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Challenges with Advanced Therapies from the EU regulatory perspective

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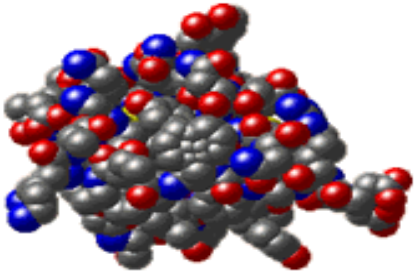
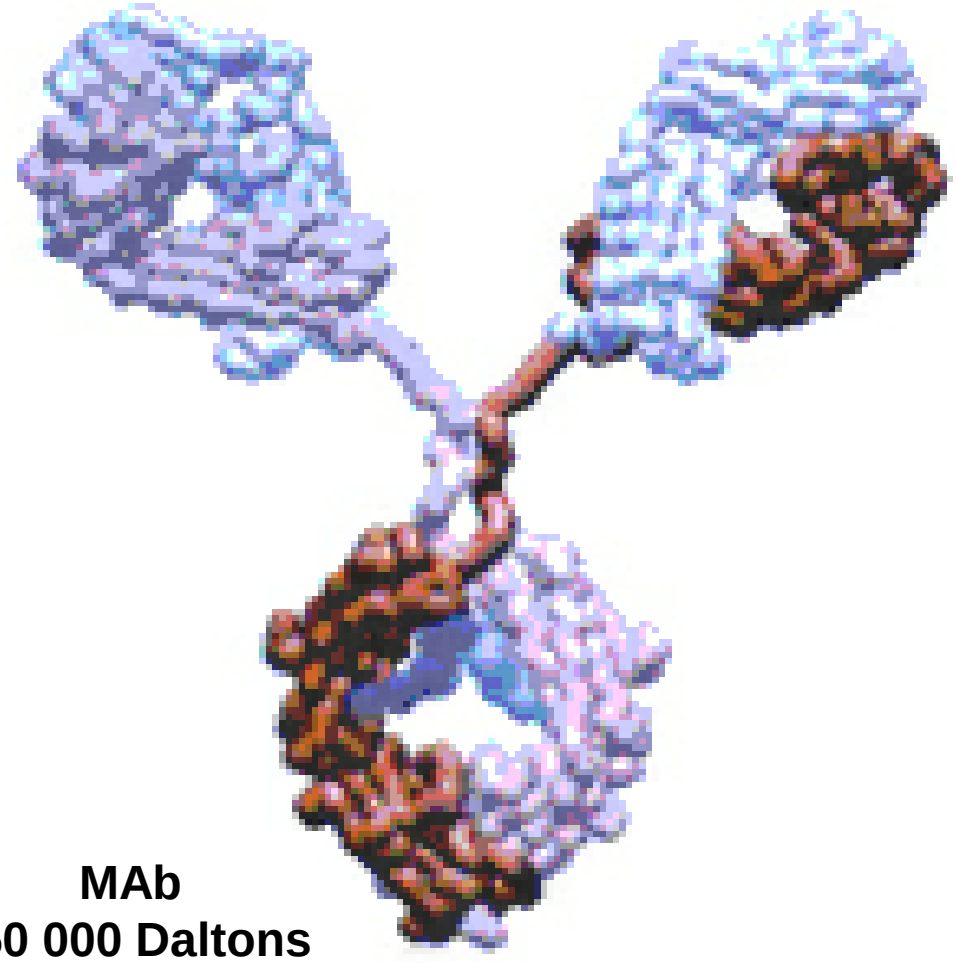
"I attend this conference as an individual expert, and do not represent the CHMP/CAT/BMWP. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CXMP/WP/SAG or reflecting the position of the CHMP/CAT/BMWP."

Biologicals are complex

Aspirin
180 Daltons



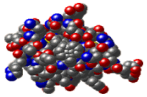
Insulin
5 700 Daltons



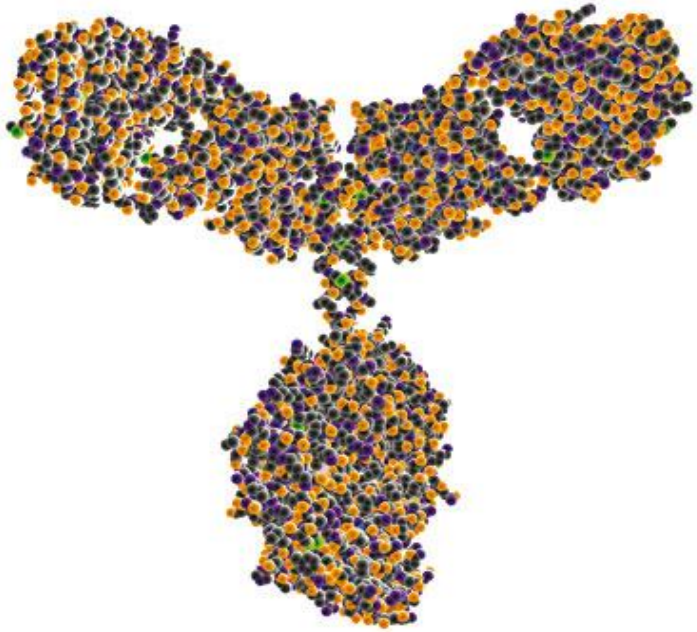
MAb
150 000 Daltons

Biologicals are complex

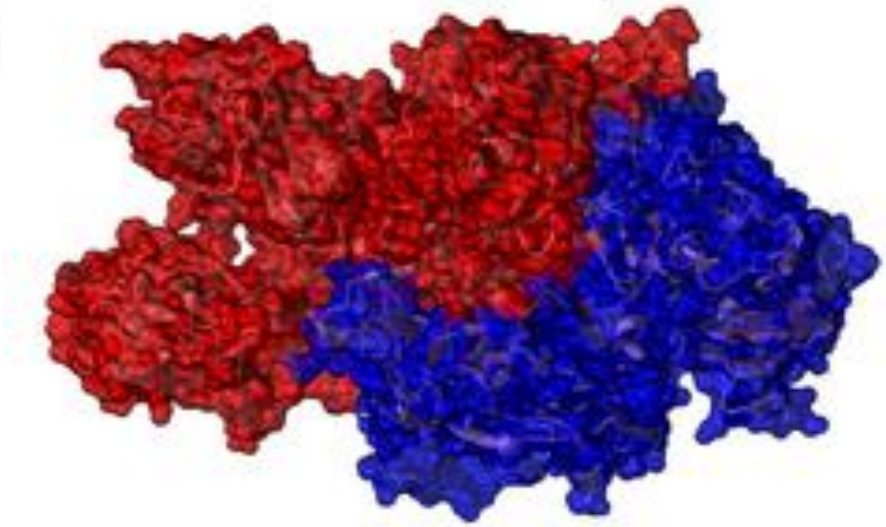
Aspirin
180 Daltons



Insulin
5 700 Daltons



Monoclonal antibody
150 000 Daltons



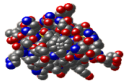
Coagulation Factor VIII
280 000 Daltons

- **high molecular weight**
- **complexity**
  (primary / secondary / tertiary / quartery structure;
  post-translational modifications)
- **heterogeneity (drug substance, drug product)**
- **process- and product-related impurities**
- **low stability of drug substance / drug product**
- **species specificity**
- **immunogenicity**

