Regulatory requirements for production of monoclonal antibodies

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Pharmaceutical Industry Financials*

- Worldwide pharmaceuticial market (2006) ~ $ 653 Billion

- Biopharmaceutical market (2006) ~ $93 Billion (~15%)

~ 2/3 of all biopharmaceuticals are produced using recombinant DNA technologies of which ~50% are monoclonal antibodies.

* Bioplan Associates 04/2008

Top Biotech Drug Revenues (2008)*

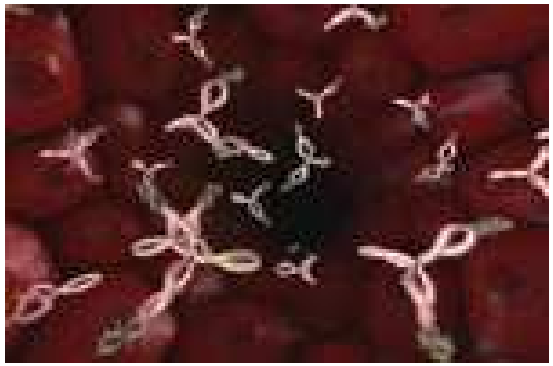
	Product	Revenue	Indication
1	***Enbrel***	$ 5.982B	Rheumatoid Arthritis, Psoriatic Arthritis
2	***Rituxan***	$ 5.082B	Non-Hodgkin's lymphoma, Rheumatoid Arthritis
3	***Humira***	$ 4.521B	Rheumatoid Arthritis, Psoriatic Arthritis
4	***Avastin***	$ 4.479B	Colorectal Cancer, Non-small-cell lung Cancer
5	***Herceptin***	$ 4.394B	Breast cancer
6	***Remicade***	$ 3.748B	Crohns Disease, Rheumatoid Arthritis
7	***Gleevec***	$ 3.700B	Chronic Myelogenous Leukemia, Gastr-intestinal Stromal Tumours
8	***Neulasta***	$ 3.318B	Neutropenia
9	***Lantus***	$ 3.159B	Types I and II Diabetes
10	***Aransep***	$ 3.137B	Anaemia
11	***Prevnar***	$ 2.716B	Streptococcus pneumoniae vaccine
12	***Taxotere***	$ 2.622B	Breast cancer, Non-small cell lung cancer, prostate cancer, gastric cancer
13	***Procrit***	$ 2.460B	Anaemia
14	***Epogen***	$ 2.456B	Anaemia
15	***Copaxone***	$ 2.262B	Multiple sclerosis

* Bioworld Market Leading Biotechnology Drugs 2009

Top Biotech Drugs (2008) – Expression Systems

	Product	Company	Expression system	Type of Molecule
1	*Enbrel*	Amgen/Wyeth/Pfizer	CHO cells	MAb Fusion Protein
2	*Rituxan*	Genentech/Roche	CHO cells	Chimeric Mab
3	*Humira*	Abbott	CHO cells	Human MAb
4	*Avastin*	Genentech/Roche	CHO cells	Humanised MAb
5	*Herceptin*	Genentech/Roche	CHO cells	Humanised MAb
6	*Remicade*	J&J/Centocor	Murine Myeloma Cells	Chimeric MAb
7	*Gleevec*	Novartis	N/A - Chemical Synthesis	Chemical
8	*Neulasta*	Amgen	*E.Coli*	*PEGylated GCSF*
9	*Lantus*	Sanofi Aventis	*E.Coli*	*Modified Insulin*
10	*Aransep*	Amgen	CHO cells	Modified erythropoietin
11	*Prevnar*	Wyeth/Pfizer	*N/A – Bacterial Culture*	*Streptococcus pneumoniae* Vaccine conjugate
12	*Taxotere*	Sanofi Aventis	N/A - Chemical Synthesis	Chemical
13	*Procrit*	Ortho Biotech	CHO cells	Erythropoietin
14	*Epogen*	Amgen	CHO cells	Erythropoietin
15	***Copaxone***	Teva	N/A - Chemical Synthesis	Chemical

Significance of Monocloanl Antibodies



The top 6 biotech drugs are monoclonal antibodies or antibody fusion proteins.

