

# GMO Technology Conference



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## The regulation of Clinical Trials on humans involving therapies containing or consisting of genetically modified organisms

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# Overview

- Introduction and role of IMB
- Regulation of medicines including GMO's
- Clinical Trials regulation
- GMO's used in clinical trials and safety considerations
- Experience and conclusion



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# Introduction

- Regulation of medicines in EU governed by Directive 2001/83/EC
- Covers **all** medicines with the objective of safeguarding public health
- At the same time fostering development and trade
- Key principles
  - Safety
  - Quality
  - Efficacy
- Irish Medicines Board is the CA in Ireland

# Irish Medicines Board Overview

- IMB Act 1995
- Implementation January 1996
- Competent Authority human medicines 19/2/96 as well as animal medicines, medical devices etc.
- New regulations made since under IMB Act
- Board membership 9 (Management role) + Scientific Committees
- Staff numbers 300 in 2013
- Self financing body – income based on application fees

# The IMB Mission

**To protect and enhance public and animal health through the regulation of human and veterinary medicines and medical devices available in Ireland, or manufactured in Ireland for Irish or export markets.**



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# Directive 2001/83/EC as amended

- Concept of risk assessment formally introduced into assessment and inspection activities
- Environmental risk to be routinely evaluated for each product [Article 8(3)(ca)] to be placed on the market
- Risk-benefit evaluation to be conducted as part of the authorisation process, and on ongoing basis
- MA holder required to supply any new information affecting the risk-benefit balance of the product on an ongoing basis as new information becomes available
- Responsibilities of MA and manufacturer more clearly defined in the Directive (e.g. Articles 6, 23, 26).



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# Advanced Therapy Medicinal Products

- EU Regulation 1394 of 2007 formally includes advanced therapy medicinal products (ATMPs) in the definition of a medicinal product
- ATMP
  - gene therapy medicinal product
  - somatic cell therapy medicinal product
  - “tissue engineered products” which are products containing engineered cells or tissues intended to replace body tissues but may contain other substances with pharmacological effects



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# Advanced Therapy Medicinal Products (2)

- Application for marketing authorisation via EU centralised procedure is compulsory (EMA)
- Post authorisation follow up of efficacy, adverse reaction etc. enhanced – at national level
- Special requirements on traceability both directions
  - back to source material
  - forward to institution and patients
- Extended record keeping 30 years
- Scientific advice to support product development from EMA especially for SME's



# ATMP (3)

## Hospital Exemption Scheme

- Article 28 of Regulation 1394/2007 opened an exemption for the limited use of ATMP in a hospital setting
- No marketing authorisation necessary where:
- Product prepared on a non routine basis according to specific quality standards
- Used in the same Member State
- In a hospital under the exclusive professional responsibility of a medical practitioner
- In order to meet the needs of a specific patient



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## Hospital exemption continued

- The manufacturing operation for such products is still subject to competent authority supervision and licensing
- The requirements of GMP must be met
- National traceability scheme for such products is required
- Pharmacovigilance requirements must be established by the institution
- Appropriate quality standards must be maintained
- Record keeping requirements (30 years) apply to the institution

# Regulation of Clinical Trials in Ireland

- The Control of Clinical Trials Acts 1987 – 1990
  - First system in Ireland for regulation of all studies in humans involving medicinal products
  - Covered Phase I – IV; including ADME studies
  - Issues of indemnity arose
- 1990 amendment needed to address immunity issue
- Hospital based ethics committees
- Trials approved by Minister for Health in consultation with NDAB
- Process was thorough but slow improved when IMB replaced NDAB as responsible authority

# European Directive 2001/20

- EU Commission saw a clear need to standardise the regulation of CT's across EU
- Variable systems operated in MS
- Some MS excluded volunteer studies (ADME)
- Other systems like that in Ireland were more thorough
- EU Directive 2001/20 on the implementation of GCP in conduct of CT's in humans adopted 4/4/2001
- 10 year revision underway



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# IMB Development in CT'S

- Clinical Trials Directive 2001/20/EC-first EU system
- Need separate manufacturers licence for IMP's
- Increased GCP and vigilance inspections
- Strict procedures/timelines for CT approval
- Revision of Control of Clinical Trials Act 1987-1990 with new regulation in place 2004
- IMB assesses scientific approval and separate REC ethical approval
- Single National Ethics Committee envisaged by Directive?