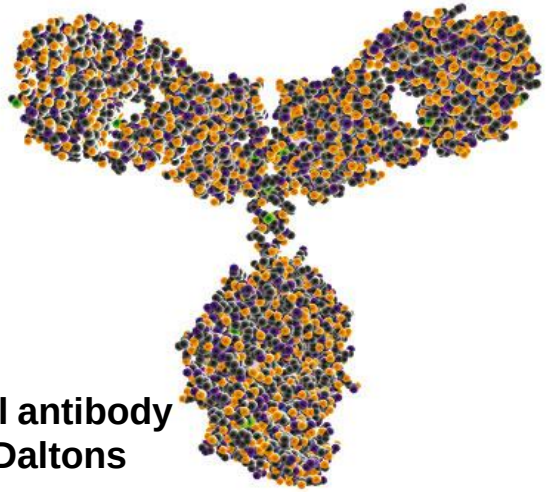
www.laborjournal.de, www.wikipedia.org

Biologicals are complex

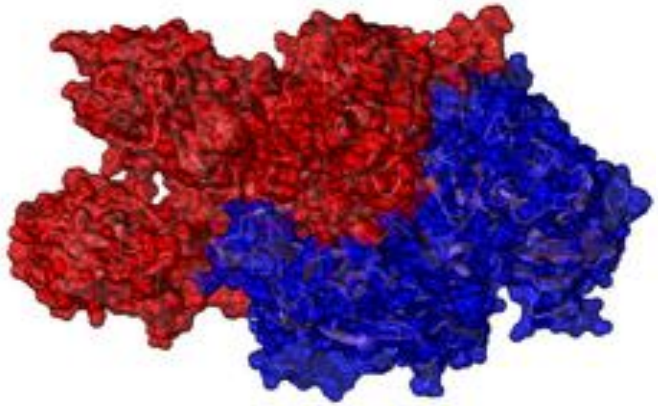
Aspirin
180 Daltons



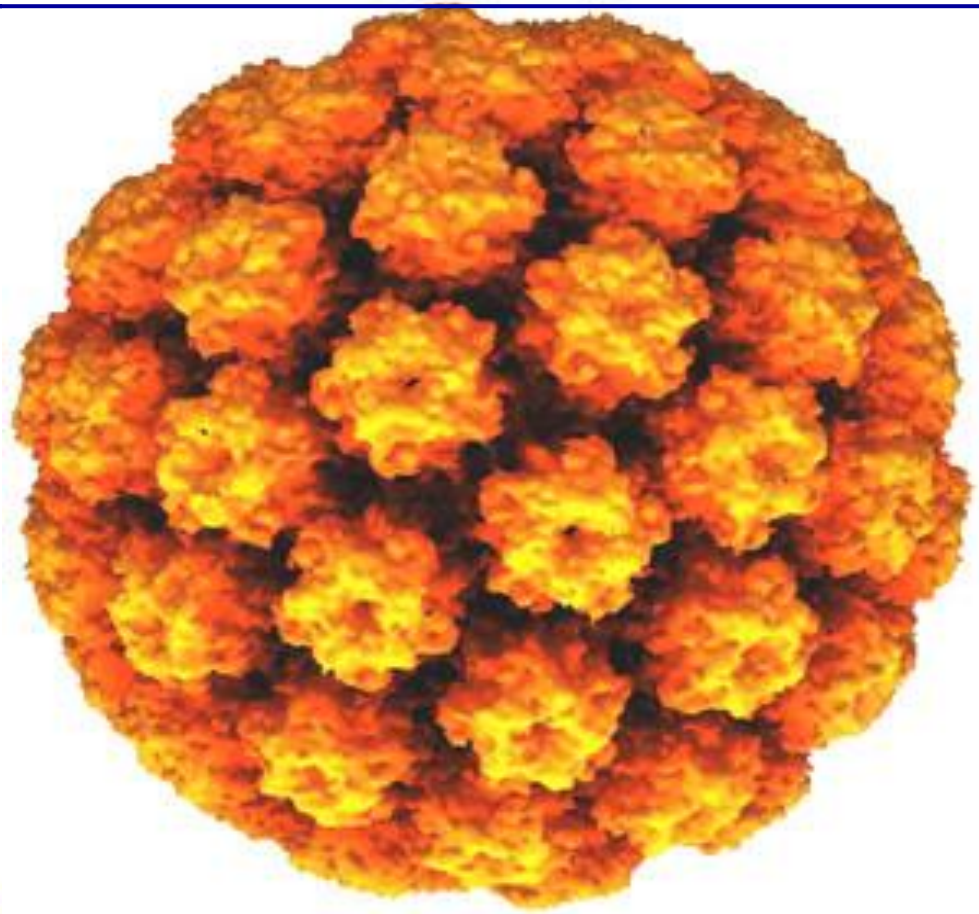
Insulin
5 700 Daltons



Monoclonal antibody
150 000 Daltons



Coagulation Factor VIII
280 000 Daltons

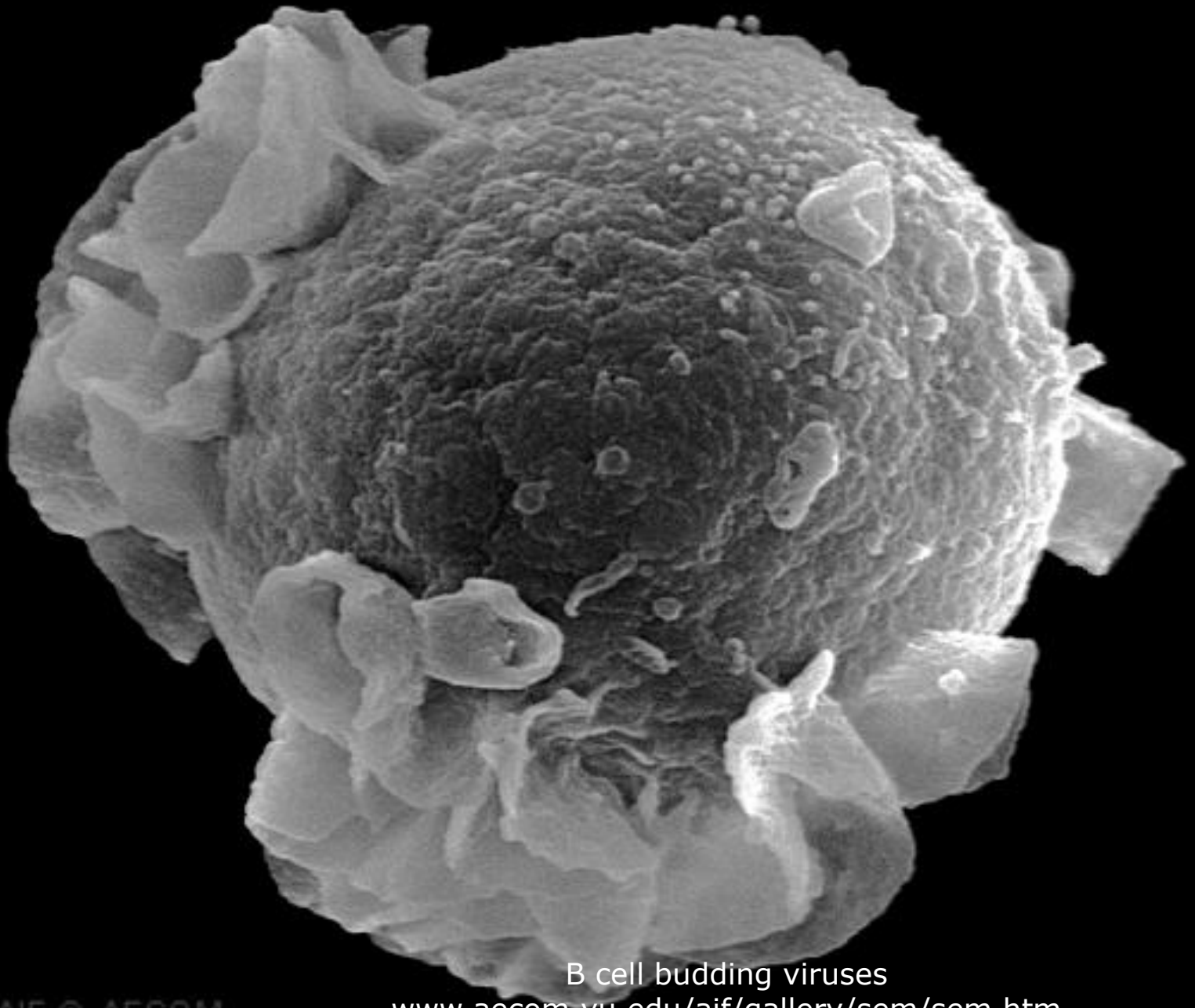


Virus-like particle

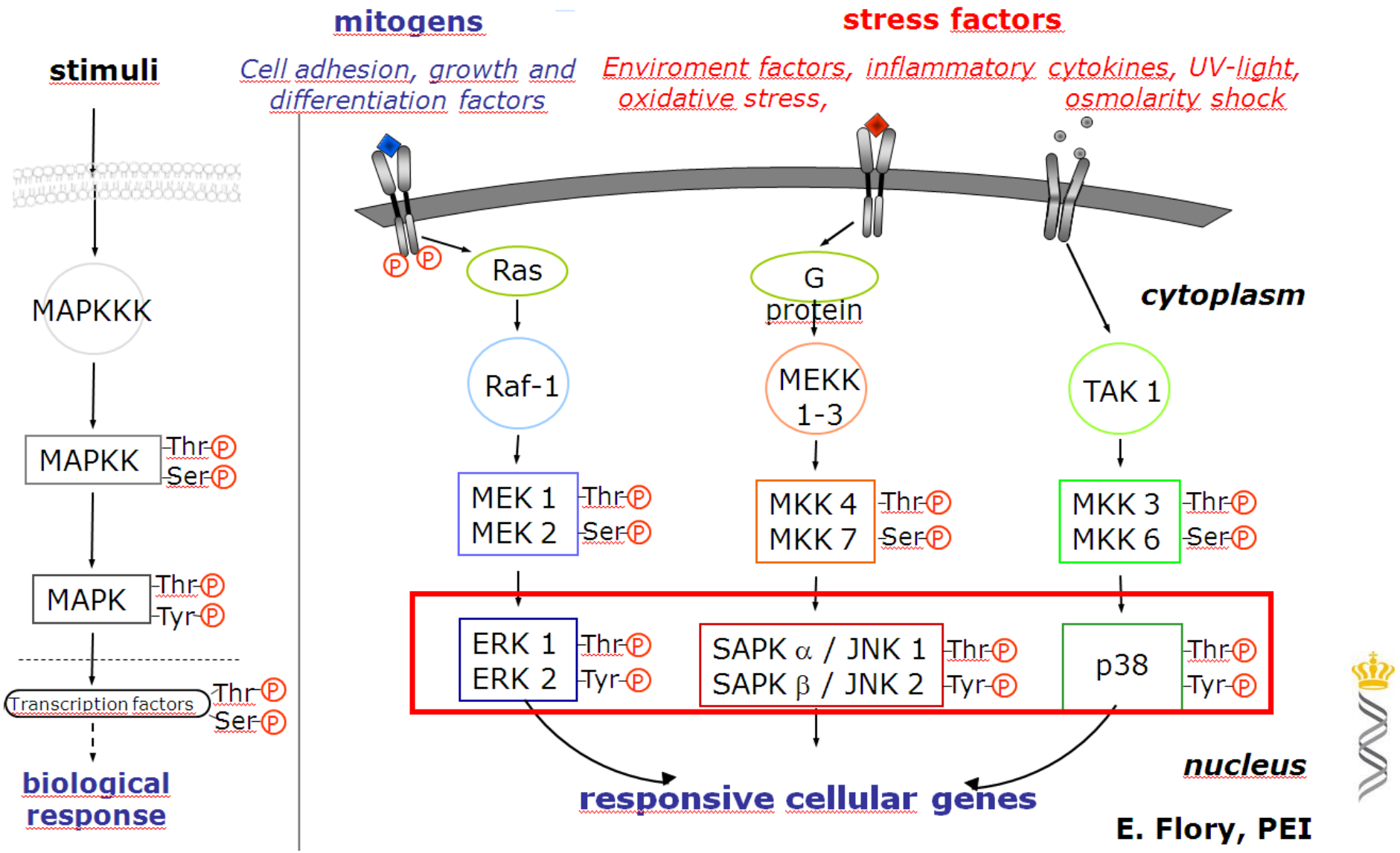
www.laborjournal.de, www.wikipedia.org, www.microbiologybites.com

Complexity of Advanced Therapies

monoclonal antibody



B cell budding viruses
www.aecom.yu.edu/aif/gallery/sem/sem.htm



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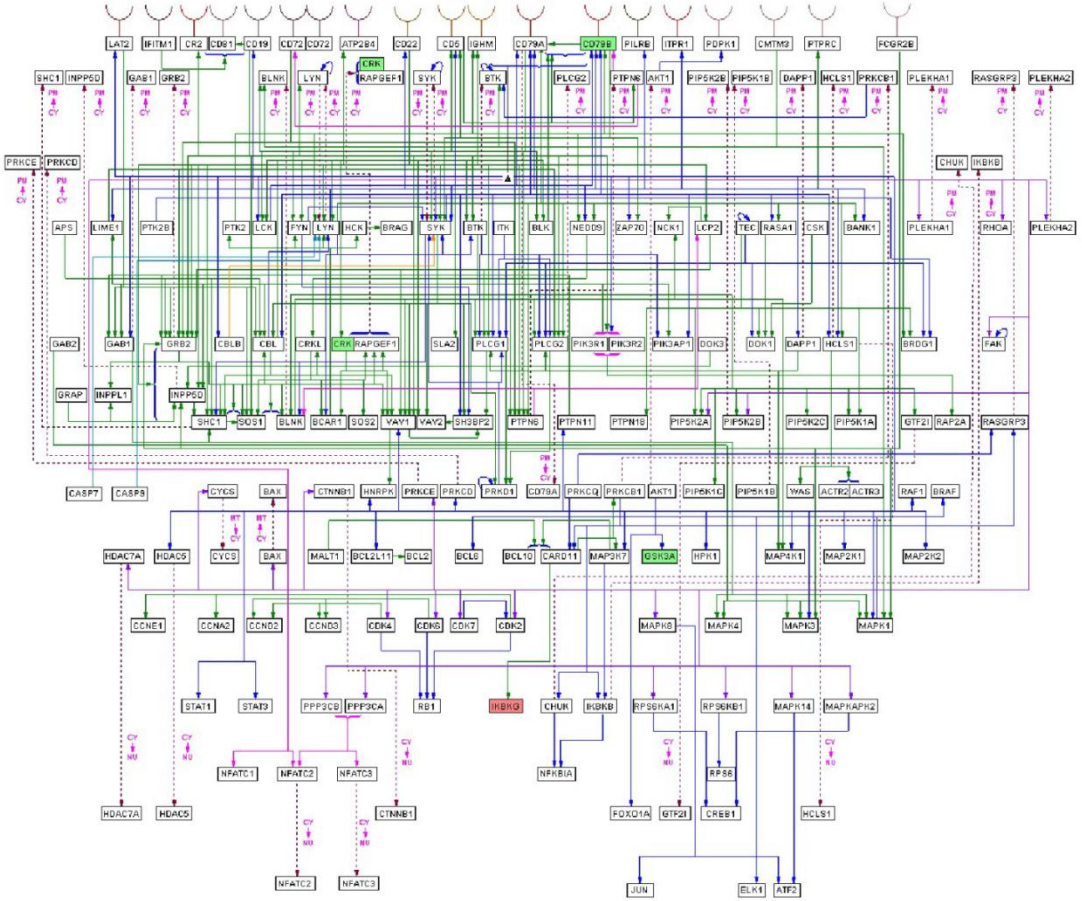
Complexity of signalling

