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Regulatory Requirements for Viral Shedding Studies for Gene Therapy Vectors in Switzerland

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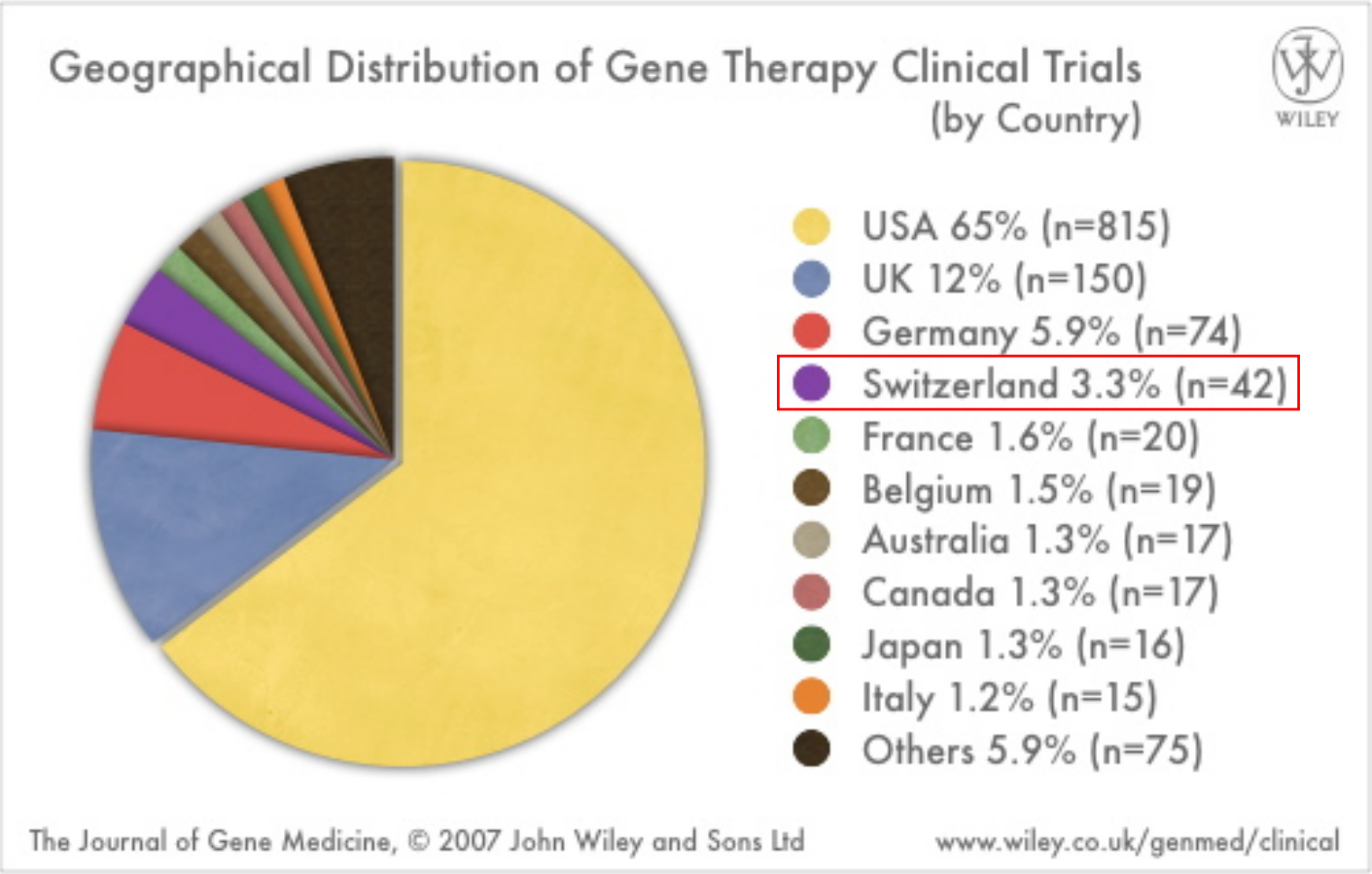
Outline

- **Part 1:** Regulatory Overview
- **Part 2:** GT/GMO ERA Guideline
- **Part 3:** Biodistribution/Shedding Studies for ERA


