ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

European Medicines Agency (EMEA)

European Society of Gene and Cell Therapy (ESGCT)

European Network of Excellence in Gene Therapy

EMEA/ICH WORKSHOP ON VIRAL/VECTOR SHEDDING

Tuesday **30 October 2007 (11.00-18.30)**

in conjunction with:

The XVth Annual Congress of the European Society of Gene and Cell Therapy

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CHMP GTWP

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Remarks

- Regulators have a medical and/or scientific education, some carry out experimental science and publish,
  - but as regulators they support product development
  - because they know legal and guideline regulations and
  - because they gain experience from the review of a variety of data presented to them in clinical trial and/or product applications.

- The contributions of the audience made during the discussions are highly appreciated.

- I would like to thank the speakers for very informative presentations.

Notes from Session 1: regulatory requirements in the ICH regions

- All regions require an assessment
  - of the shedding probability and
  - of the risks for adverse effects in humans (not being the patient) resulting from this.

- These assessments are applied
  - at the stage of clinical trial and
  - at the stage of licensing (marketing authorisation).

- The experimental assessment is made
  - in nonclinical studies and
  - in some, but not all clinical studies.

- There is a stepwise and a case-by-case approach in all ICH regions.

Notes from Session 1: regulatory requirements in the ICH regions

- The risk assessments made are based on
  - data with the respective product,
  - data accumulated on the vector class and
  - theoretical scientific assumptions about risks.

- There is no per se and general requirement for transmission studies.

- The concern is
  - adverse effects resulting from transmission of vector nucleic acids, vector sequences, recombined viruses/organisms/new pathogens to
  - humans, animals, less so plants, micro-organisms.
- Environmental reservoirs preserving entities possibly transmitted may also be in the focus.

Notes from Session 1: regulatory requirements in the ICH regions

- The risk assessment may be based on experimental assessment of the specific product in nonclinical studies of the
  - biodistribution (non-target distribution to organs, tissues, specific cell types) of vector based on PCR,
  - presence of vector nucleic acid sequences in bodily fluids and excreta,
  - presence of infectious vector or micro-organism/vector derived from vector or micro-organism/vector mobilising vector
  - probability of transmission to humans, animals, non-living reservoirs for later transmission of infectious vector or micro-organism/vector derived from vector or micro-organism/vector mobilising vector.

Notes from Session 1: regulatory requirements in the ICH regions

- If some of the listed experimental assessments are
  - not available,
  - incomplete or
  - have not been collected or
  - if the risk is not considered to be existant or
  - if it is considered to be low,

  - there is a theroetical assessment substituting for this.

Notes from Session 2: nonclinical and clinical assessments

- Excreta
  - urine,
  - faeces,
  - saliva,
  - semen,
  - breast milk,
  - plasma/ blood,
  - sputum,
  - swabs (buccal, vaginal,..).

Notes from Session 2: nonclinical and clinical assessments

- Tissues, organs for biodistribution
  - serum
  - BM,
  - brain,
  - heart,
  - kidney,
  - liver,
  - lung,
  - etc.

Notes from Session 2: nonclinical and clinical assessments

- Appropriate animal models for shedding studies
  - mice,
  - rats,
  - rabbits,
  - small animals appropriate to mimick shedding similar to that expected from humans.

- Appropriate animal models for transmission studies:
  - mice,
  - primates,
  - others?

Notes from Session 2: nonclinical and clinical assessments

- Assay validation
  - level of sensitivity of the PCR and the infectivity assays,
  - quality of the samples, their collection and their storage.

- Shedding assays
  - product nucleic acids,
  - infectious/transmissible entities such as non-replicating and replicating viruses.
- Assays
  - No shedding by a specific excreta assumed if vector nucleic acids were not detected at three consecutive time points by PCR or RT-PCR.

Notes from Session 2: nonclinical and clinical assessments

- Assays
  - It may suffice to use the same route of administration in the animal model as to be used or used in humans.
  - It may suffice to use the identical absolute maximum product dose in animals that will be used in humans.
  - A wost case scenario may not have to be experimentally investigated if suitable experience is available.

Notes from Session 2: nonclinical and clinical assessments

- Non-pathogenic vectors/viruses may still require shedding studies.
- May experience showing absence of shedding or absence of observed adverse effects in humans relating to shedding lead to absence of requirements for experimental assessment of shedding/transmission?
  - Do some products pose no risk?
  - Are some products not shed, i.e. not detectable in secreta to the sensitivtiy of the assays used?
- Should household contacts or hospital personnel be tested for presence of vector, e.g. in their blood?