Overlap and location of positive and negative modulators of NFk-B signalling identified in a cell-based screen within the T-cell receptor signaling pathway



Halsey et al, Genome Biology 2007

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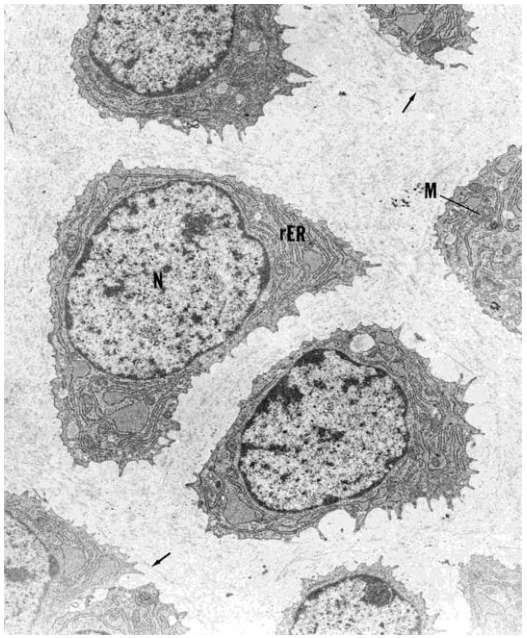
Challenges with cell-based products

- Cells are complex systems
  - Cells are <u>dependent</u> on their (micro-)environment
    - Species-specificity
    - Disease-specificity
  - Cells are <u>reactive</u> to their environment
  - Cell cultures can become heterogeneous
  - Cells might de-differentiate
    (e.g. during longer cell culture)
  - Cells might migrate („biodistribution")
  - Cells are fragile and (sometimes) mortal



=> Regulatory consequences:

√ Need for adequate characterization
√ but also necessity to accept limitations

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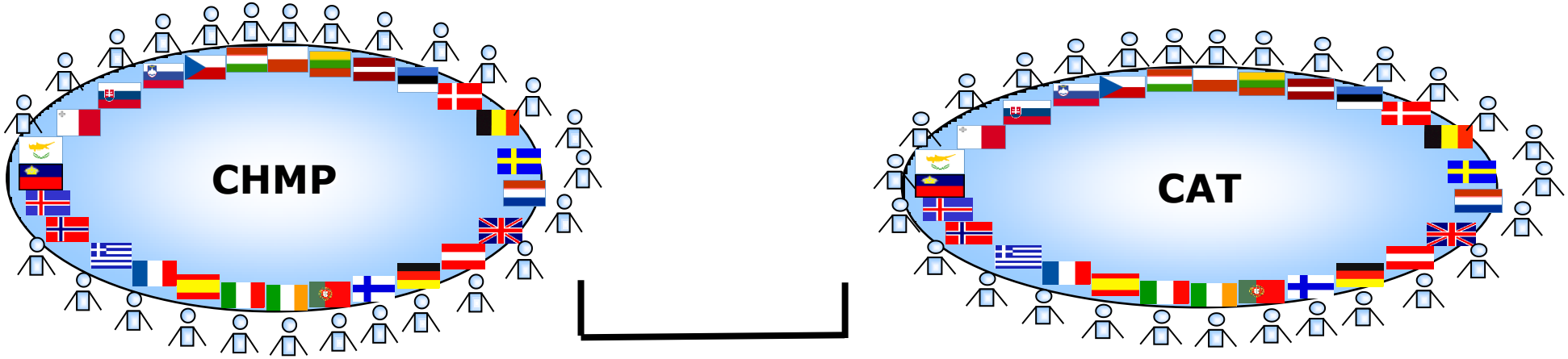
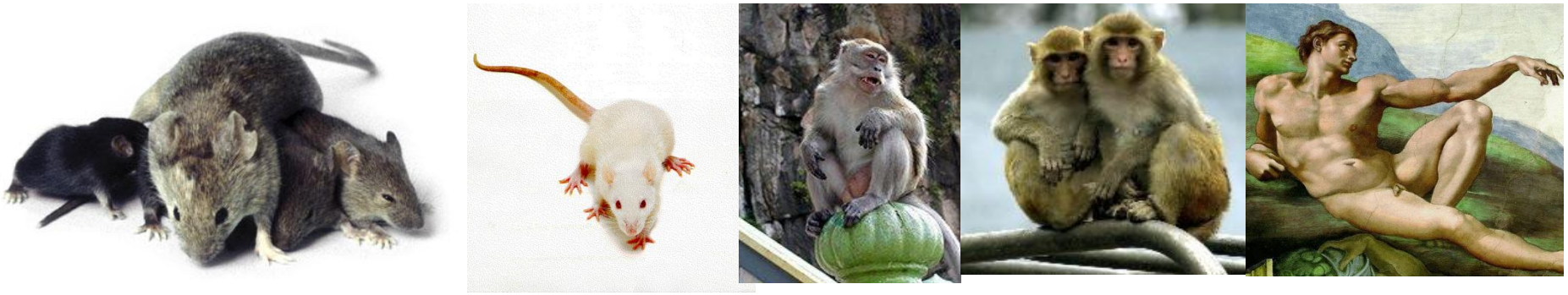
The Committee for Advanced Therapies (CAT)



Reg. 1394/2007, Art. 8

Challenges with cell-based medicinal products

- **Non-clinical evaluation**

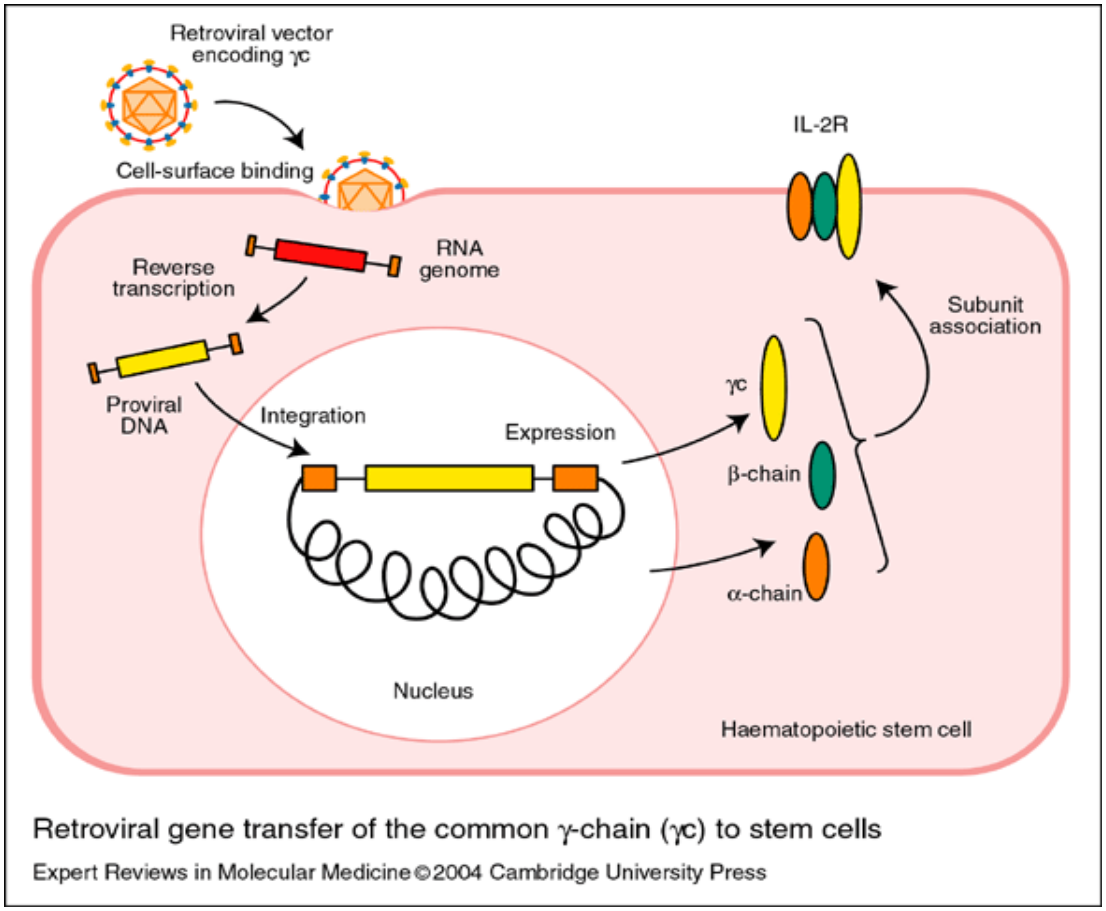


A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)*.

*NfG on preclinical safety evaluation of biotechnology derived pharmaceuticals (CPMP/ICH/302/95; ICH S6)

- **Cell surface molecules (receptors, integrins,…)**
- **Secreted factors like cytokines**

Gene transfer medicinal products



Retroviral gene transfer of the common γ-chain (γc) to stem cells

Vector-related issues clearly to be distinguished from effects mediated by expression of the gene

= added complexity as compared to biotechnological products of having additional test components (vector, genetic material)

Clinical challenges with gene transfer

- **„How to target only the target“**

  Example:

  Gene therapy medicinal products which substitute for an organ or tissue-specific gene defect, but with multilocular occurrence (skin, muscle, bone,…)

  - **How to administer locally to ensure desired local distribution?**
  - **Impact on patient when administered multilocally**
    (more than 20 injections per patient etc.)
  - **Impact of additional devices on safety**
    (e.g. tissue damage and enhancement of immunogenicity?)

Clinical challenges with gene transfer

- How to control the clinical trial?
  - For proof-of-principle
    - Patient as own control
      (comparing pre- and post treatment) might be acceptable, depending on the effect size / severity of the defect / historical data)
  - For pivotal trial
    - Control group usually required to distinguish effect of gene defect correction from usual best supportive care (e.g. dietary measures for metabolic conditions)
      => gene transfer usually represents a monotherapy, not an add-on to standard of care
- How to blind the trial?
- How to measure clinical outcome?
  - For many gene defects there is no available treatment and thus no validated clinical endpoints.

