




Is there a need for a new regulatory pathway for biologics?

AT Europe 2017
Brussels
16 March 2017

famhp
Federal agency for medicines and health products


Alan Fauconnier

.be



Disclaimer

- Alan Fauconnier is quality assessor at the Federal Agency for Medicines and Health Products (FAMHP), the Belgian regulatory authority competent for medicinal products.
- Alan Fauconnier is also delegate at the Biologics Working Party (BWP) of the CHMP (EMA/London).
- However, this presentation represents a personal view which may not necessarily reflect the views of the FAMHP, the BWP, the CHMP, the EMA, the EDQM and/or other regulatory bodies.



2 .be

Agenda

- Past
- Present
- Future



3

.be

PAST



4

.be

When it all began...

The thalidomide disaster

- ❑ Between 1957 and 1961
- ❑ In about 50 countries
- ❑ Developed and sold by Chemie Grünenthal..
- ❑ under at least 40 different names (Contergan, Talimol, Distaval, Softenon...)
- ❑ Indicated for nausea and insomnia for pregnancy
- ❑ \pm 10.000 children with phocomelia



5

.be

Directive 65/65/EEC

- ❑ No product can be marketed in the EEC without an authorisation
- ❑ Application for authorisation has to contain specific information
- ❑ Application must be reviewed by Competent Authority in Member State
- ❑ Assessment from CA can be shared
- ❑ All changes to product must be notified



Directive 65/65/EEC



Laying down the basic concepts and definitions Medicinal product

Any substance or combination of substances presented for treating or preventing disease in human beings or animals.

Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions" in human beings or in animals is likewise considered a medicinal product.



7

.be

Directive 65/65/EEC



Proprietary medicinal product

Any ready-prepared medicinal product placed on the market under a special name and in a special pack.

COUNCIL DIRECTIVE
of 26 January 1965
on the approximation of provisions laid down by law, regulation or administrative
action relating to proprietary medicinal products
(65/65/EEC)



**As as opposed to the magistral formula or
official preparations**



8

.be

The early EU regulation of biologics



- 1975 : setting up the first EU Committee, i.e. Committee for Proprietary Medicinal Products (CPMP) Brussels
- 1987 : concertation procedure for « high-technology medicinal products, particularly those derived from biotechnology » i.e.
 - *recombinant DNA technology,*
 - *controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells,*
 - *hybridoma and monoclonal antibody methods*



9

.be

Quality



Ad hoc Working Party on Biotechnology/Pharmacy

working group of the CPMP addresssing the quality of biotech medicinal products



10

.be

Vaccines, toxins or serums and allergens



Directive 89/342/EEC

- composition of the product expressed in terms of biological activity or of protein (instead of mass or volume).
- Batch release by official control laboratories



11

.be

Infected blood scandal

- HIV contamination of haemophiliacs in 1984-1985
- Realize the seriousness in 1986 onwards
- France: scandal culminated in April 1991
- Thousands of infections worldwide
- In FR, 2000 persons contaminated (50%)



12

.be

Plasma & blood derived MP



Directive 89/381/EEC

- ▣ quantitative particulars ... shall be expressed ... by units of biological activity.
- ▣ Viral safety measures.



13

.be

The early EU regulation of biologics



Regulation 2309/93

- ▣ 1993
- ▣ establishing the European Agency for the Evaluation of Medicinal Products (EMA)
- ▣ laying down the Centralised Procedure (CP)
- ▣ Mandatory for biotech medicinal products
- ▣ CPMP/CVMP
 - housed by the EMA (London)
 - grant opinions...
 - to the European Commission which issues Decisions



14

.be

The turn of the millenium



- ▣ historic Directive 65/65/EEC repealed...
- ▣ ... and replaced by Directive 2001/83/EC
- ▣ occurrence of new biotherapeutic products/practices



15

.be

Gene therapy



Première médicale de portée mondiale à l'hôpital Necker. Deux bébés-bulles sauvés par la thérapie génique. Leur traitement par modification des gènes a réussi.

Par Corinne Bensimon — 28 avril 2000 à 23:45

Medical world premiere at the at hospital Necker. Two babies «in the bubble» saved by gene therapy. Their treatment by gene modification has succeeded.