It is expected by 2014 that the six best selling pharmaceutical drugs will be monoclonal antibodies as patent protections expire on existing best selling drugs.

Monoclonal antibodies will become an even more significant class of drug in the future.

A European biopharmaceutical group specialised in therapeutic proteins

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1st October 2008

Presentation of LFB

What is LFB?

- One of the top European pharmaceutical companies manufacturing and commercialising human plasma-derived medicinal products
- A key player in the biotechnology field in France

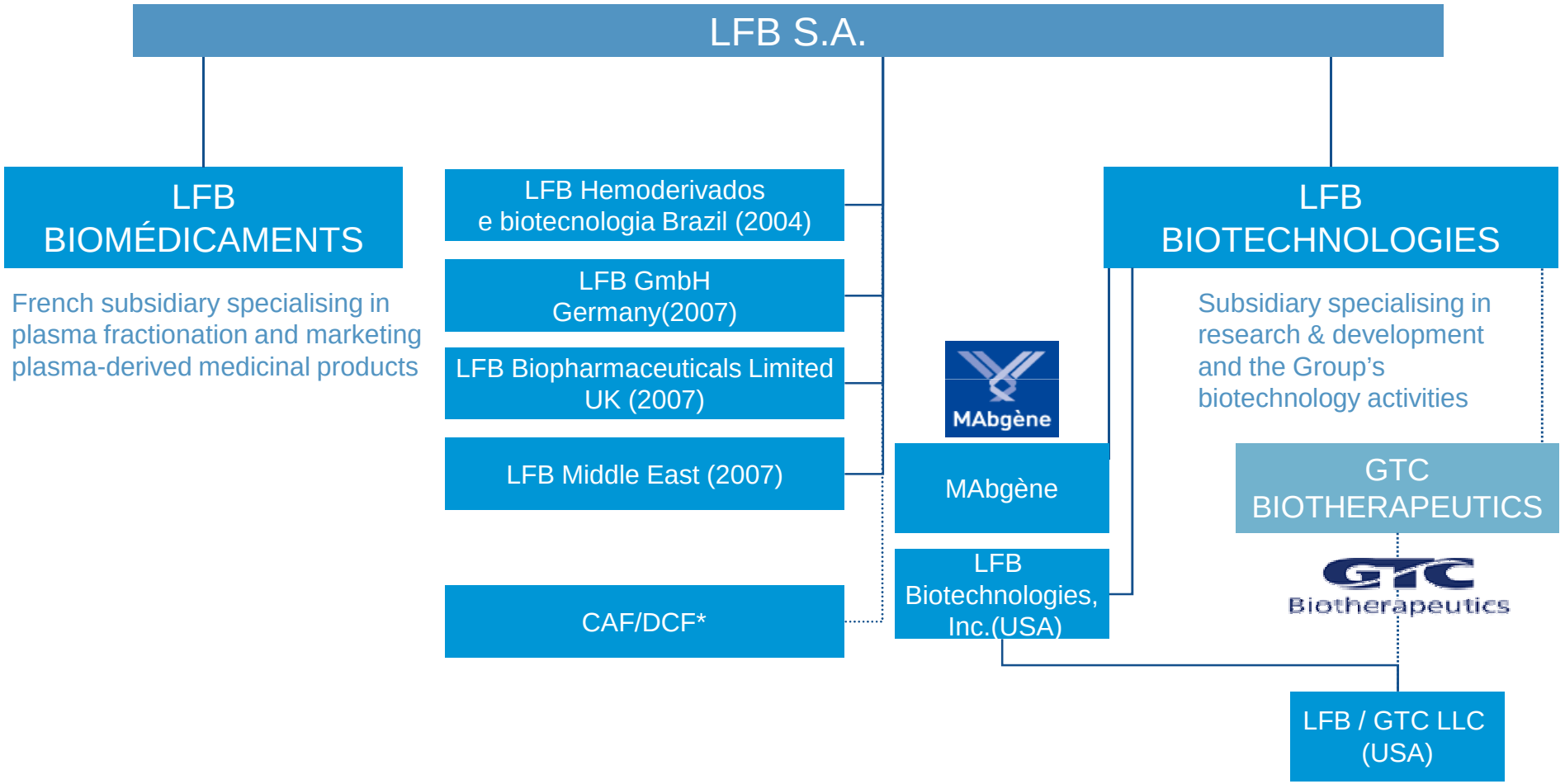
A fully biopharmaceutical group focused on biological and biotechnological medicinal products