Geographical Distribution of Gene Therapy Clinical Trials
(by Country)
WILEY
USA 65% (n=815)
UK 12% (n=150)
Germany 5.9% (n=74)
Switzerland 3.3% (n=42)
France 1.6% (n=20)
Belgium 1.5% (n=19)
Australia 1.3% (n=17)
Canada 1.3% (n=17)
Japan 1.3% (n=16)
Italy 1.2% (n=15)
Others 5.9% (n=75)
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www.wiley.co.uk/genmed/clinical

Gene therapy of germline cells

- Correction of a genetic defect in spermatocytes, oocytes

➔ **forbidden by the Swiss Law (Fed. Const. Art. 119)**

Gene therapy of somatic cells

- Correction of a genetic defect in cells of the body
- No hereditary transmission of the therapeutic gene

➔ **Law on therapeutic products / Law on Tx**

Gene Therapy Clinical Trials
Legal Basis

- Swiss Law on Medical Products and Medical Devices (HMG, *SR 812.21)*
- Ordinance on Clinical Trials with Therapeutic Products (OClin, *SR 812.214.2)*

The following Clincial Studies need an approval by Swissmedic (OClin, Section 5, Art 16)

a) Introduction of genetic information into somatic cells (somatic gene therapy)

b) Clinical trials with therapeutic products that contain genetically modified organisms in the sense of the Ordinance on Contained Use

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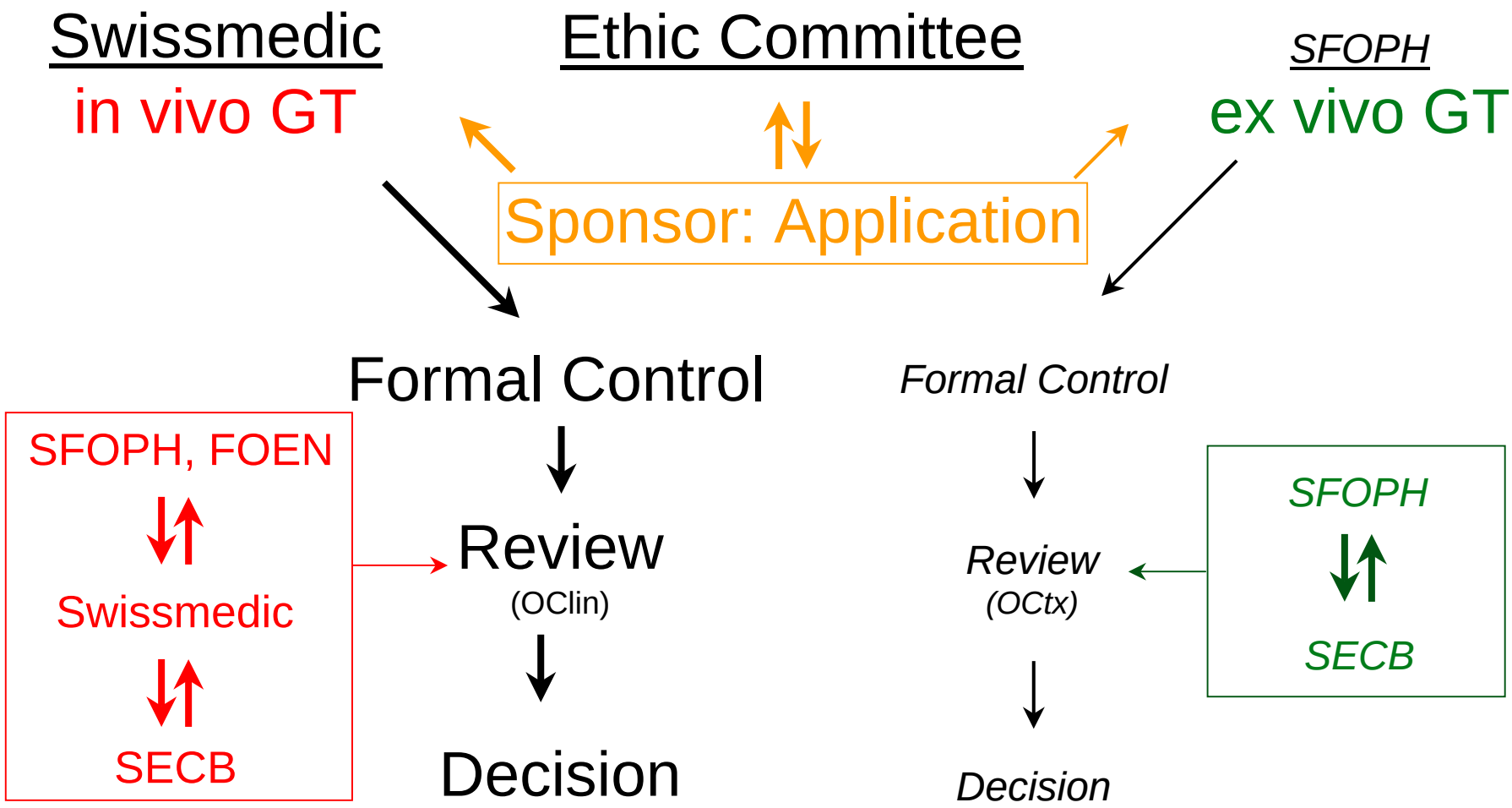
Part 1: Regulatory Overview