Borders to ethics

- **Important: Adverse events that are to be expected must be seen in the light of the benefit**
  - **Even for integration / tumourigenicity! (e.g., gene therapy for a severe disease that would take a lethal course within the first years of life)**

Research article

Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1

Salima Hacein-Bey-Abina,[1,2] Alexandrine Garrigue,[2] Gary P. Wang,[3] Jean Soulier,[4] Annick Lim,[5] Estelle Morillon,[2] Emmanuelle Clappier,[5] Laure Caccavelli,[1] Eric Delabesse,[6] Kheira Beldjord,[7,8] Vahid Asnafi,[7,8] Elizabeth MacIntyre,[7,8] Liliane Dal Cortivo,[1] Isabelle Radford,[8] Nicole Brousse,[9] François Sigaux,[4] Despina Moshous,[10] Julia Hauer,[2] Arndt Borkhardt,[11] Bernd H. Belohradsky,[12] Uwe Wintergerst,[12] Maria C. Velez,[13] Lily Leiva,[13] Ricardo Sorensen,[13] Nicolas Wulffraat,[14] Stéphane Blanche,[10] Frederic D. Bushman,[3] Alain Fischer,[2,10] and Marina Cavazzana-Calvo[1,2]

[1]Department of Biotherapy, Hôpital Necker–Enfants Malades, Assistance Publique–Hôpitaux de Paris (AP-HP), Université René Descartes, and INSERM, Centre d'Investigation Clinique intégré en Biothérapies, Groupe Hospitalier Universitaire Ouest, AP-HP, Paris, France. [2]INSERM U768, Université René Descartes, and Hôpital Necker–Enfants Malades, Paris, France. [3]Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA. [4]Institut Universitaire d'Hématologie (IUH), Université Denis Diderot, and Hematology Laboratory AP-HP, Hôpital St-Louis, Paris, France. [5]Unité de développement des lymphocytes, Département d'Immunologie, Institut Pasteur, and INSERM U668, Paris, France. [6]Hematology Laboratory and INSERM U563, Centre de Physiopathologie de Toulouse Purpan, University Hospital Purpan, Toulouse, France. [7]Hematology Laboratory, [8]INSERM EMIU0210, [9]Department of Pathology, and [10]Department of Pediatric Immuno-Hematology, Hôpital Necker–Enfants Malades, AP-HP, and Université René Descartes, Paris, France. [11]Department of Pediatric Hematology, Oncology and Clinical Immunology, Heinrich-Heine University, Düsseldorf, Germany. [12]Department of Infectious Diseases and Immunology, University Children's Hospital Munich, Munich, Germany. [13]Department of Pediatrics, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA. [14]Department of Pediatrics, Section of Immunology, University Medical Center Utrecht, Utrecht, The Netherlands.

The Journal of Clinical Investigation http://www.jci.org Volume 118 Number 9 September 2008

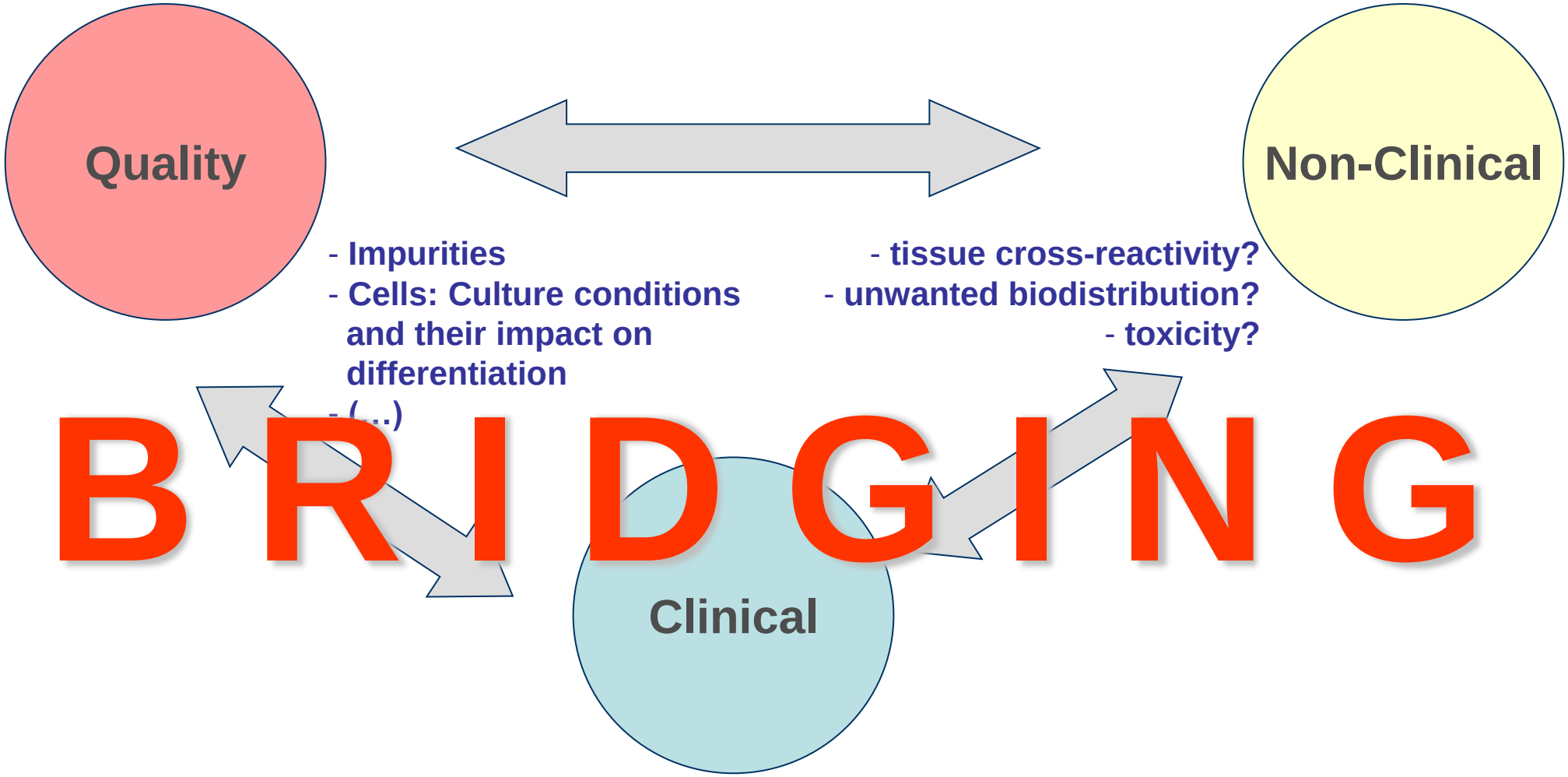
http://www.geneticsandsociety.org/

Borders to ethics

- **Important: Adverse events that are to be expected must be seen in the light of the benefit**
  - **Even for integration / tumourigenicity!**
    (e.g., gene therapy for a severe disease that would take a lethal course within the first years of life)

- **Importance of long-term follow-up and risk management**
  - **Legislation: Opens possibility to long-term follow-up of efficacy => important e.g. for tissue engineering products, where efficacy might be apparent only after many years**

A multidisciplinary approach is required



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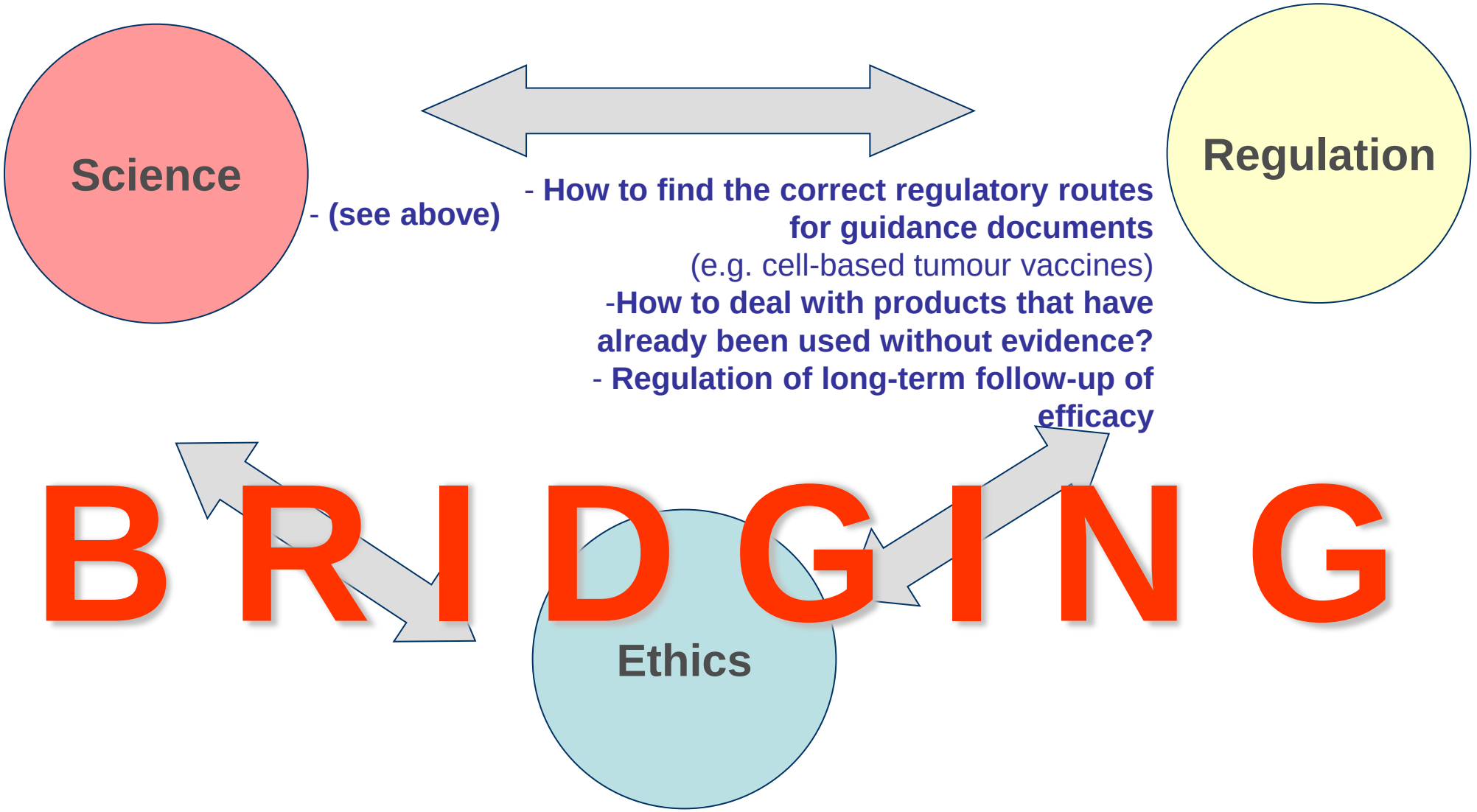