16

.be

Cell therapy



Viable autologous cartilage cells expanded ex vivo, indicated for the repair of cartilage defects of the femoral condyle of the knee



17

.be

Regulating the new therapies



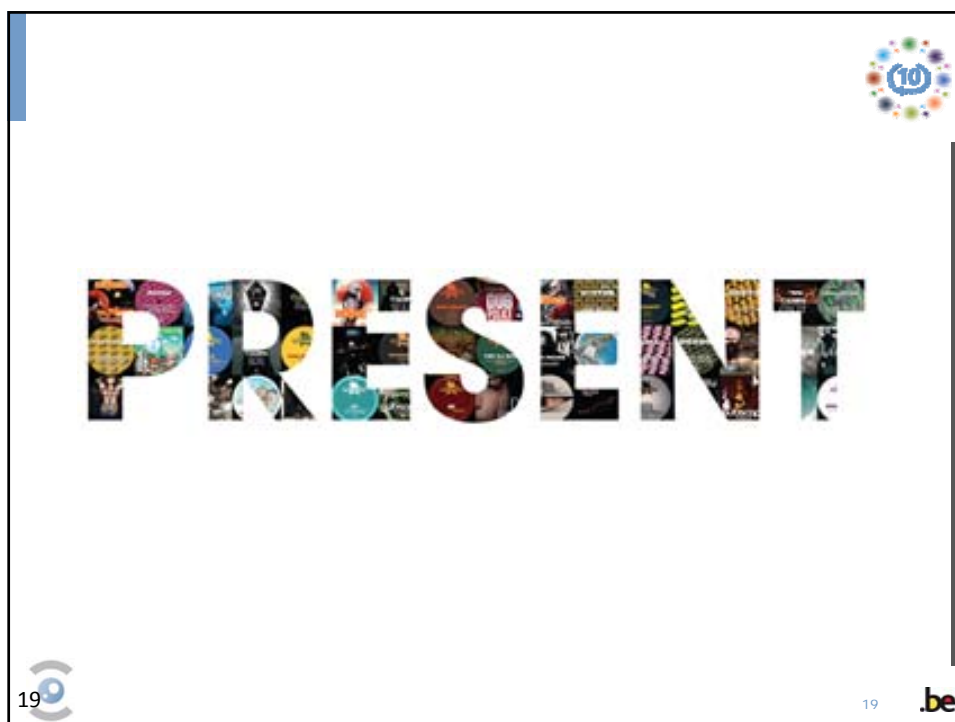
Community legislator is seeking to regulate these new therapies...

but the regulatory framework on that time was not quite suitable



18

.be



New provisions

Directive 2003/63/EC amending 2001/83/EC

- ▣ Replacement Annex I : CTD format introduction
- ▣ Including Part IV on « Advanced Therapy Medicinal Products » (ATMP)
 - Gene therapy medicinal products (GTMP)
 - Somatic cell therapy medicinal products (SCTMP)

L 159/88 EN Official Journal of the European Union 27.6.2003

PART IV

ADVANCED THERAPY MEDICINAL PRODUCTS

Advanced therapy medicinal products are based on manufacturing processes focused on various gene transfer-produced bio-molecules, and/or biologically advanced therapeutic modified cells as active substances or part of active substances.

For those medicinal products the presentation of the Marketing Authorisation application dossier shall fulfil the format requirements as described in Part I of this Annex.

Modules 1 to 5 shall apply. For Genetically Modified Organisms deliberate release in the environment, attention shall be paid to the persistence of the Genetically Modified Organisms in the recipient and to the possible replication and/or modification of the Genetically Modified Organisms when released in the environment. The information concerning the environmental risk should appear in the Annex to Module 1.

New regulations



- ❑ **Regulation 726/2004** (repealing and replacing 2309/93) establishing the European Agency for the Evaluation of Medicinal Products (EMA) laying down the Centralised Procedure
- ❑ **Directive 2004/23/EC** : **Tissues and cells**
- ❑ **Regulation 1394/2007** : **ATMP**
 - Committee for Advanced Therapies (**CAT**)
 - covers GTMP and SCTMP
 - plus tissue engineered products (**TEP**)
 - & combined ATMP (with a « medical » device)
 - **Hospital exemption** (no licensing required under conditions)



21

.be

Shaping the regulation



Directive 2004/27/EC amending 2001/83/EC

- ❑ Autologous SCTMP/TEP do not fit with the concept of proprietary medicinal product:

Any ready-prepared medicinal product placed on the market under a special name and in a special pack
- ❑ Removal of « proprietary medicinal » definition and replacement by

Medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.



22

.be



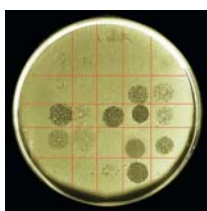
Future regulatory development

- Seeds of future regulation can be found in the currently applicable one
- 1394/2007 introduced an exemption in the application of Directive 2001/83/EC: Marketing authorisation is not required for...

*Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non- routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription **for a custom-made product for an individual patient.***

Phage therapy

Collection of phages: each phage is tested on the bacteria isolated from the patient



On the basis of the « phagogram », a cocktail of phages will be formulated in a medicinal product for treating an infection with the corresponding bacterial isolate.

meaning that:

- ▣ cocktails customized for patient
- ▣ adapted over time if the phage resistance profile of bacteria is evolving.
- ▣ new phages could be added to the collection

NO PREDETERMINED COMPOSITION



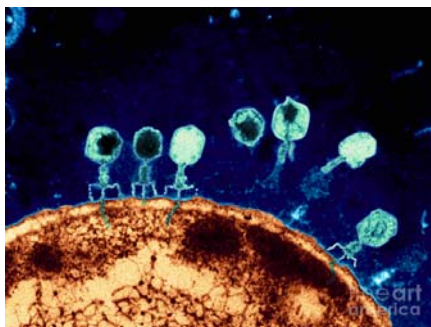
25

.be

Phage therapy

Phage therapy medicinal products (PTMP) have no predetermined composition...

... not in accordance with the requirement for qualitative and quantitative composition to be fixed in advance, specified in the application and reported in the product information (Dir. 2001/83/EC)



26

.be

Industrially-prepared versus custom-made



Customized PTMPs are somewhere between magistral formulas and industrially made medicinal products

A situation not addressed within the current European regulatory framework



27



Industrially-prepared versus custom-made



- Industrially prepared active pharmaceutical ingredients (API)
 - Licensing process: approval of regulatory authorities (RA)
 - Quality and safety (non clinical) driven
 - GMP compliance
 - QP release
 - Under responsibility of industry and RA
- Custom made finished product
 - Magistral formula
 - Efficacy and safety (clinical) driven
 - Under the responsibility of prescriber and (hospital) pharmacist



28



New regulatory framework



- ❑ Instead of addressing the licensing of the finished product as a whole...
- ❑ ... licensing of part of the process, e.g. API quality & safety
- ❑ Gives rise to the concept of **Biological Master File (BMF)**



29



Biological Master File concept



BMF

- ❑ initial licensing preceding the marketing authorisation
- ❑ ensures appropriate control of (at least) part of the process, in contrast to the weakly controlled magistral formula process
- ❑ introduces liability of API manufacturer and RA
- ❑ valuable in other contexts
- ❑ SME-supportive



30



BMF as applied to biosimilar regulation



Biosimilars

- relies on the approval of a MAA
- including a comprehensive quality (Q) package
- extent of non-clinical (NC) and clinical (C) package depends on the similarity with at reference product as determined at the quality level.
- Thus, the required clinical development can only be designed after the quality comparability exercise has been achieved.



31



BMF as applied to biosimilar regulation



instead of submitting the application in a single package, including Q, NC & C as a whole:

- uncoupling the Q comparability exercise from the C assessment.
- Q comparability exercise submitted beforehand as BMF
- On the basis of the licensed Q comparability exercise...
- ... C development could be optimally designed



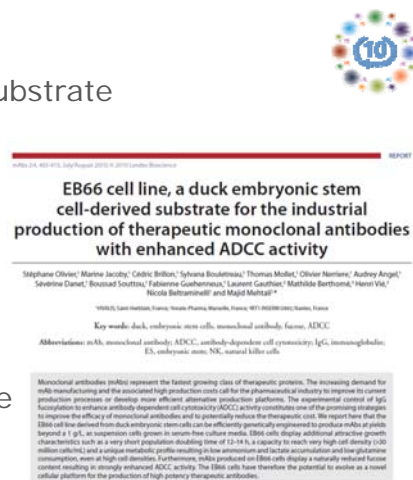
32



BMF: a win-win concept

e.g. Premarket licensing of cell substrate

- ❑ SME would advocate to its customers that the cellular material has already been reviewed and approved by RA.
- ❑ pharmaceutical company could be confident that the cell substrate on sale is meeting the regulatory requirements and quality pharmaceutical standards.
- ❑ RA could avoid reassessment of the cell substance section since it is already covered by the BMF licensing.



33



Conclusions

- ❑ Biotherapeutics formerly required the setting of novel regulatory pathways
- ❑ In the future, they could pave the way to the regulation of tailor-made health products needed within the context of personalized-medicine.



34



Phages as a model



Phages were recognised as highly valuable models during the early days of molecular biology

I am please to imagine that the Phage Group pioneers would have appreciated learning that the model they chose decades ago remains so in the separate but promising context of personalized-medicine.



Max Delbrück and Salvador Luria



Thanks



36

.be

Contact



Federal Agency for Medicines and Health Products – FAMHP

Place Victor Horta 40/40
1060 BRUXELLES

tel. + 32 2 528 40 00
fax + 32 2 528 40 01
e-mail welcome@fagg-afmps.be

www.afmps.be



37



Your medicines and health products,
our concern