Notes from Session 3: product-specific considerations

- Adenovirus
  - Shedding is known and
  - risks have not been encountered.

- AAV
  - is extensively biodistributed,
  - shedding is known,
  - virus Is non-pathogenic
  - risks are estimated to be very low.

- Platform studies should be accepted.

Notes from Session 3: product-specific considerations

- Seneca Valley Virus
  - animal virus, non-pathogenic,
  - selectivity for human cancers,

  - minimal toxicity in animals including primates,
  - transmission studies in mice showed no detectable transmission,
  - biodistribution study done in mice by PCR,
  - infectious virus studies difficult due to inhibitors,
  - RT-PCR and infectious virus assays correlate exellently,

  - i.v. administration in patients showed no dose-limiting toxicity,
  - isolation of patients, disinfect secreta, monitored viral shedding,
  - shedding not fully correlated with viral load in serum,
  - neutralising antibodies may reduce/prevent shedding or transmission,

Notes from Session 3: product-specific considerations

- Measures taken to reduce the risk of transmission
  - barrier contraception for patients,
  - patient isolation until no shedding could be detected,
  - gogles, masks, appropriate goun, gloves, for hopsital staff and other contacts during time of shedding,
  - non acceptance as blood, organ, tissue or cell donors,
  - avoid contact with humans suffering from acute virus infections,
  - personal hygiene,
  - disinfection measures including faeces and urine, toilets,
  - negative pressure in patient room/treatment ward/theater.

Conclusions (1)

- The viral/vector shedding issue may not include considerations for
  - containment/isolation of the patient,
  - biosafety level of the wards,
  - measures for handling/inactivating product,
  - measures assuring quality of samples and exact sampling regimen.

- Assessment of viral/vector shedding and related risks does not take into account
  - formal differences between GMO- and non-GMO entities, because the same principles apply,
  - definitions of “gene therapy product”, which are different between the regions.

Conclusions (2)

- Defining the terminology
  - What is biodistribution?
    - Distribution of vector nucleic acid and/or delivery vector to target and non-target organs, tissues and cells.
  - What is shedding?
    - Presence of infectious/transfection-capable delivery vector in excreta.
  - What is transmission or environmental risk?
    - Transmission of vector nucleic acids to humans or animals by transmission of infectious/transfection-capable delivery vector, replicating virus/micro-organism, recombination product encompassing vector nucleic acids

Conclusions (3)

- Defining the shedding issue
  - What is the adverse effects related to shedding, which we are concerned about?
    - Example from live virus vaccines are vaccine-related poliomyelitis induced by transmission of vaccine virus reverted to wildtype poliovirus, transmitted to contact persons of the vaccinee and causing disease.
    - Ehtically: tranmission of GMO, vector nucleic acid or infectious vector particles ot other humans
  - Are we concerned
    - only for humans,
    - also for animals,
    - for public and animal health,
    - plants, micro-organisms, viruses?

Conclusions (4)

- Are we concerned
  - only for humans,
  - also for animals,
  - for public and animal health,
  - plants, micro-organisms, viruses?

  - We are mostly concerned for humans including
    - health care workers, hospital staff
    - family contacts
    - other humans (not being the patient).

Conclusions (5)

- When should shedding data with the specific products be collected?
  - During non-clinical studies,
  - Maybe already prior to first clinical use,
  - Followed by a theoretical scientific assessment of the risk for other human beings (not being the patient).

  - Also during (at least) one clinical study at an early time of product development (phase I or II?).

- Assessment of shedding risks needs a data basis on
  - Risk of transmission to animals and
    the risk of them presenting a reservoir for additional transmission to humans,
  - Risk of persistence in reservoirs (sewage)
    and the risk of them presenting a reservoir for additional transmission to humans.

Conclusions (6)

- What should be the excreta assessed in nonclinical and clinical studies?
  - Clear list available (faeces, urine, gargle, urine, swabs etc.).
- What are the appropriate/usual assays?
  - PCR, RT-PCR,
  - infectious virus assays
- Are their instances for which transmission studies may be useful/required?
  - ?

Conclusions (7)

- What is the required assay sensitivity?
  - Assay according to state of science and technology at time of submission.
- What shedding or transmission data do not usually have to be collected?
- Which products may not require any shedding assessment?
  - Genetically modified cells not containing replicating virus.
  - Products for which convincing scientific evidence for absence of shedding or absence of adverse effects on humans from transmission or absence of persistence in and transmission from reservoirs is available.
- When can theoretical scientific considerations replace experimental data?
  - See above.