- (see above)

- How to find the correct regulatory routes for guidance documents
(e.g. cell-based tumour vaccines)
-How to deal with products that have already been used without evidence?
- Regulation of long-term follow-up of efficacy

- How to perform first-in-human trials?
- How to deal e.g. with the risk of inserational mutagenesis?

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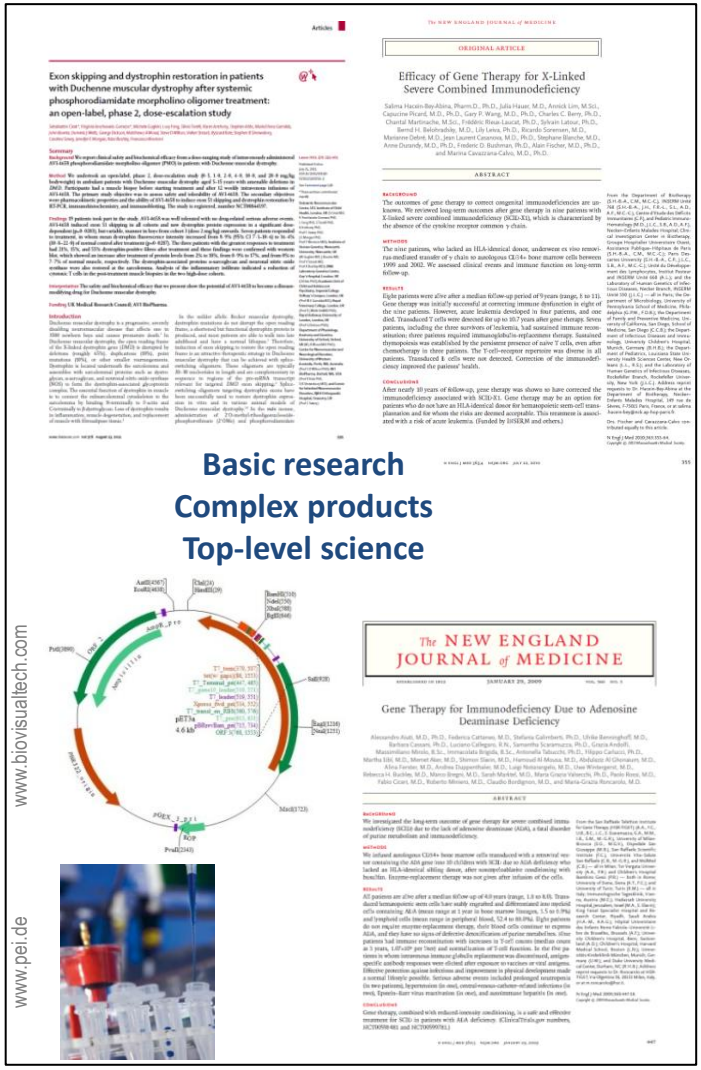
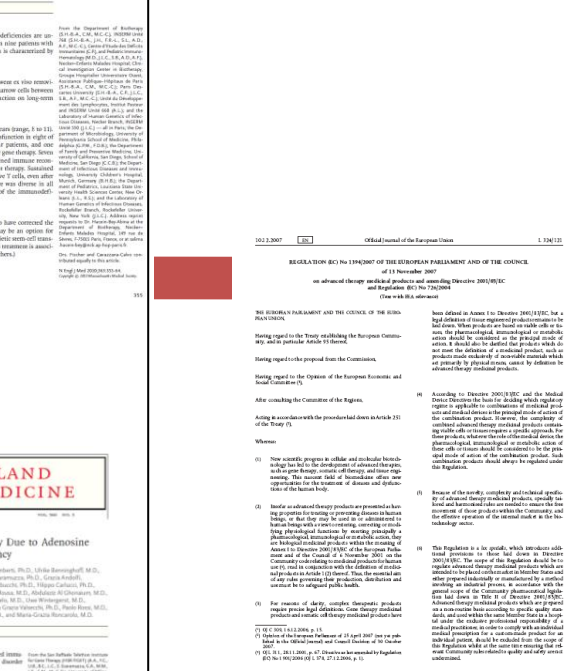
Our environment: The „academic gap“ and „small company gap“



Basic research
Complex products
Top-level science



Regulation 1394/2007
(„ATMP regulation“)

Directive 2009/120/EC
amending Directive 2001/83/EC
(”revised Annex I”)

Marketing authorisation

Translation into a medicinal product
(”translational medicine”)

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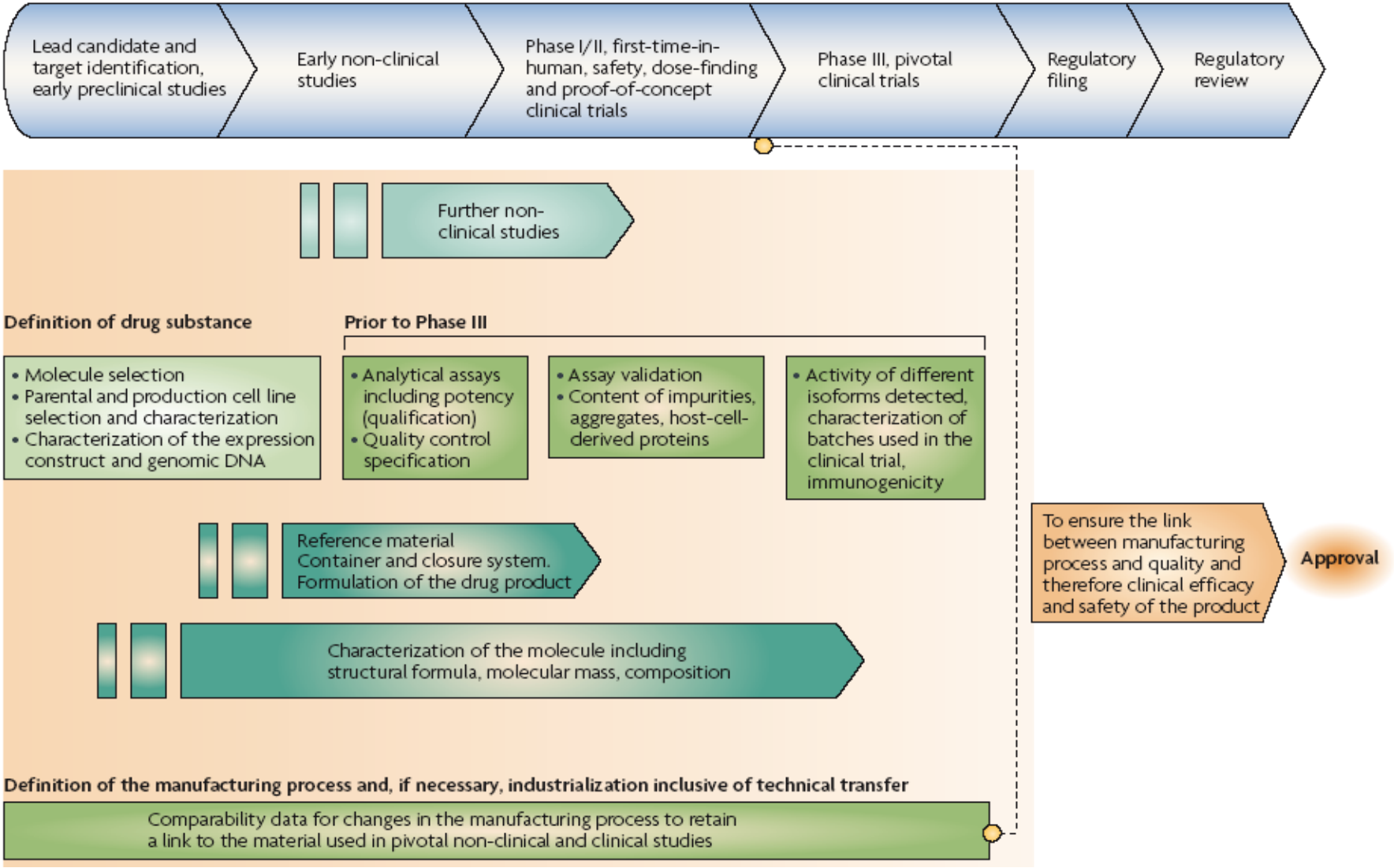
Development prior to approval



