



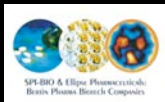
**Galenic development of biotech molecules  
Key points and propositions**

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**Who we are**

**Health & Life sciences division  
of Bertin technologies**



## Who we are



Three complementary business units of the Bertin Technologies Group:

**ellipse**  
pharmaceuticals

**Innovation & Services for Pharmaceutical Development**

**SPI**  
*bio*

**Tools & Expertise for Pharmaceutical R&D**

**bertin**  
technologies

**Medical Devices & Equipment for Life science laboratories and environmental surveillance**



**ellipse**  
pharmaceuticals  
bertin

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## Strategic partnerships



- Scientific Board made of academics and industrials
- Strong academic backing
  - Institut de Pharmacie Industrielle de Bordeaux
  - CRPP
  - ENSCPP
  - ESTBB...
  - Universités Paris V & XI
- CEA Sciences du vivant
  - Proteomic platform
  - Access to a wide range of sophisticated analytical methods for the characterization of proteins in a GLP environment



**ellipse**  
pharmaceuticals  
bertin

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## The demand in the biotech domain

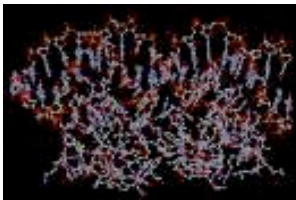


- One third of the total of the molecules in clinical development
- On 324 biotech molecules 280 are proteins and 118 are antibodies
- In 2006 60 molecules in phase III worldwide
- More than 150 diseases are concerned
  - Cancer, autoimmune, metabolic, neurodegenerative
- In 2010: 12% of the Pharmaceutical market share

Sources : (A.D.Little 2006)

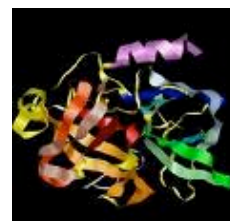


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## Scope of the talk

### Therapeutic proteins and peptides



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## Summary



### Main key points to face as a partner

#### Some technological approaches

*Success and difficulties*

#### Conclusion



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## Cultural aspects



Quantitatively most of the actors are start-up with a strong backing from academic environment

Very good scientific level but:

- Lack of knowledge of regulatory requirements
- Complicated process or analytical approaches coming from academic know how, difficult to transfer in a GMP/GLP environment
- Needs to redo or validate key development steps to fulfill regulatory dossiers when its not to late!!!



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## Difficulties for Staffing



- Combination of several scientific and technical domains
  - Biochemistry
  - Analytics
  - Pharmaceutical process
  - Polymers
  - Regulatory
- Lack of specific and appropriate academic programs covering all those aspects
- Needs to built up multidisciplinary teams around a project and to mix cultures



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## Patent environments



- A lot of interesting technological plate-forms are available
  - Medusa®, Zydys®, Flashtab®, Crossject®....
- Mostly dedicated to Big pharma partners
- Identified needs for freely accessible technologies for small and medium size biotech companies
- Possibilities to propose additional intellectual properties with “generic” technologies applied to specific molecules or indications.



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## Lack of GMP platforms



- Only few GMP platforms available in Europe dedicated to the specific requirements of the formulation of biotech molecules.
  - Process, analytics, regulatory...
- Even worse for highly potent biotech molecules.
- A lot of identified platforms are also proposing their own technologies and show low motivations for external demands.
- Difficult to catch interests of partners for the manufacturing of few demonstrating pilot batches while industrialization is always forecasted years after.



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## Summary



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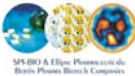


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## Technological approaches and examples



- Most frequently asked questions
  - Optimization of freeze drying cycles
  - Solubilization (Microemulsions)
  - Alternative routes of administration (sublingual devices)
  - Sterilization (Amber®)



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## Freeze Drying



- Most commonly used stabilization technique for therapeutic proteins and peptides
- Needs to optimize the scale up (from laboratory batches to pilot and industrial batches)
- Main parameters to manage
  - Shelf life
  - Denaturation
  - Aggregation
  - Industrial cost price
  - Reproducibility

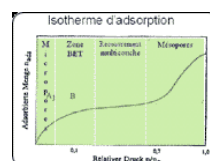
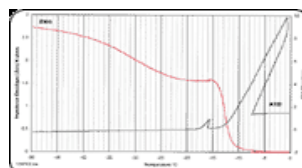
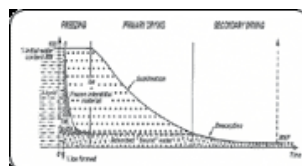


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## Key points to face an approaches