Conclusions (8)

- How can the samples taken and assays carried out represent the whole sample, e.g. of urine?
  - RCR testing in vector batches required to represent the whole volume of the batch.

Conclusions (9)

- Regional considerations
  - Do all non-clinical shedding studies require GLP?
  - Do all non-clinical shedding studies have to be done with the GMP clinical trial material?

Definition of shedding in gene therapy

- Shedding in the field of gene therapy

  may be defined as

  - dissemination and/or transmission of
  - gene therapy product or product-related vector or infectious agent
  - from bodily fluids and excreta of the treated subject or patient
  - to humans other than the patient,
  - taking presistence in animals, plants or other environmental reservoirs into account as a possible reservoir for transmission to humans.

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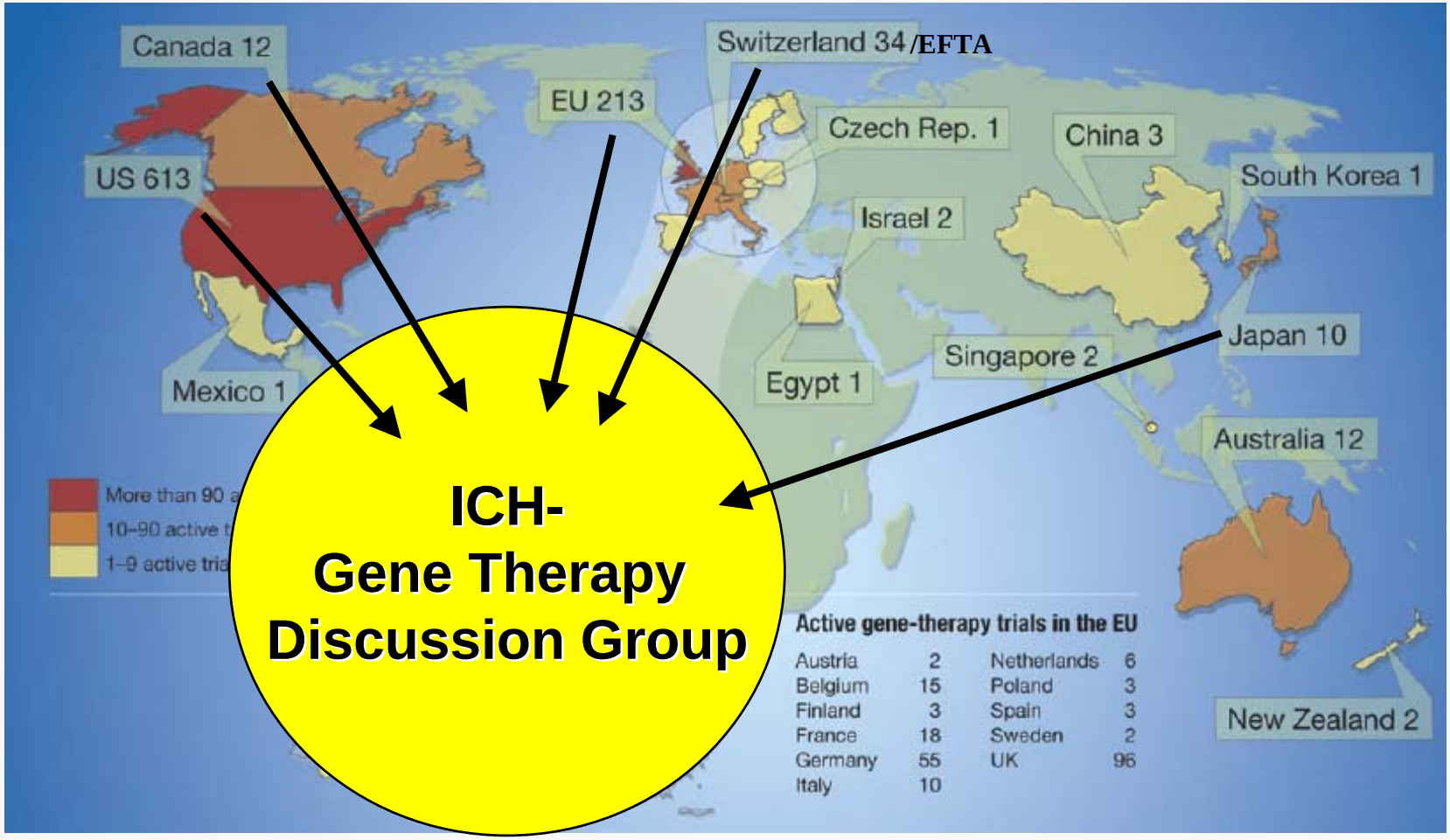
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