Requirements for the approval

- Clinical trial according to ICH E6 Guideline (GCP)
- Investigational products according to cGMP
- Preclinical data on biodistribution/Shedding, toxicology, pharmacology (ICH S6, ICH M3, EMEA NfG)
- Positive opinions of EC, SFOPH, FOEN and SECB

Approval by Swissmedic (max. 90 days after Dok. i.O.)

Risks for humans and the environment

- Risks for trial participants
- Risks for personal in laboratory and hospital
- Risks for relatives / friends
- Risks for the human population
- Risks for the environment

Environmental risk assessment

➔ERA Guideline for Clinical Trial Applications

OClin (Section 5; Art. 16, Art. 17, Art. 26)

Art. 16 Par. 2

Data on environmental risk assessment
(Effects on people and the environment)

Authorities involved
Vklin,
Art. 17, Par. 2
Art. 26, Par. 2

- Swissmedic
- Swiss Agency for the Environment
- Swiss Federal Office of Public Health
- Swiss Expert Committee for Biosafety

Excluded from the Guideline are

Risk assessment for subjects participating in the clinical trial	Ordinance on clinical trials Art. 6 Par. 1
Risk assessment for clinical personnel	Ordinance on workers protection from hazards due to microorganisms
Risk assessment of R&D and manufacturing of the product	Ordinance on contained use of GMO
Risk assessment related to the placing on the market of the product	Guidelines to be developed

Decision tree based on vector shedding

Shedding of product	No		→ No release into the environment	**Case A**
Yes				
Shedding limited to very short time	Yes	Trial subjects in contained space	→ No release into the environment	**Case B1**
No				
Medium to long term shedding	Yes	Trial subjects in the environment	→ Release into the environment	**Case B2**

Case A: no shedding

General information

- **Characteristics of the product and the clinical trial**

Information on biodistribution and shedding

- **Pre-clinical biodistribution and shedding studies**
- **Evaluation of the analytical methods used**

Risk assessment

- **With respect to the confirmation of lack of shedding**

Safety measures

- **Avoid the release of the product or any contaminated material**

Case B1: short transient shedding

General information

- **On the characteristics of the product and the clinical trial**

How are trial subjects monitored during shedding

- **Containment and treatment of shedded material**
- **Methods to determine end of shedding phase**
- **If applicable status of immunity of personnel and visitors with respect to the shedded product**

Risk assessment

- **With respect to any persons likely getting into contact with the shedded product**

Safety measures

- **To avoid the release of the product or any contaminated material into the environment**
- **To avoid the release through close contact persons**

Case B2: medium / long term shedding

General information

- **On the characteristics of the product and the clinical trial**

Detailed information on the products characteristics

- **Time scale and extent of shedding**
- **Stability of the product and likelihood of persistence**
- **Host range, cell tropism, mode of transmission**
- **Pathogenicity, infectivity, low susceptibility to immune response of host**
- **Replication-competent, likelihood of reversion to replication-competence**
- **Likelihood of recombination with, wildtype or other organisms**
- **Expression of toxins, cytokines, growth factors or other inserts interfering with, cell-cycle control, strong promoters, enhancers**

Case B2: medium / long term shedding

- **Detailed risk assessment for people and environment**
- **Detailed description of safety measures**
  - Minimizing the shedding
  - Protect contact persons, prevent 3rd party exposure
  - Prevent dispersal of the product in the environment
  - Monitoring of the product in the environment
  - Monitoring of the effects in the environment
  - Sensitivity and reliability of the methods