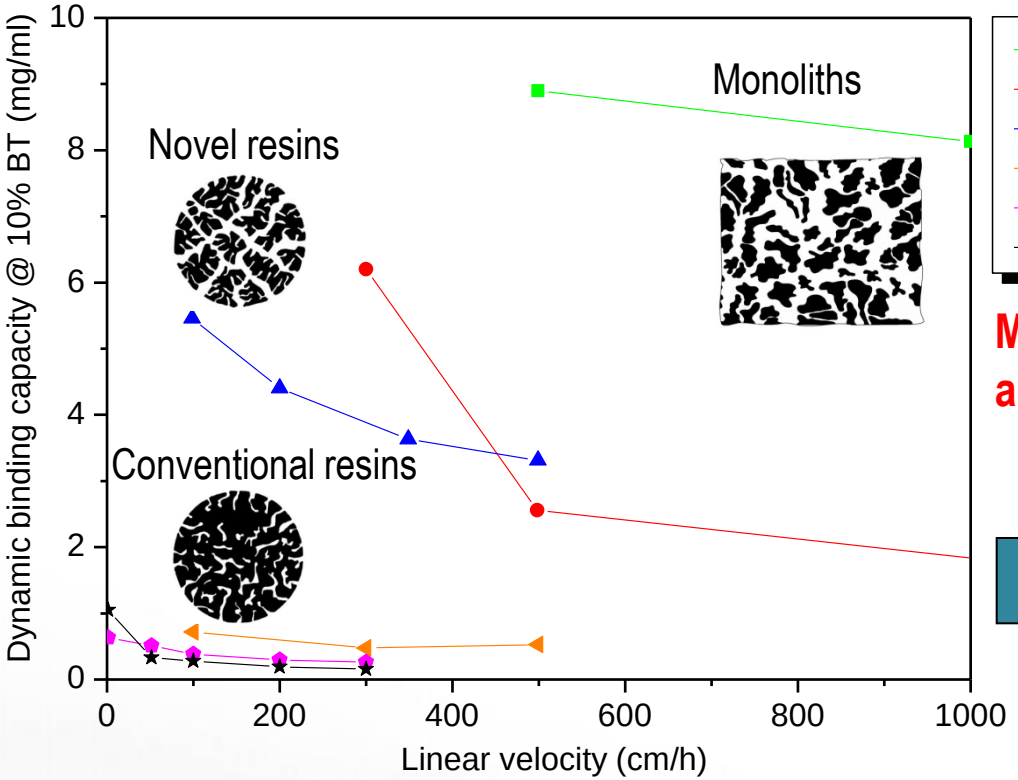
- Boehringer Ingelheim (BI) is a leading contract manufacturer of plasmid DNA for gene therapy use
- BI and BIA Sep jointly developed a novel CIM® based cGMP production process for plasmid DNA
- 15 fold increase in productivity
- 2004 Frost&Sullivan Technology Leadership Award

2004 FROST & SULLIVAN Technology Leadership Award

Boehringer Ingelheim

Partnership with Boehringer Ingelheim

Plasmid DNA purification



- CIM® DEAE
- Q Ceramic Hyper D 20
- Fractogel EMD DEAE (S)
- Source 30 Q
- Toyopearl DEAE 650-M
- DEAE Sepharose

Membranes do not provide resolution and were therefore not further tested!

Currently used for CP III trials

15-fold increase in productivity

- High binding capacity at relevant flow rates
- High elution concentration - pDNA eluted in lower volume (important for SEC!)
- Fast process (no product loss due to oxidative degradation or enzymatic attack)

Economic benifits for the customer

Plasmid DNA purification

1 ml CIM monolith – BIA Sep

Calculations		
Buffer	76,3	ml buffer/mg pDNA
Time	23,6	min/mg pDNA
Recovery	85%	
Purity	cGMP grade	

Costs using columns for 1 Run		
Quantity of purified pDNA	5,10	mg pDNA
€ (Column costs)	114	€/mg pDNA
€ (column+buffer)	114	€/mg pDNA
€(column+buffer+work)	123	€/mg pDNA

Costs using columns for 10 Runs		
Quantity of purified pDNA	51	mg pDNA
€ (Column costs)	11,4	€/mg pDNA
€ (column+buffer)	11,8	€/mg pDNA
€(column+buffer+work)	21,1	€/mg pDNA

Costs using columns for 20 Runs*		
Quantity of purified pDNA	102	mg pDNA
€ (Column costs)	5,7	€/mg pDNA
€ (column+buffer)	6,1	€/mg pDNA
€(column+buffer+work)	15,4	€/mg pDNA