Figures in 2008

- 352 million € turnover: 9% growth
- 3rd pharmaceutical company serving hospitals in France
- 6th fractionator worldwide
- 1st french biotech company
- €66 million R&D budget: 19% of turnover
- 1531 employees
- €29.2 million industrial investments

500,000 patients treated each year
with the 19 LFB plasma-derived medicinal products
to care for 80 severe and sometimes rare pathologies

Organisation



*Minority stakes

Current LFB Biotechnologies Development Pipeline

- 2 monoclonal antibodies (MAbs) using EMABling® technology:

Anti-Rhesus D (RhD) (human)
Anti-CD20 (chimeric)

- 3 transgenic recombinant proteins with GTC:

Factor VIIa, Factor IX and anti-CD20 monoclonal antibody

Regulatory aspects of monoclonal antibody development

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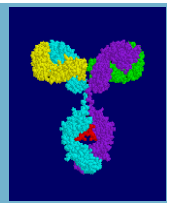
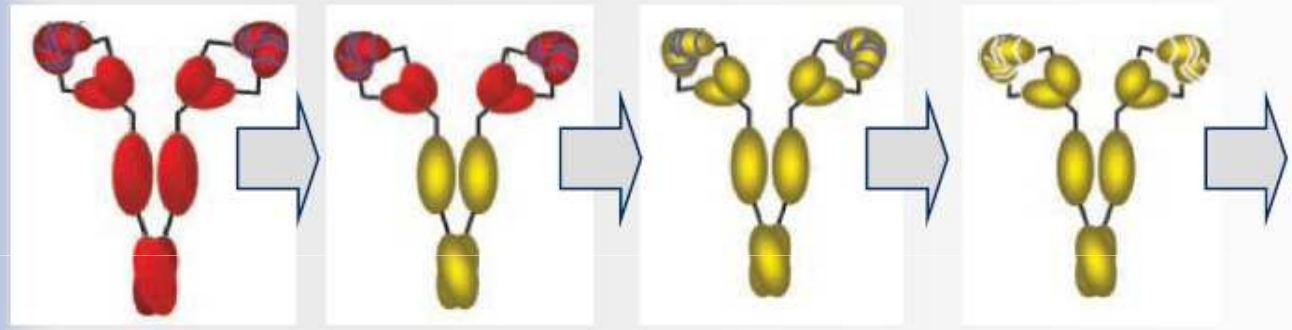
mAbs development: technological evolution



Evolution of monoclonal antibodies („-mab“):

= murine
= human



Murine mAb
100% mouse
„-omab“
Arcitumomab (CEA-Scan®) (1996)

Chimaeric mAb
33 % mouse
„-iximab“
Infliximab (Remicade®) (1999)

Humanized mAb
10% mouse
„-zumab“
Trastuzumab (Herceptin®) (2000)

Fully Human mAb
100% humain
„-umab“
Adalimumab (Humira®) (2003)

New constructs
- bispecific antibodies
- diabodies
- single chain fragments
- engineered Fc mAbs
- conjugated mAbs
- ...