- Appropriate choice of excipients
  - Cryo and lyoprotectants
- Optimisation of the freezing cycle
  - Favours sublimation rather than melting
  - Crystal size
  - Crystallinity versus amorphous state
  - To shorter the duration of the process
- The tools
  - Differential thermal analysis
  - Impedance/resistivity
  - Kinetic of crystallisation
  - Specific area
  - Residual humidity



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## Solubilization



- Early needs
  - First in vitro and preclinical trials
  - Clinical trials
- Prerequisite for parenteral routes
- Several approaches
  - Complexation, Co-solvents, surfactants, solid dispersions  
microemulsions....
- Problems to consider
  - Tolerance
  - Shelf life
  - Industrial cost price



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## Microemulsions as a tool for the solubilization of therapeutic peptides and proteins



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### Microemulsions

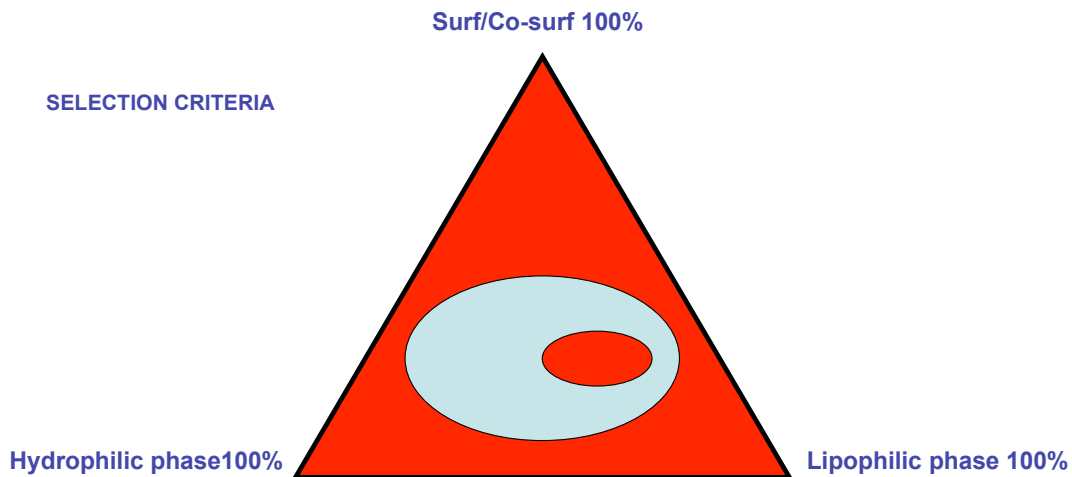


- Isotrope solutions made of immiscible solvents and co-solvents
- Compositions:
  - Lipophilic and hydrophilic phases
  - Combination of Surfactants and Co-surfactants
- No energy required
- Spontaneous formation
- Size of the drops (10 to 200 nm)
- High solvation properties



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## Methodology



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## Microemulsions and biotech API



- Possibility to combine API with various solubility profiles (insoluble peptides or proteins with sugars)
- Soft process compatible with fragile molecules
- Improve bioavailability
- Open new routes of administration (pulmonary, sublingual, intramuscular...)
- Example of a “generic technology” who can lead to intellectual properties when applied to a specific candidate



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## Generic Orodispersible & Transmucosal Devices



- Field of applications
  - Small peptides or proteins
  - vaccines
  - Highly potent drugs
- Two generic technologies
  - Freeze drying
  - Orodispersible tablets



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## Oro dispersible freeze dried devices



- Highly charged devices (high levels of excipients and low concentrations of water)
- Short duration of freeze drying cycles
- Very good hardness of the devices
- No intellectual properties associated as such

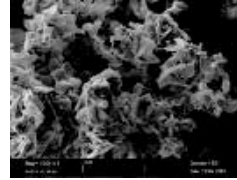


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## Orodispersible devices



- Direct compression
- Simple manufacturing process
- Unpatented
- Key points
  - Simple process
  - Use of soluble excipients exhibiting different size distributions (fragilization of the tablet)
  - No plasty taste
  - Easy scall up
  - No intelectual proprerties associated as such.