Particle based - GEH

Calculations		
Buffer	108,0	ml buffer/mg pDNA
Time	70,0	min/mg pDNA
Recovery	79%	
Purity	cGMP grade	

Costs using columns for 1 Run		
Quantity of purified pDNA	4	mg pDNA
€ (Column costs)	227	€/mg pDNA
€ (column+buffer)	228	€/mg pDNA
€(column+buffer+work)	257	€/mg pDNA

Costs using columns for 10 Runs		
Quantity of purified pDNA	40	mg pDNA
€ (Column costs)	23	€/mg pDNA
€ (column+buffer)	24	€/mg pDNA
€(column+buffer+work)	53	€/mg pDNA

Costs using columns for 20 Runs		
Quantity of purified pDNA	79	mg pDNA
€ (Column costs)	11	€/mg pDNA
€ (column+buffer)	12	€/mg pDNA
€(column+buffer+work)	42	€/mg pDNA

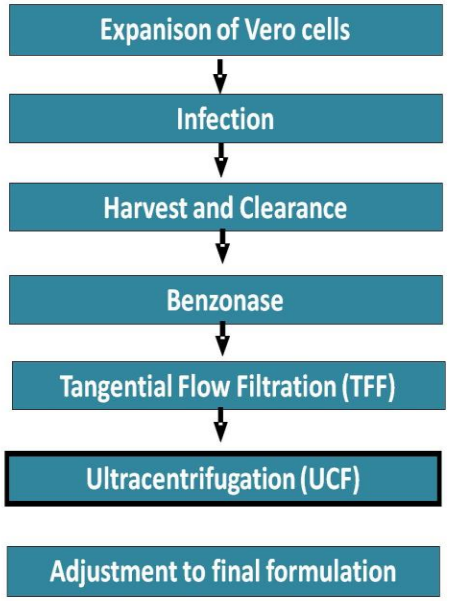
Example 2: Avian Flu Vaccine

European consortium to develop Avian flu, Flu and SARS vaccines under lead of Avir GHB, Vienna:

- BIA Sep co-developed a proprietary production process
- Successful transfer to industrial contract manufacturer
- **BIA Sep to sell industrial columns for the process**

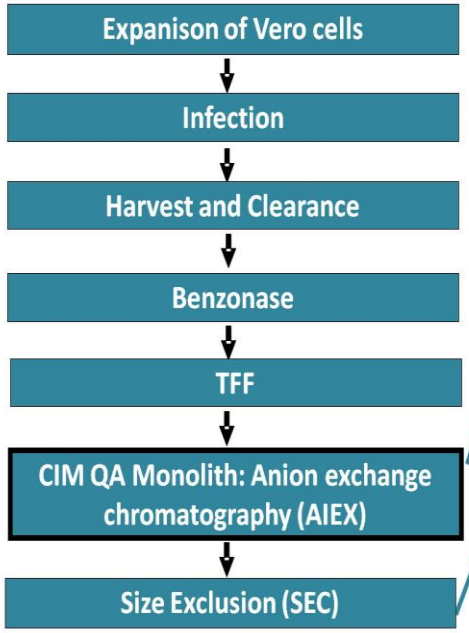
Economic benifits for the customer – to compare with centrifugation

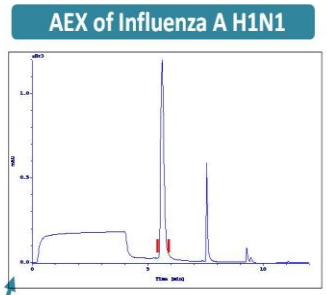
CENTRIFUGATION BASED PURIFICATION PLATFORM