Schneider CK and Schäffner-Dallmann G (2008). Nat Rev Drug Discov 7(11): 893-899

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MANAGERIAL AND DECISION ECONOMICS
Manage. Decis. Econ. **28:** 469–479 (2007)
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/mde.1360

The Cost of Biopharmaceutical R&D: Is Biotech Different?

Joseph A. DiMasi[a,*] and Henry G. Grabowski[b]

[a] *Tufts Center for the Study of Drug Development, Tufts University, USA*
[b] *Department of Economics, Duke University, USA*

The costs of developing the types of new drugs that have been pursued by traditional pharmaceutical firms have been estimated in a number of studies. However, similar analyses have not been published on the costs of developing the types of molecules on which biotech firms have focused. This study represents a first attempt to get a sense for the magnitude of the R&D costs associated with the discovery and development of new therapeutic biopharmaceuticals (specifically, recombinant proteins and monoclonal antibodies [mAbs]).

We utilize drug-specific data on cash outlays, development times, and success in obtaining regulatory marketing approval to estimate the average pre-tax R&D resource cost for biopharmaceuticals up to the point of initial US marketing approval (in year 2005 dollars). We found average out-of-pocket (cash outlay) cost estimates per approved biopharmaceutical of $198 million, $361 million, and $559 million for the preclinical period, the clinical period, and in total, respectively. Including the time costs associated with biopharmaceutical R&D, we found average capitalized cost estimates per approved biopharmaceutical of $615 million, $626 million, and $1241 million for the preclinical period, the clinical period, and in total, respectively. Adjusting previously published estimates of R&D costs for traditional

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The ATMP landscape in Europe

commentary

Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive

Romaldas Maciulaitis[1,2], Lucia D'Apote[3], Andrew Buchanan[3], Laura Pioppo[3,4] and Christian K Schneider[1,5,6]

doi:10.1038/mt.2012.13

The first two authors contributed equally to this work.

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Correspondence: Christian K Schneider, c/o Danish Medicines Agency, Axel Heides Gade 1, DK-2300 Copenhagen, Denmark. E-mail: chsc@dkma.dk

Molecular Therapy vol. 20 no. 3 march 2012

Analysis of the EudraCT database (2004-2010):
318 trials with ATMPs

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Paper calls for continued support for development of advanced therapies

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News

13/03/2012

Paper calls for continued support for development of advanced therapies

The European Medicines Agency needs to continue reaching out to academic institutions, charities and small companies developing advanced-therapy medicines, according to a paper published in the journal *Molecular Therapies* earlier this month.

The paper, written by members of the Committee for Advanced Therapies (CAT), its secretariat and other European Medicines Agency staff, found that the main sponsors of clinical trials of advanced-therapy medicines performed in the European Union (EU) between 2004 and 2010 often have limited financial resources and a limited capacity to navigate regulatory procedures.

It argues that this causes a translational gap between development of these medicines and reaching later regulatory milestones, and that regulators need to continue working towards closing this gap in a proactive manner.

The paper emphasises the numerous ways in which organisations developing advanced-therapy medicines can engage in dialogue with the Agency and receive guidance on regulatory procedures. These include scientific advice, meetings with the Innovation Task Force, and classification or certification of medicines as advanced-therapy medicinal products by the CAT. The CAT has also run focus groups to discuss aspects of the development of advanced-therapy medicines with its stakeholders, and organised a scientific workshop with learned societies.

Advanced-therapy medicines are medicines that are made from genes and cells. They may offer groundbreaking new treatment opportunities for many diseases and injuries. All advanced-therapy medicines intended for marketing in more than one EU Member State are authorised centrally via the European Medicines Agency, following scientific evaluation by the CAT.

The analysis presented in the paper, which looked at clinical studies in the EU Drug Regulating Authorities Clinical Trials (EudraCT) database, found that over three-quarters of the advanced-therapy medicines under development were cell-based medicines. Most medicines were being studied in cancer, followed by conditions affecting the heart, blood vessels and blood.

Related information

- Clinical development of advanced therapy medicinal products in Europe: Evidence that regulators must be proactive
- Advanced therapies
- Committee for Advanced Therapies (CAT) work programme 2010 - 2015 (18/11/2010)

Contact point:

info@ema.europa.eu

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The ATMP landscape in Europe

commentary

Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive

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[1]*Committee for Advanced Therapies (CAT), European Medicines Agency, London, UK;* [2]*Clinics of Nephrology, Institute of Physiology and Pharmacology, Lithuanian Health Science University, Kaunas, Lithuania;* [3]*European Medicines Agency, London, UK;* [4]*University of Pharmacy, Palermo, Italy;* [5]*Danish Medicines Agency, Copenhagen, Denmark;* [6]*Twincore Centre for Experimental and Clinical Infection Research, Hannover, Germany*
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E-mail: chsc@dkma.dk

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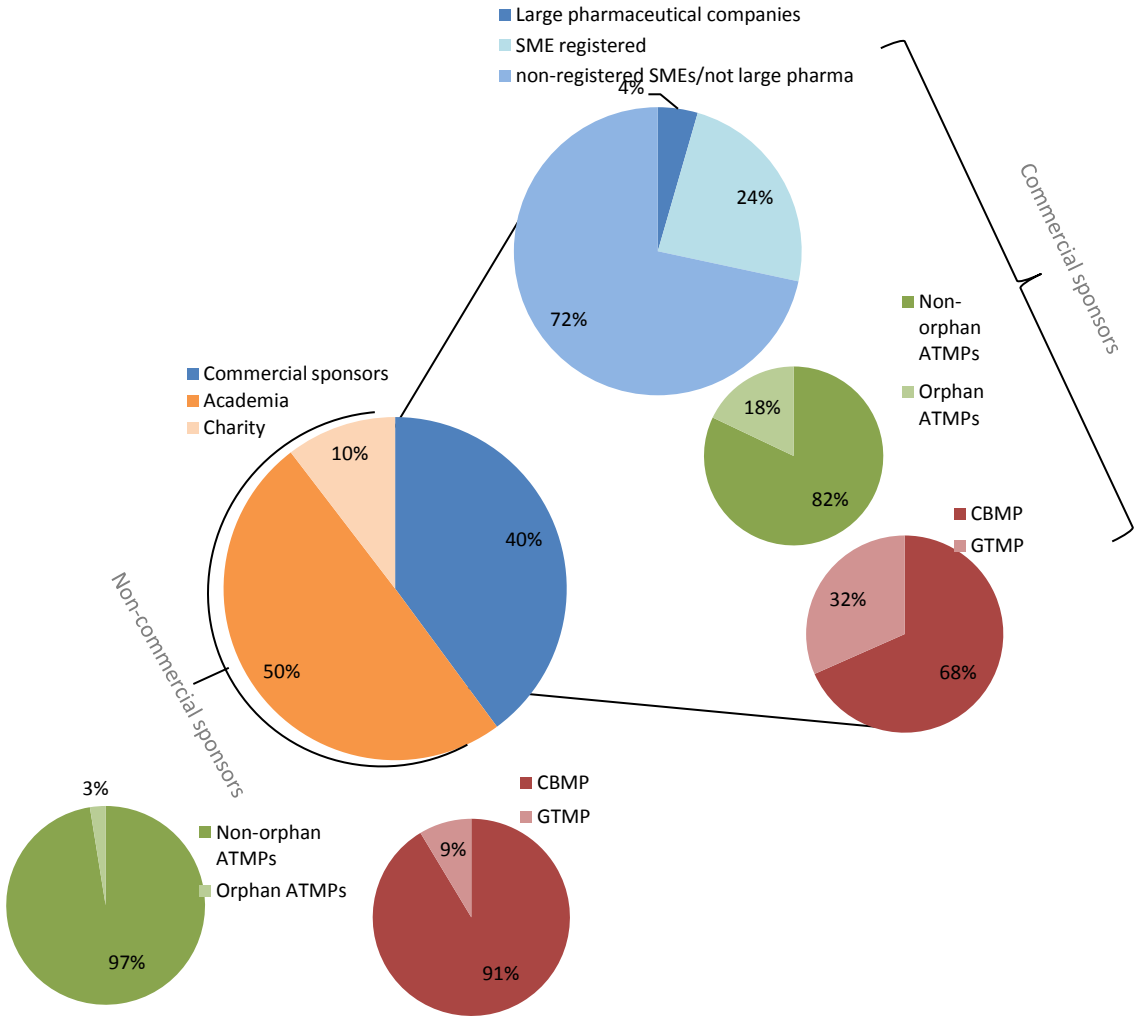

