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Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

GLP-vaatimukset ATMP-valmisteiden turvallisuustutkimuksissa

Keskustelutilaisuus ATMP-toimijoille GLP-vaatimuksista
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Lainsäädännöllinen tausta

ATMP (advanced therapy medicinal products) ovat lääkkeitä, joiden markkinoille saattaminen edellyttää myyntilupaa, jonka arviointi tapahtuu keskitetysti EMAn kautta, ja myyntiluvan myöntää Euroopan komissio koko Euroopan yhteisön alueelle.

- *Dir 2001/83/EC as amended*
  - *Annex I Part IV (Dir 2003/63/EC)*
  - *Reg 1394/2007*

- Lääkkeitä koskevat yleiset myyntilupavaatimukset
  - Ei-kliiniset (farmakologis-toksikologiset) tutkimukset on suoritettava hyvän laboratoriokäytännön (GLP) periaatteiden mukaisesti
    - *Annex I Part I (Dir 2003/63/EC)*

- ATMP tuotteita koskevat lisäksi erityiset vaatimukset
    - *Annex I Part IV (Dir 2009/120/EC)*

Kliiniset lääketutkimukset

- Kliiniseen tutkimukseen osallistuvan tutkimushenkilön suojelu varmistetaan kutakin kliinistä tutkimusta edeltävien toksikologisten kokeiden tuloksiin perustuvalla vaarojen arvioinnilla, …
  - *Dir 2001/20/EC*
  - Lääkkeiden tutkimiseen liittyviä analyyttisiä, farmakologis-toksikologisia ja kliinisiä standardeja ja tutkimussuunnitelmia koskevat yhdenmukaiset säännöt (*Dir 2001/83 as amended*).
- Komission ohje kliinisten lääketutkimusten vaatimuksista
  - *2010/C 82/01*
  - *ICH M3 (R2) guideline*
  - *Tutkimusten on täytettävä GLP vaatimukset*

Nonkliiniset farmako-toksikologiset vaatimukset

Annex I of dir 2001/83/EC

- **Farmakologia**
  - Primääri farmakodynamiikka (PD)
  - Sekundääri PD
  - Safety farmakologia
- **Farmakokinetiikka** (ADME)
- **Toksikologia**
  - Kerta-annostus ja toistuva annostus
  - Genotoksisuus
  - Karsinogeenisuus
  - Lisääntymis- ja kehitystoksisuus
  - Paikallinen siedettävyys
  - Immunotoksiuus
  - Immunogeenisuus
  - Ympäristöriskin arviointi

Ohjeistot ja GLP-vaatimukset

ICH ohjeistot

- **M3 (R2)** Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals
  - primary PD studies (in vivo and/or in vitro) are not generally conducted in accordance with GLP
  - Specific provisions on GLP requirements of acute tox studies
  - General toxicity studies should be conducted according to GLP regulations

- **S 1 A** The need for carcinogenicity studies of pharmaceuticals
- **S 1 B** Testing for carcinogenicity of pharmaceuticals
- **S 1 C (R2)** Dose selection for carcinogenicity studies of pharmaceuticals
- **S 2 (R1)** Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use

- **S 3 A** Toxicokinetics: A guidance for assessing systemic exposure in toxicology studies
  - for those toxicity studies whose performance is subject to GLP the concomitant toxicokinetics must also conform to GLP
  - TK studies retrospectively designed to generate data under conditions which closely mimic those of the toxicity studies should also conform to GLP when they are necessary for the evaluation of safety.

- **S 3 B** Pharmacokinetics: Guidance for repeated-dose tissue-distribution studies
- **S 4** Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)
- **S 5 (R2)** Detection of toxicity to reproduction for medicinal products and toxicity to male fertility

- **S 6** (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals
  - Toxicity studies are expected to be performed in compliance with GLP
  - however, it is recognised that some studies employing specialised test systems which are often needed for biopharmaceuticals, may not be able to comply fully with GLP
  - Areas of non-compliance should be identified and their significance evaluated relative to the overall safety assessment
  - In some cases, lack of full GLP compliance does not necessarily mean that the data from these studies cannot be used to support clinical trials and marketing authorisations

- **S 7 A** Safety pharmacology studies for human pharmaceuticals
  - The safety pharmacology core battery should be conducted in compliance with GLP
  - Follow-up and supplemental studies should be conducted in compliance with GLP to the greatest extent feasible.
  - Safety pharmacology investigations can be part of toxicology studies; in such cases, these studies would be conducted in compliance with GLP.
  - Due to the unique design of, and practical considerations for, some safety pharmacology studies, it may not be feasible to conduct these in compliance with GLP. Data quality and integrity should be ensured even in the absence of formal adherence to the principles of GLP.
  - Any study or study component not conducted in compliance with GLP should be adequately justified, and the potential impact on evaluation of the safety pharmacology endpoints should be explained.