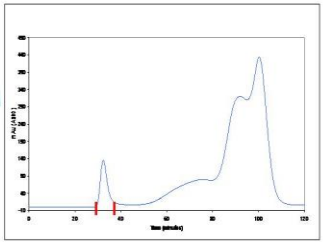


Infectious virus yield	11.4 %
DNA removal	99.50 %
Protein removal	97.4 %

MONOLITH BASED PURIFICATION PLATFORM







Infectious virus yield	47.3 %
DNA removal	99.96 %
Protein removal	97.8 %

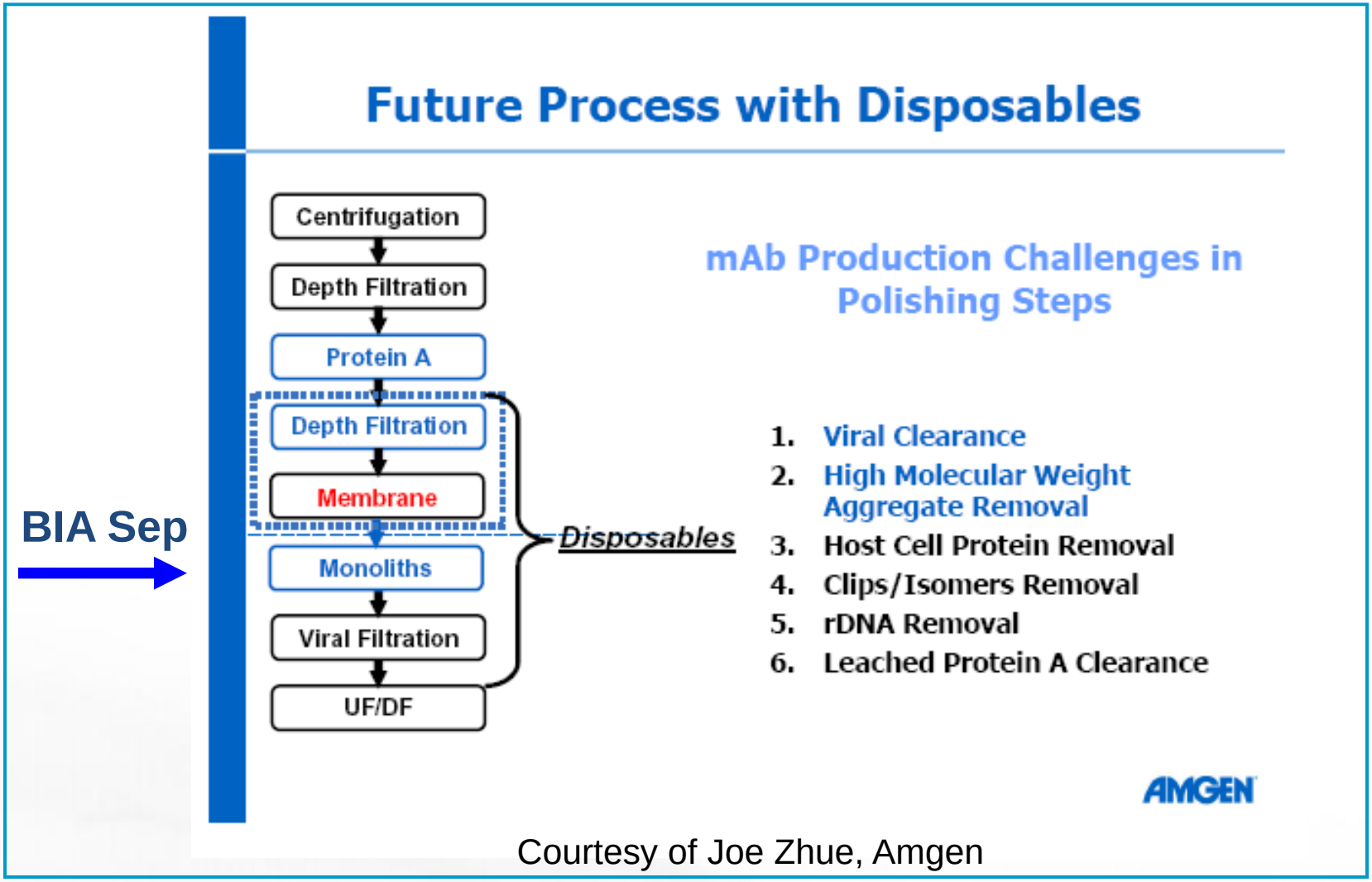
E. Roethl et al., GreenHillsBiotechnology, BioProcess International, Raleigh, NC, 2009

Economic benifits for the customer – to compare with conventional chromatogr.

Average values	CIM® QA	Mustang® Coin Q	Q Sepharose™ XL	Celufine Sulfate
Virus Recovery	54%	35%	35%	27%
DNA Depletion	96%	95%	95%	91%
Protein Depletion	95%	94%	98%	99%
Dynamic Binding Capacity	**10.3** $\log_{10}$ TCID50/mL Support	**10.3** $\log_{10}$ TCID50/mL Support	**9.0** $\log_{10}$ TCID50/mL Support	**8.4** $\log_{10}$ TCID50/mL Support

