Environmental assessments and shedding studies for gene therapy products in the US and in the EU

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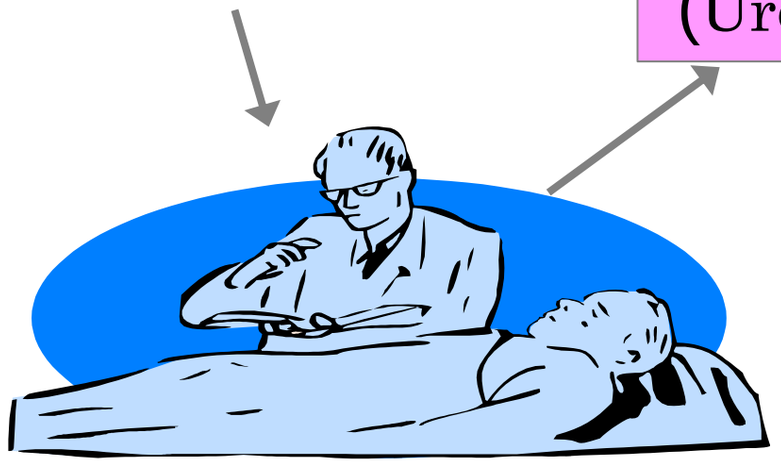
Environmental Assessment for Gene Therapy Products and Virus-shedding Study

Virus Vector



Administration

Viral Shedding

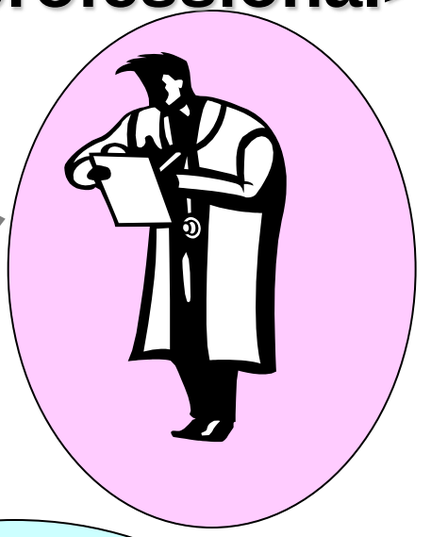
secretion・Emissions
(Urea, faeces, sputum)

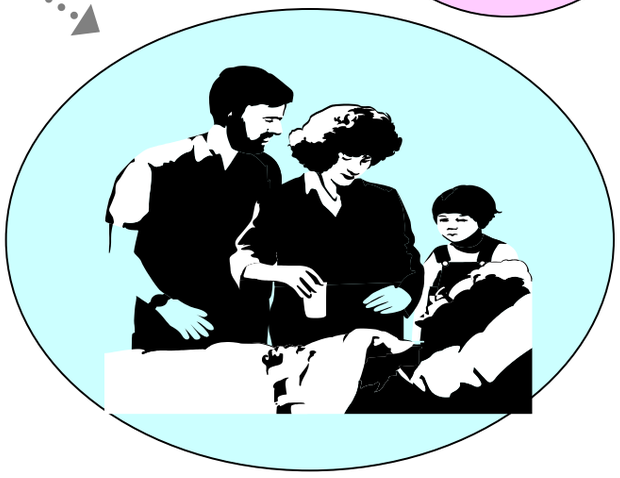
???

???

???

<Health Care professional>





<Family>

<Environment>

Environmental assessment and guideline for viral shedding in USA

- **USA does not ratifiy the Cartagenus law**
- According to US federal law, the sponsor should submit the e**nvironmental assessment about gene therapy product.**
  - **The National Environmental Policy Act of 1969 (NEPA); Revision of Policies and Procedures (Final Rule) 1997**
  - federal law 21CFR25
  - **Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products**
    （Guidance for Industry, FDA CBER, March 2015）
  - **Design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic products**
    （Guidance for Industry, FDA CBER, 2015)

FDA Guideline for the Environmental Assessment: IND Approval

- **The sponsor should submit the following data in IND**（21CFR25.15(a)）
  - ✓ **Environmental assessment**
  - ✓ **Claim for categorical exclusion**

- **In the case of no categorical exclusion**：
  Extraordinary circumstances indicate that the specific proposed agency action may significantly affect the quality of the environment
  - ✓ Extraordinary circumstances：Specific or unknown risk on human、Risk on Endangered Species of Wild Fauna and Flora (CITES)

- In most cases, IND for a clinical study using a GTVV will not significantly affect the quality of the environment because, in brief, these clinical trials are closely monitored and are limited to a designated study group.