Immunogenicity

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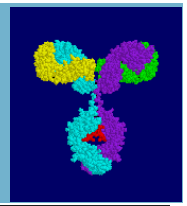
Regulatory Guidelines



	Quality	Safety	Efficacy
ICH	**Q5A :** Viral safety evaluation of Biotechnology Products derived from cell lines of Human or Animal Origin (1997) **Q5B** Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products **Q5C :** Stability testing of biotechnological/Biological Products. **Q5D :** Derivation and characterisation of cell substrates used for Production of r-DNA derived Protein Products **Q5E** : NfG on biotechnological/Biological products Subject to changes in their Manufacturing Processes (2004) **Q6B** : **Test procedures & acceptance criteria** for biotechnological & biological products (1999) **Q7A** : GMP guidance for API clinical materials (2001)	**S6** : **Preclinical safety evaluation** of biotechnology-derived pharmaceuticals (1997) **M3** : Non clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (2009)	
EMEA	**EMEA/CHMP/BWP/157653/2007:** Development, Production, Characterisation and Specifications for monoclonal antibodies and related products (2008) **3AB1A** Production & QC of medicinal produtcs derived by recombinant DNA technology (1995) **EMEA/CHMP/BWP/398498/05 :** Virus safety evaluation of biotechnological investigational medicinal products (IMP)(2009) **CPMP/BWP/268/95** : Virus validation studies(1996) **EMEA/410/01 :** Minimising the Risk of transmitting BSE-TSE agents (2004) **CPMP/BWP/1793/02** : NfG on the use of Bovine Serum (2003) **CPMP/BWP/3207/2000 Rev.1:** Guideline on **Comparability** of Medicinal Products containing Biotechnology-derived Proteins as Active Substance. Quality Issues *(2003)*	**CPMP/SWP/1094/2004** Guideline for the evaluation of control samples in **non-clinical safety studies**: checking for contamination with the test substance (2004)	**CHMP/89249/2004** clinical investigation of the **pharmacokinetics** of therapeutic proteins (2007)
		CPMP/BMWP/14327/2006 Guideline on **Immunogenicity** assessment of biotechnology-derived therapeutic proteins (2007, revised Avr.2008)	**CPMP/SWP/28367/07** Guideline on strategies to identify and mitigate risks for **first-in-man** clinical trials with investigational medicinal products (2007)
		CHMP/BWP/101695/2006 : Guideline on **Comparability** of Biotechnology-derived Medicinal Products after a change in the manufacturing process – Non clinical and clinical issues*(2006)* **CPMP/SAWP/72894/2008** **Biomarkers** qualification : guidance to applicants (draft for comments, 2008)	
European Pharmacopeia	**Monograph #2031 :** Monoclonal antibodies for human use (2008). **Monograph #0784 :** Products of recombinant DNA technology (2008)		
FDA	**Points to consider** in the manufacture & testing of monoclonal antibody product for human use (1997) **Guideline** for submission of chemistry, manufacturing and controls information for a therapeutic recombinant DNA-derived product or a mAb for in-vivo use (1996)		
	Guidance for industry : cGMP for phase I investigational drugs (2008) **Guidance for Industry** - Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs (draft, sept.2008)		