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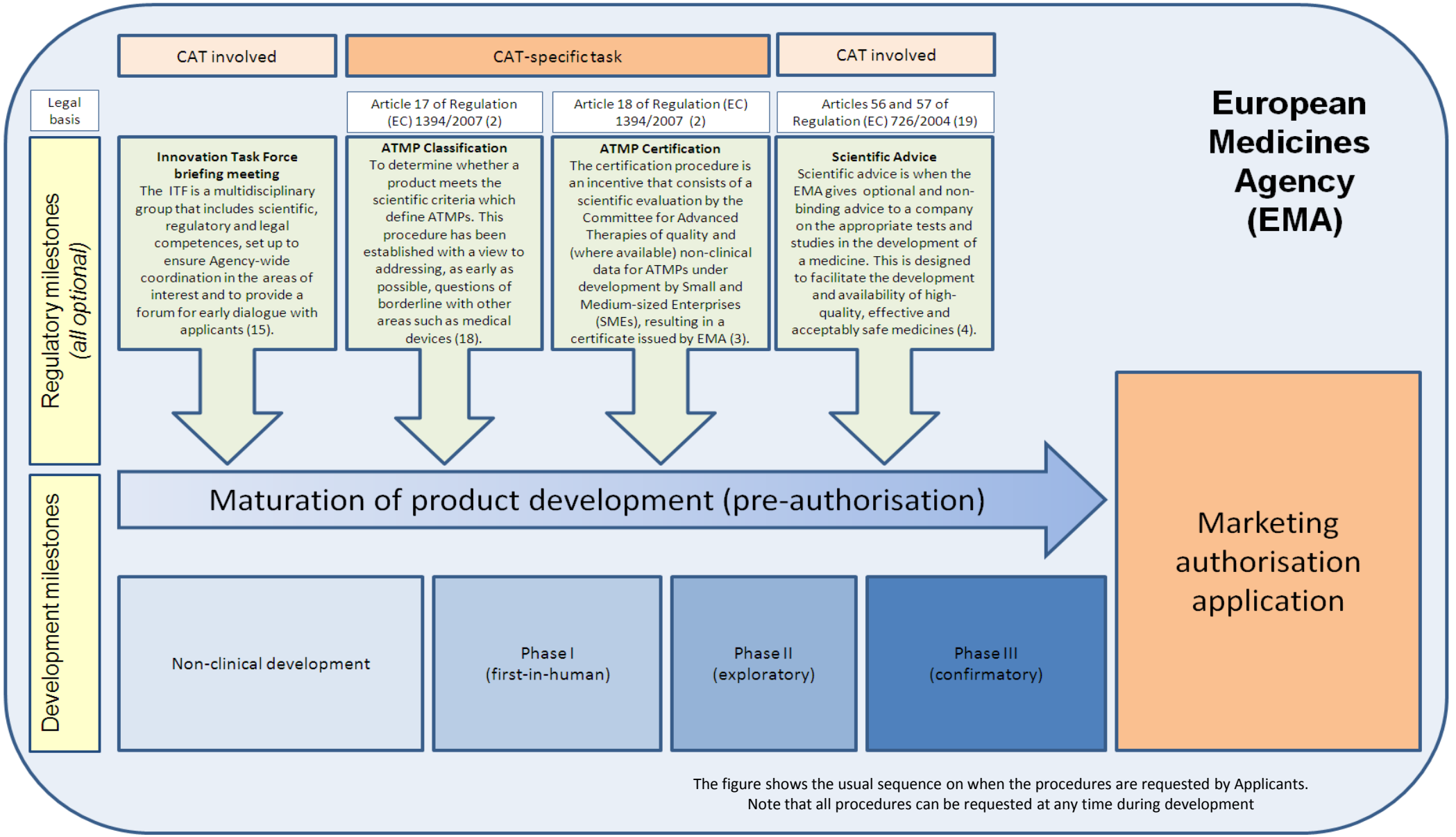
ATMP development and involvement of CAT



The figure shows the usual sequence on when the procedures are requested by Applicants.
Note that all procedures can be requested at any time during development

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  - Herbal products

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Innovation Task Force (ITF)

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The **Innovation Task Force (ITF)** is a multidisciplinary group that includes scientific, regulatory and legal competences, set up to ensure Agency-wide coordination in the areas of interest and to provide a forum for early dialogue with applicants.

▸ Mandate of the Innovation Task Force

Briefing meetings

The scope of the briefing meetings covers regulatory, scientific and other issues arising from the development of new therapies and technologies, -omics, nanotechnologies and combination borderline products.

The ITF, within eight weeks of receipt of a request from an applicant, arranges free-of-charge briefing meetings to facilitate the informal exchange of information and the provision of guidance early in the development process. Where appropriate, this is done in liaison with Agency scientific committees, working parties and expert groups, and takes into account ongoing international activities.

Briefing meetings are also meant to complement and reinforce existing formal regulatory procedures (e.g. designation of orphan medicinal products, CHMP scientific advice etc).

▸ Standard Operating Procedure for organisation of briefing meetings

Microsoft office documents

Important note on document formats: All Microsoft Office documents submitted to the European Medicines Agency must be in a format compatible with MS Office 2003. Office 2007 and Office 2010 formats cannot currently be accepted.

Contact point:

Requests for information on the ITF should be sent to ITFsecretariat@ema.europa.eu and/or info@ema.europa.eu

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800ba1d9

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  - Compassionate use
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  - Advanced therapies
    - EU Regulation
    - ATMP classification

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Interested parties to the CAT

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Call for interest - participation of interested parties in activities of the Committee for Advanced Therapies (CAT)

In January 2009 a new scientific committee started operating the European Medicines Agency, the Committee for Advanced Therapies (CAT). The CAT is a multidisciplinary committee who plays a central role in the scientific assessment and development of advanced therapy medicinal products (ATMPs).

ATMPs differ from conventional medicines in that they are based on genes and cells. There are three types of advanced therapy products defined in the relevant legislation: gene therapy products, somatic cell therapy products and tissue engineered products.

ATMPs are cutting edge innovative products that require specific expertise represented in the CAT. New guidance documents addressing the specificities of these products needs to be developed and the fast progress in the scientific field needs to be follow in order to allign the regulatory requirements to the current goal standards in science.

To succeed in the implementation of the ATMP legislation the CAT is fostering an active dialogue with industries, developers, academia, patients and clinicians to exchange scientific views and further develop the regulatory framework for the authorisation of ATMPs.

Involve your organisation in CAT activities

CAT recognizes the importance to establish a fruitful dialogue and working relationship with stakeholders in the field of advanced therapies.

The aim of this call is to establish a list of organisations with a view to creating permanent forum for interaction between the CAT and its interested parties.

Some examples of CAT interactions with interested parties may be:

- Participation in hearings with the CAT (general annual hearing or ad-hoc topic specific hearings) and its working parties.
- Proactive consultation in guideline under development.

The first CAT hearing with the interested parties is expected to be held on 11 September 2009