Maurer et al., Purification of Biological Products, Waltham, MA/USA, 2007

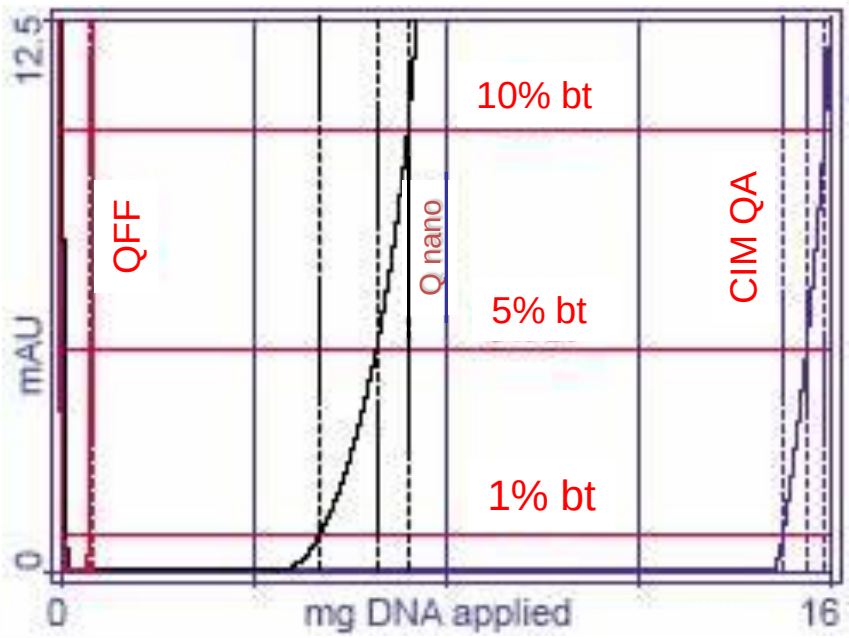
Example 3: Monoclonal antibody with JSR

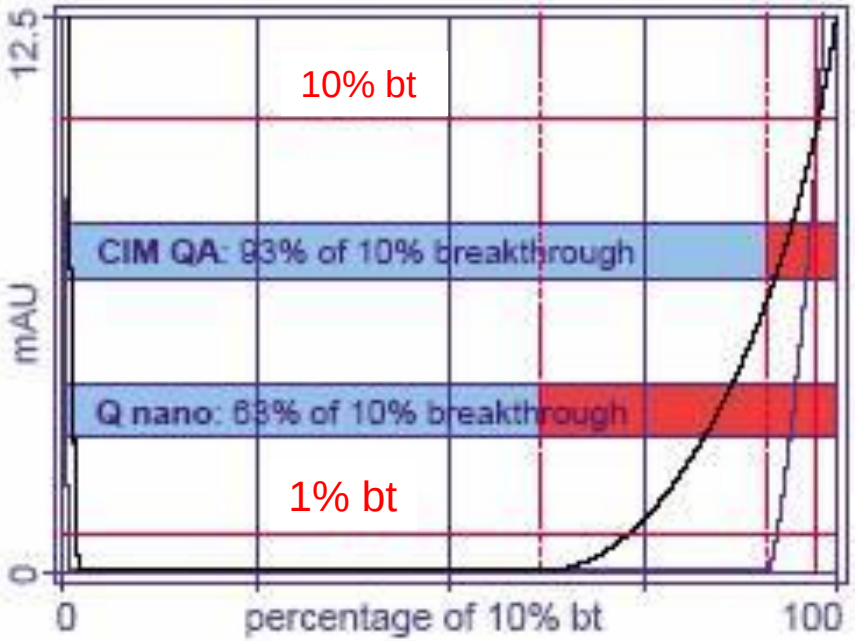


Courtesy of Joe Zhue, Amgen

Economic benifits using monoliths

DNA Removal





Membrane: earlier breakthrough, shallower slope

CIM® QA: later breakthrough, steeper slope

Lower Binding Capacity
4.8 mg/mL no-bt capacity = Membrane

Higher Binding Capacity
14.3 mg/mL no-bt capacity = CIM® QA

Important implications for manufacturing of therapeutic antibodies

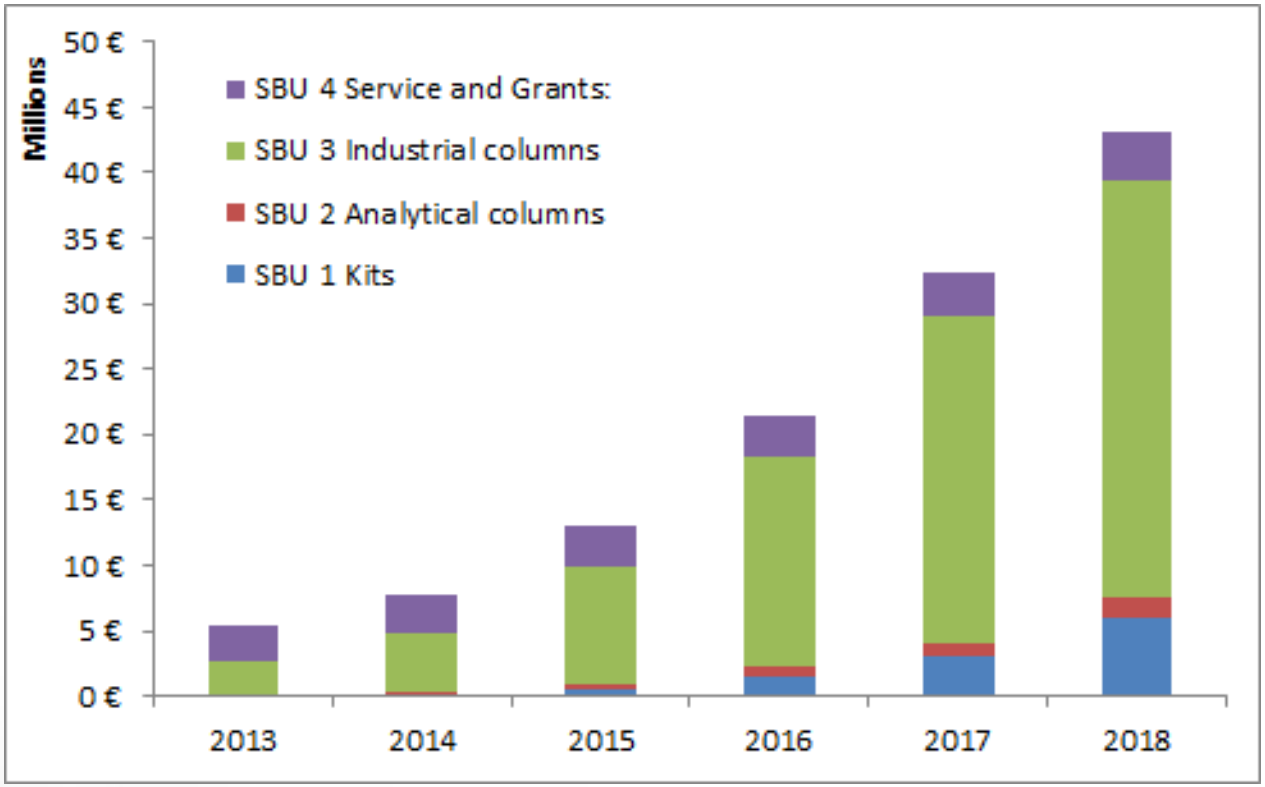
CIM® Becoming Industry Standard for Production of Complex Biomolecules

- Drug Master Files (DMF) for CIM® DEAE, QA and SO3 columns in place, HIC in preparation.
- First drug purified using CIM® monoliths passed CPIII trial (pDNA for gene therapy).
- More than 50 projects in CPI – CPIII trials (various Influenza, various Adenovirus, bacteriophages, various IgMs, Inter-alpha-inhibitors).
- More than 200 projects in pre-clinical trials (Influenza A and B virus (eggs, Vero and MDCK cells), Rabies virus, Rotavirus, AAV, various Adenovirus subtypes, Hepatitis A, Vaccinia, Mulv, MVM, Feline calicivirus, Japanese encephalitis, Crimean-Congo