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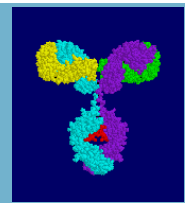
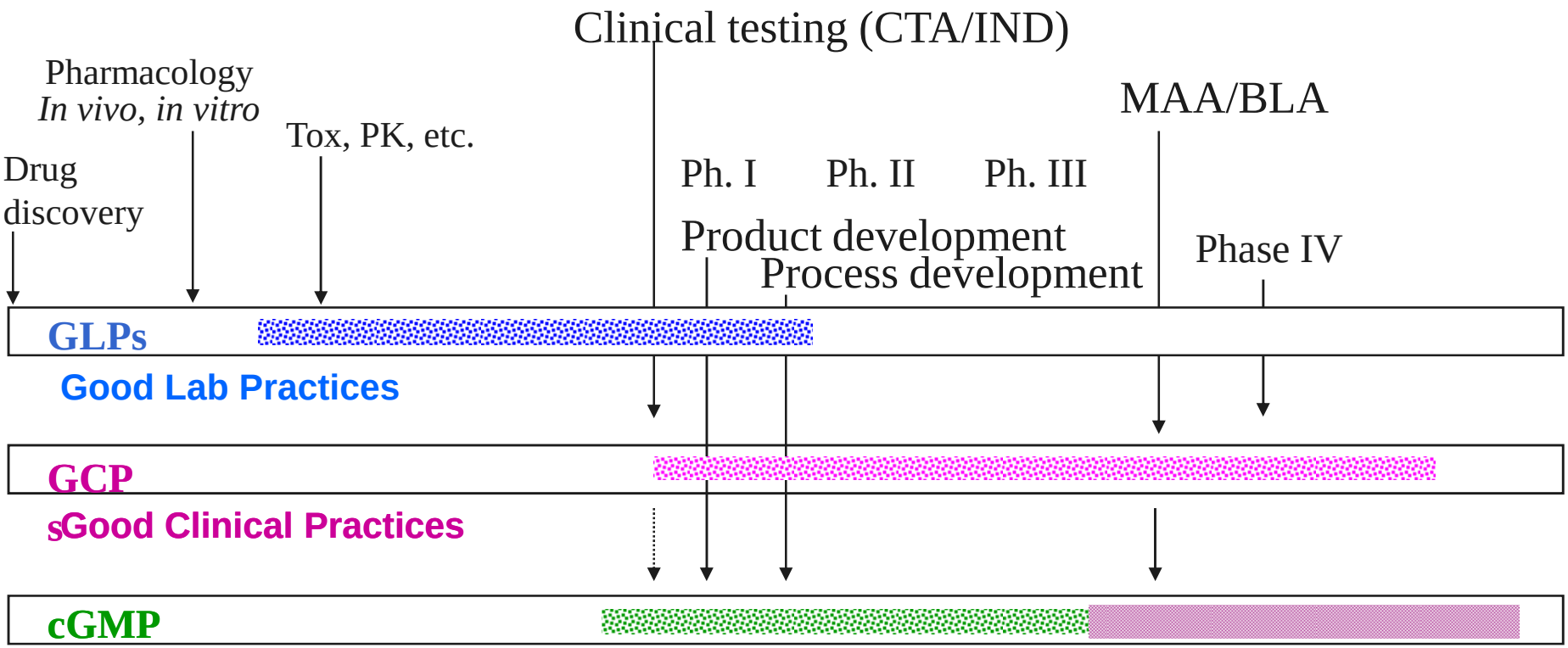
Stages in the Clinical Development Process



Each stage brings it's own regulatory challenges



CTA : Clinical Trial autorisation
IND : Investigational New Drug
BLA: Biologics License Application
MAA: Marketing Authorisation