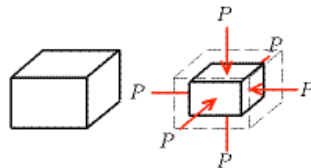


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## Sterilization Amber®

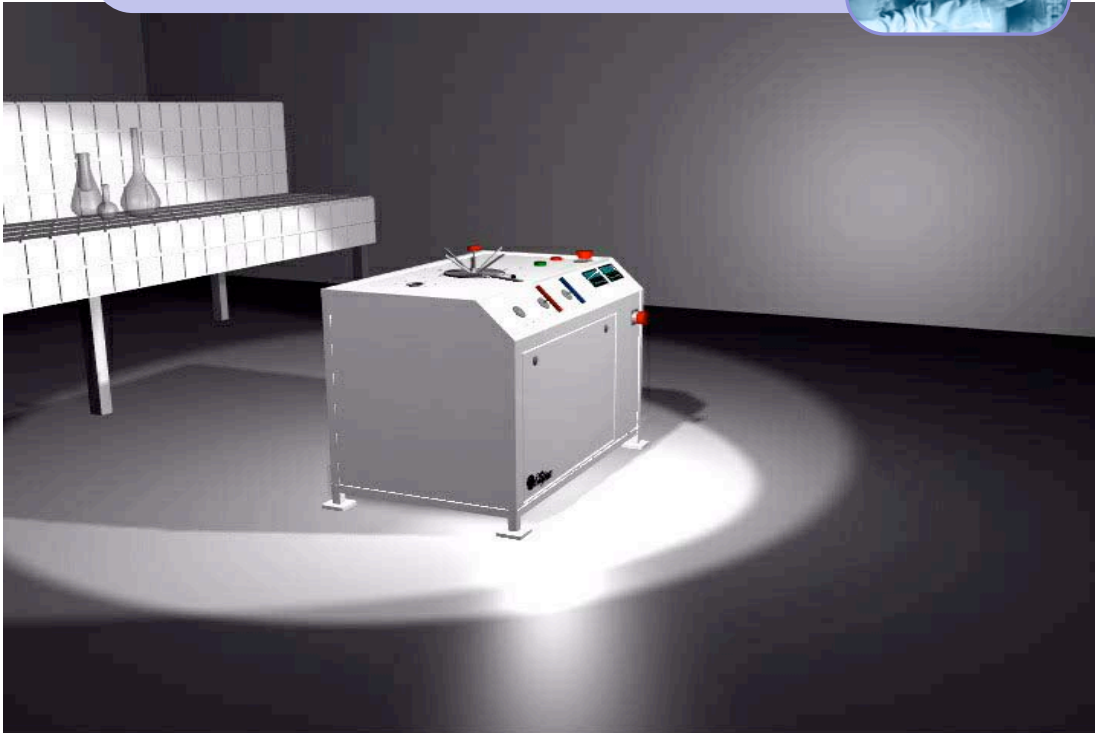


- New patented process dedicated to the sterilization of fragile molecules;viscous slurry of polymeric depot formulations or monolithic implantable sustained release device
- The idea: Application of isostatic pressures of several thousand bars at room temperature for few minutes



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## The Equipment



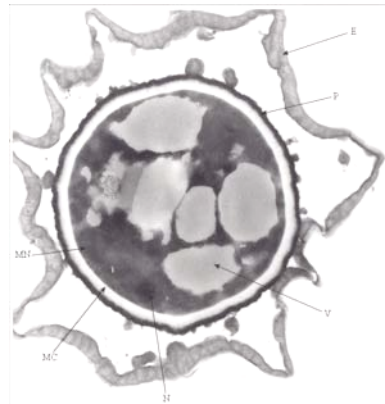
## Microbiological decontamination



6 log reduction on all the tested strains recommended by Pharmacopoeias at room temperature

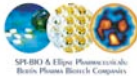
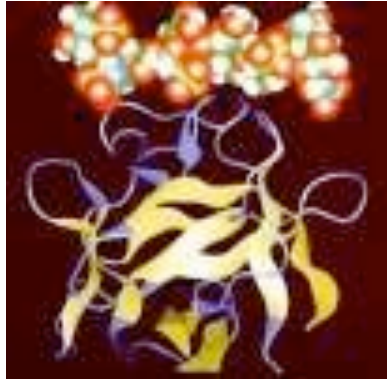


*Before HP*



*After HP  
(500 MPa, 10 min., 25°C)*

## Fragile molecules

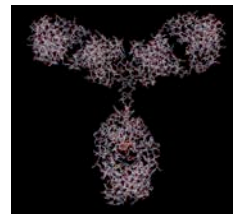
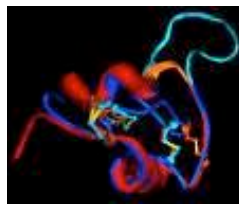


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## Tested fragile systems



- Recombinant insulin
- Heparin
- Monoclonal antibody
- Colloidal carriers and depot systems
- No conformational change while decontamination is reached in all cases
- Difficulty : to overcome regulatory barriers.



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## Conclusions



- Formulation of each biotech molecules is a case study
  - Necessity to forecast ASAP Agencies requirements
  - To differentiate pertinent analytical methods for scientific purposes and routine
  - To identified the right partners in concordance with the goals to be reached (size, motivation, cost, localization...)
  - To be open to original solutions coming from other domains of activities



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## Thank you to be there

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