- **S 7 B** The non-clinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals
  - Principles and recommendations described in ICH S7A also apply to the studies conducted in accordance with the present guideline.
  - In vitro IKr and in vivo QT assays when performed for regulatory submission should be conducted in compliance with GLP.
  - Follow-up studies should be conducted in compliance with GLP to the greatest extent feasible.

- **S 8** Immunotoxicity studies for human pharmaceuticals
  - Immunotoxicity studies are expected to be performed in compliance with GLP.
  - It is recognized that some specialized assays might not comply fully with GLP.

- **S 9** Non-clinical evaluation for anticancer pharmaceuticals

EU ohjeistot, joissa GLP kannanotto

- Guideline on repeated dose toxicity
  - Repeated dose toxicity studies should be carried out in conformity with the GLP

- GUIDELINE ON THE NON-CLINICAL INVESTIGATION OF THE DEPENDENCE POTENTIAL OF MEDICINAL PRODUCTS
  - Studies referred to under the first tier – except those belonging to the safety pharmacology regarding the CNS as outlined under ICH S7A - generally do not need to meet the requirements of GLP, although scientifically high standards should also be maintained in these studies.
  - The behavioural pharmacology studies for investigating dependence potential should be conducted in compliance to GLP to the greatest extend possible.
  - When studies are not conducted in compliance with GLP, study reconstruction should be ensured through adequate documentation of study conduct and archiving of data.
  - Any study or study component not conducted in compliance with GLP should be adequately justified, and the potential impact on evaluation of the behavioural pharmacology endpoints should be explained.

- GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-INHUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS
  - Although GLP compliance is not mandatory for pharmacodynamic and pharmacokinetic studies, they should be of high quality and consistent with the principles of GLP.

- Guideline on bioanalytical method validation
  - The validation of bioanalytical methods used in non-clinical pharmaco-toxicological studies that are carried out in conformity with the provisions related to Good Laboratory Practice should be performed following the Principles of GLP.
  - Aspects of method validation not performed according to GLP should be clearly identified and their potential impact on the validation status of the method indicated.
  - Methods used in pre-clinical studies not required to be performed to GLP should be fit for purpose but not necessarily developed in a GLP facility.

ATMP guidelinet, joissa GLP kannanotto

- Reflection paper on *in-vitro* cultured chondrocyte containing products for cartilage repair of the knee
  - The necessity of conventionally designed, GLP-compliant toxicity studies depends on the nature of the product and should follow a risk-based approach.
  - Safety endpoints may be incorporated into proof of concept studies in justified cases. These studies should be GLP-compliant if feasible.
- GUIDELINE ON NON-CLINICAL TESTING FOR INADVERTENT GERMLINE TRANSMISSION OF GENE TRANSFER VECTORS
  - Non-clinical safety studies addressing the risk of germline transmission should be performed according to the principles of GLP.

Yleiset vaatimukset	Erityiset vaatimukset ATMP-tuotteille		
	Geeniterapia	Somaattinen soluterapia	Kudosmuokkaus-tuotteet
Farmakologia Prim PD Sec PD Safety pharmacology	Proof-of-concept Target selectivity	Proof-of-concept Tissue interation Bioactive molecules	Proof-of-concept Tissue interaction
Farmakokinetiikka ADME	Biodistribution, persistence, clearance, mobilisation, germ line transmission, shedding	viability, longevity, distribution, growth, differentiation and migration	viability, longevity, distribution, growth, differentiation and migration
Toksikologia Single ja repeat dose		Can be included in POC studies	Can be included in POC studies
Genotoxicity	(-)	(-)	(-)
Carcinogenicity	Tumourigenic potential	Tumourigenic potential	Tumourigenic potential
Repro- dev toxicity	Fertility, reproductive potential	(-)	(-)
Other toxicity	Integration Immunogenicity	Immunogenicity, immunotoxicity, xenopathogen transmission	Immunogenicity, immunotoxicity, Xenopathogen transmission

Tiivistelyä

- Nonkliiniset tutkimukset GLP-vaatimusten mukaan
  - Yleistäen safety farmakologia ja toksikologia
  - Kaikki pivotaaliset tutkimukset, joihin nonkliininen turvallisuustieto perustuu

- Farmakologiset karakterisointi- ja proof-of-concept –tutkimukset yleensä non-GLP
  - Kun pivotaalisia safety-end pointeja liitetään POC-tutkimukseen, on sen oltava GLP

- Täysi GLP-komplianssi ei aina mahdollinen
  - Voidaan perustellusta syystä poiketa (tuotteesta johtuvista syistä)
  - Noudatettava GLP-periaatteita mahdollisimman tarkasti
  - Non-GLP ja sen mahdollinen vaikutus turvallisuuden kokonaisarviontiin perusteltava
  - Arvioidaan aina tapauskohtaisesti

Mahdollisia sudenkuoppia

- Kliinisten lääketutkimusten hyväksyntä kansallisten viranomaisten vastuulla
- Myyntilupa-asiat EMAn vastuulla
  - Tulkintaerot
- Hae tieteellistä neuvontaa (kansallinen/EMA)