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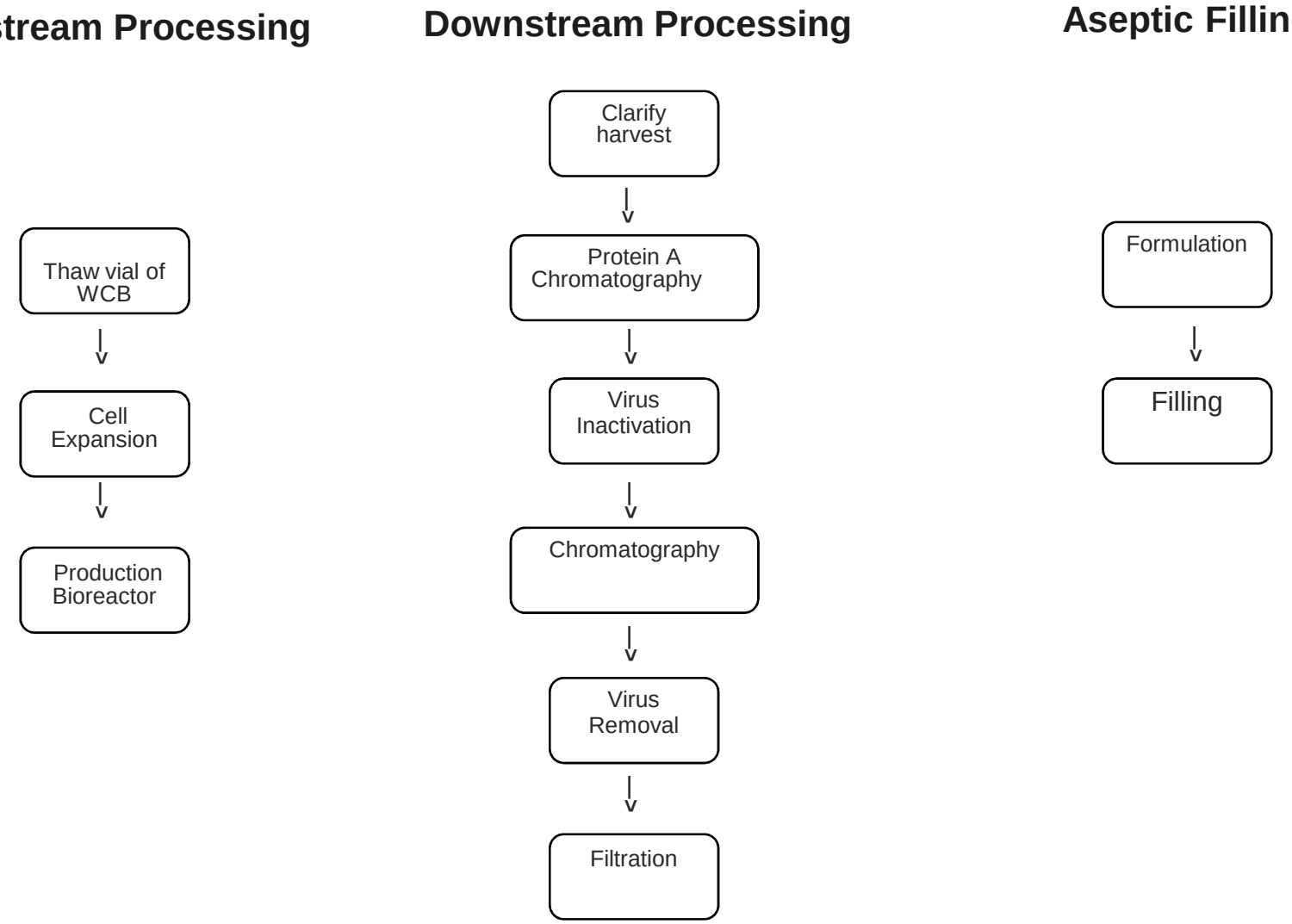
Manufacturing Process for mAbs



Master and Working Cell Banks (MCB & WCB)

- MCB and WCB required as per guidelines ICH Q5B &Q5D
  - MCB derived from the selected cell clone containing the expression construct
  - WCB derived by expansion of one or more ampoules from MCB
- This two-tired cell banks system ensures consistent starting material for each lot of product
- Testing required for MCB and WCB characterisation
  - Identity (phenotypic and/or genotypic characteristics)
  - Purity (absence of adventitious agents: viruses, mycoplasma, bioburden; no contamination by other cell lines)
- Necessary to determine & document stability of MCB and WCB.

Process Development and Scale-Up

- Potential Changes to process during development:

  Modify the cell line (e.g. to improve stability of productivity)

  Modify the culture medium (e.g. to improve productivity)

  Modify process steps (e.g. to reduce HCP contamination)