hemorrhagic fever, Hantaan virus, VLP (Hepatitis B, HPV, Influenza, Adenovirus), Ebola, bacteriophages (Lambda, T4, VDX10, Pseudomonas phage), Tomato and Pepino Mosaic virus, pDNA, IgM, various proteins).

Moved to a new, state of the art, 4,200 m² facility in Oct 2011 (12 M EUR investment)

Revenue forecast

by 2014 – start of the exponential growth



Different CIM® products represents about 85% of revenues.

RoI - long term profitability

Biopharmaceutical product is defined by the molecule and the production process (incl. purification) to produce that molecule.

Registration of the product usually for the lifetime of the patent protection.

Purification resins are locked in the process during this time; 15 – 20 years.

Management board

CEO and CBDO: *Ales Strancar, PhD, Assist.Prof. (50)*

COO: *Desa Piskernik, PhD (51)*

CFO: *Franz Krejs, PhD (70)*

CTO: *Milos Barut, PhD (45)*

Director R&D: *Nika Lendero-Kranjc, PhD, (32)*

Deputy BDO ands Vice president business development Asia: *Charles Lim, PhD (59), former GE Healthcare Biosciences Business Director*

Vice president business development NA: *Bill Kuhlman (52), former Bio-Rad Process Chromatography Division Manager*

Highly experienced management

Thank you!