# Clinical Trials – New EU Developments

- EU Commission consultation 2010 and 2011
- Proposing a new EU regulation to standardise approval process and timelines across EU
- Single application through EU e-portal
- One MS will become Reporting MS in charge of approval process including ethical aspects in parallel
- Short timeframes to encourage application
- Restricted grounds for rejection
- Simplified extensions of approved trials to other MSs

# Environmental Issues

- Genetic modification of microorganism such as bacteria and viruses may have significant environmental impact
- Deliberate release is defined as the intentional introduction of a GMO into the environment with no constraint measures
- Includes use of GMO's in patients e.g. in clinical trials
- Effect of GMO could include
  - spreading
  - undergoing genotypic or phenotypic change
  - competing with existing species
  - infecting tissues
  - transferring genetic material to other microorganisms, humans or animals



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# Environmental Risk Evaluation

- Genetically modified organisms can have significant environmental impact
- All applications for MA for products containing a GMO or GMM must be authorised centrally in EU (EMA)
- Directive 2001/18/EC requires an applicant to conduct an environmental risk assessment (ERA)
- Part C of 2001/83/EC does not apply to a medicinal product containing a GMO provided ERA has been completed



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# Environmental Risk Evaluation (2)

- The MA application made to EMA must contain the environmental impact documentation including the ERA
- The ERA and other environmental documentation in accordance with Annex II of 2001/83/EC will be evaluated by the appropriate environmental competent authority (such as EPA)
- The environmental CA in the country where product is to be first placed on the market reviews these data
- EMA designated rapporteur collaborates with environmental CA to ensure that the ERA is satisfactory
- In this way the requirement in medicines legislation for ERA is satisfied
- The product cannot be authorised in the absence of satisfactory ERA
- Single evaluation is then valid for all EU



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# Environmental Risk Assessment (3)

- Effect of GMO on the environment includes living or non-living, human or non-human inhabitant, component or compartment of the ecosystem
- Evaluates dispersal, accidental dissemination, disposal or excretion of the product
- Effects could be direct – infection of a family member through contact or indirect further recombination with a wild type strain
- Once satisfactory review of ERA has concluded, product can be marketed
- Conditions of marketing authorisation will include information to patients on risks, precautions and directions for safe use and disposal



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# GMO's used in clinical practice

- Gene therapy products
- Genetically modified cells and tissues
- Tissue-engineered products
- Products containing genetically modified microorganisms e.g. viruses, bacteria, viral and non-viral vectors, vaccines etc
- Combination GMO medicinal product with medical device



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# Clinical Trials of GMO's

- Relative lack of clinical experience of GMO's
- Such products might persist in humans for an extended period even after a single administration
- GMO's might have extended duration of effect even after the product has been cleared from the recipient
- Unexpected effects might evolve over time e.g. stem cells which proliferate and differentiate
- Safety evaluations likely to involve extended subject monitoring



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## Clinical Trials of GMO's (2)

- Risks may be enhanced by the need to use an invasive procedure to deliver product to the target site
- GMO's and their products (proteins) might elicit a specific immune response causing an adverse response or suppressing a beneficial response
- Patients treated might develop antibodies which might jeopardise a future transplantation



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# Cell therapy product considerations

- Dynamic nature of living cells
- Cells carry a variety of molecules on their membrane and express a variety of control factors
- These molecules and factors give rise to different effects and may change over time
- Cells differentiate *in vivo*
- Cells might develop undesirable autonomous functions
- Stem cells might differentiate and be transformed into tumours
- Cells might migrate away from the target site and give rise to unwanted effect elsewhere
- Autologous cell therapy might double the risk to the subject

# Gene therapy product considerations

- Expression of a delivered gene may be uncontrolled and unbalance normal function
- Genes integrating into recipient DNA to give long term expression
- Genetic integration could activate or switch off neighbouring genes giving rise to possible adverse events
- Gene therapy products might carry a risk of possible bacterial or viral shedding



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# Genetically modified microorganism as medicines

- Genetically modified viruses or bacteria used as therapeutic agents e.g. vaccines
- Viral or non viral vectors used to deliver genes can generate therapeutic consequences in themselves
- Will elicit an immunological response which may or may not be desired
- A desired response might well be obtained in an otherwise healthy patient – e.g. vaccine
- Furthermore vaccines are administered to whole populations of otherwise healthy individuals including children



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# Experience to date

- Limited numbers of GMO medicinal products on the market
- EU approved 2 ATMPs- 1CTP and 1 GTP
- There appear to be a number of such products in various stages of clinical development
- Many such developments in SMEs or campus based companies
- IMB has approved only 1 CT with a gene therapy medicinal product to date



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# Conclusion

- So while application for authorisation for marketing ATMP's including products containing GMO's must be made centrally in EU
- Applications for approval of clinical trials of these IMP's is made nationally in each Member State in accordance with harmonised rules and timelines
- MS urged to collaborate where trials planned in more than one country
- However a consultation with the relevant environmental authority is required in each EU MS where the trial takes place



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# Abbreviations and acronyms

|        |   |
|--------|---|
| ADME   | Absorption, distribution, metabolism, elimination   |
| ATMP   | Advanced Therapy Medicinal Product                  |
| CA     | Competent (= Licensing) authority                   |
| CT     | Clinical Trial                                      |
| EMA    | European Medicines Agency (London)                  |
| ERA    | Environmental Risk Assessment                       |
| GCP    | Good Clinical Practice                              |
| GMP    | “ Manufacturing Practice                            |
| IMP    | Investigational Medicinal Product (i.e. used in CT) |
| MA (H) | Marketing Authorisation (Holder)                    |
| SME    | Small and medium sized enterprises                  |

IMB [www.imb.ie](http://www.imb.ie)

EMA [www.ema.europa.eu](http://www.ema.europa.eu)



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# Questions

Thank you for your attention

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