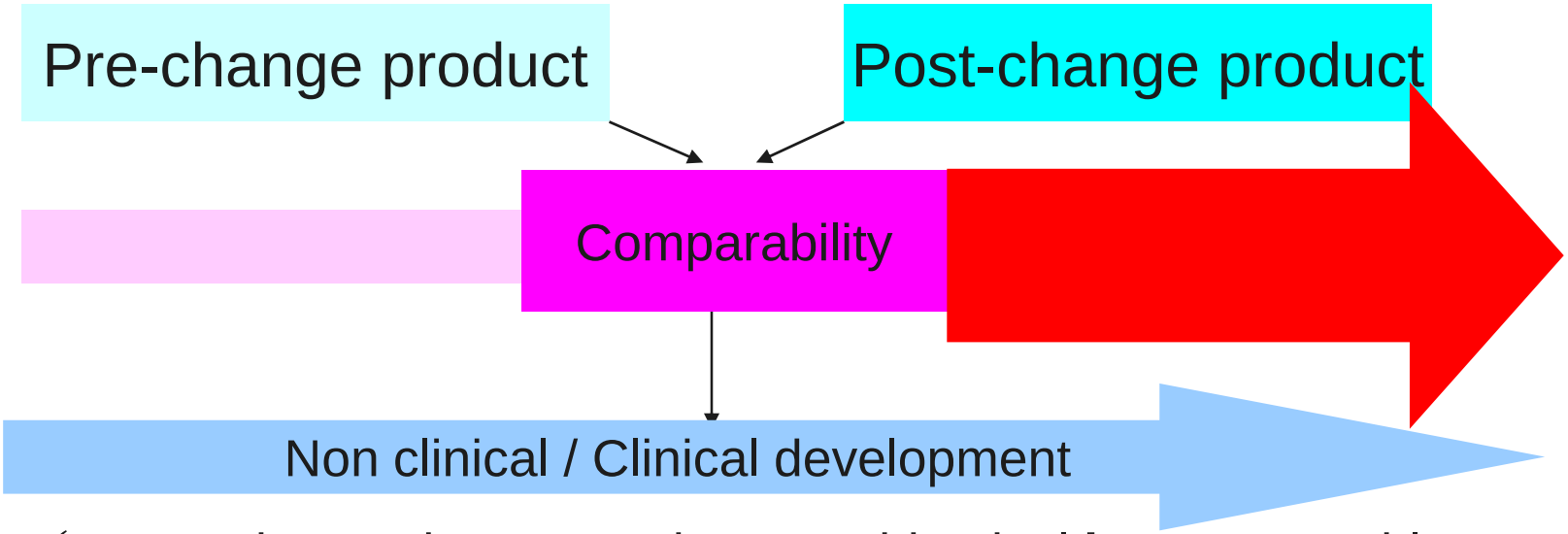
  Scale-up of process (e.g. to reduce unit costs)

  Change of facility (e.g. for process scale-up)

  Change fo technology (e.g. stainless steel to dispoable bioreactor)

Each modifiation must be evaluated for regulatory impact and comparability demonstrated by means of thorough analytical testing

Comparability during clinical development



✓Pre- and post-change products not identical **but** comparable

✓Sequential comparability plan

Analytical > In vitro bioactivity > In vivo bioactivity > non clinical > clinical

⇒ Good knowledge of the product, process and of relationship between the quality attributes and safety and efficacy of mAbs essential

Viral Safety testing

- Guidelines: ICH Q5A & EMEA guideline on investigational products
- Potential sources of contamination
  - Nature of cell line used (mammalian cells) ⇒ endogenous viruses
  - Raw material used ⇒ viral contaminants
  - Manufacturing ⇒ introduction of viruses into the product
- Biological safety based on complementary measures
  - Virus testing of production cell line & viral safety of biological raw materials
  - Virus testing of unprocessed bulk harvest
  - Capacity of the production process to inactivate and/or eliminate viruses

  (Need to have at least two complementary dedicated viral elimination/inactivation steps, *e.g.* solvent-detergent treatment + nanofiltration)

Immunogenicity

- EU Guideline on immunogenicity assessment of biotech-derived proteins

  (Guideline on immunogenicity of mAbs currently evaluated)

- Immunogenic response to mAb influenced by
  - Patient and disease-related factors
  - Product-related factors (human or not, post-translational modifications, impurities, formulation, immunomodulatory and funtional properties of the mAb, administration scheme)

Can affect key funtional parameters

Safety (risk of anaphylactic reactions or delayed hypersensitivity)
Bioavailability (PK/PD profile) as immune complexes enhance clearance
Efficacy, in case of neutralizing anti-drug antibodies (ADA)
Physiological function of endogenous counterparts, in case of cross-reacting ADA (“high risk products” e.g. refractory anemias with rEPO)

Immunogenicity assessment

Not easy to prdict from animal models
Must be part of the clinical monitoring

Future Challenges

- The greater use of disposable systems – validation of extractables and leachables

- Emergence of the Biosimilars' market to compete with existing monoclonals

Regulatory requirements for production of monoclonal antibodies

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