FDA Review of Environmental Assessment for IND of GMO products

- **Key Issues of Environmental Assessment for Human Gene Therapy Investigational New Drug Applications (INDs).**

✓ Collection of viral shedding data to evaluate the environmental assessment

✓ Measures to mitigate the potential risk for securing the safety of the investigational study

- Environment Reviewer is responsible for evaluation of the environmental risk)
- Emergency of replication competent virus is concern risk for replication incompetent virus vector including recombinant viral vaccine
- Recommend to collect the viral shedding data about 10 number of patients

➡If the viral shedding risk is low, it may be skip to collect the data of viral shedding.

- If the data or monitoring protocol is not enough, FDA submit the clinical hold to the sponsor

FDAのEnvironmental Assessment of Human Drug and Biologics Applications：(BLA)

- **BLA of gene therapy products：the sponsor should submit EA**

➢ categorical exclusion（Substances that Occur Naturally in the Environment）are;

- ✓ contain functional protein-coding sequences from one or more species within a *single* genus to “occur naturally in the environment” for purposes of 21 CFR 25.31(c).
- ✓ differ from a wild-type substance only in attenuating point mutations or deletions to be substances that “occur naturally in the environment” for purposes of 21 CFR 25.31(c)
- ✓ have been killed or inactivated by undergoing a specific manufacturing step designed to eliminate their ability to replicate to be substances that “occur naturally in the environment”
- ✓ consist of genetically-modified human cells to be substances that “occur naturally in the environment”

FDAのEnvironmental Assessment of Human Drug and Biologics Applications：（BLA）

- **BLA of gene therapy products：the sponsor should submit EA**
- **Identification of Substances Subject to the Proposed Action**

  “Identification of Substances Subject to Proposed Action”; “Identifying and Assessing Potential Environmental Effects”; “Mitigation Measures”; and “Alternatives to the Proposed Action.”

➢ **Identification of Substances Subject to the Proposed Action**

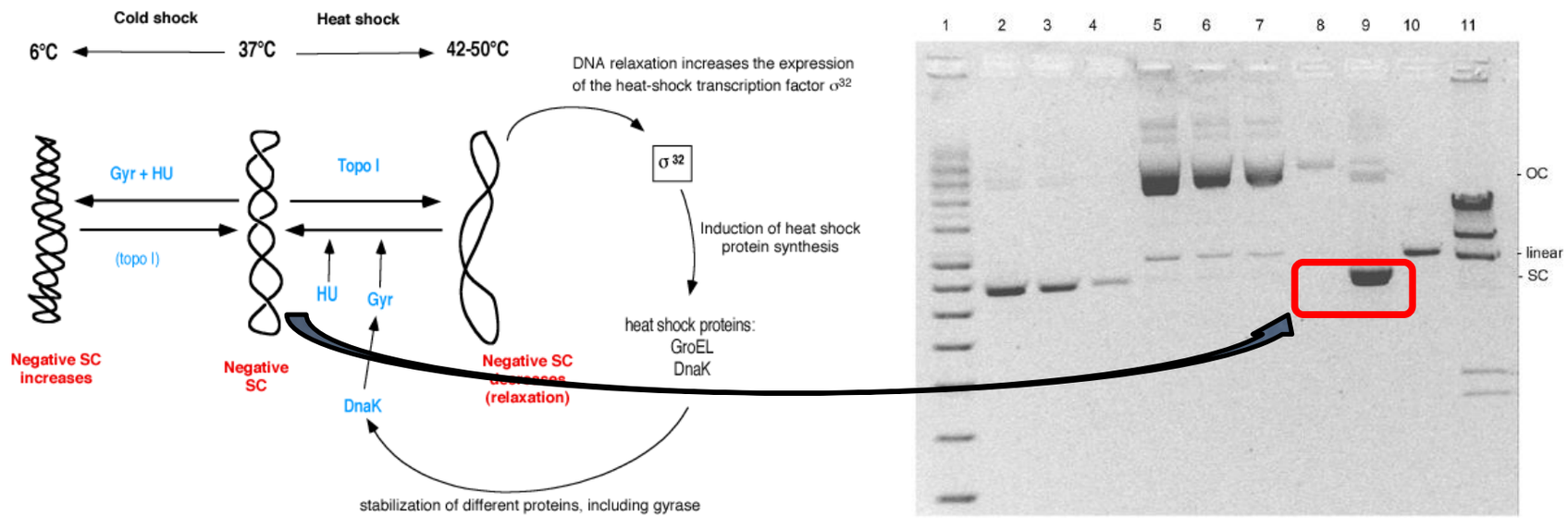
To identify known and potential variants of the GTVVs released into the environment.

- ✓ Identifying and Assessing Potential Environmental Effects
- ✓ Is the vector virulent, pathogenic, What is known regarding the genetic stability and prevalence of gene exchange in natural populations of the strain or vector?
- ✓ the product have traits that may give it a selective advantage over natural organisms?
- ✓ Assessing the magnitude of potential environmental effects

➢ What is known about the effectiveness of monitoring and mitigation plans?

FDA Environmental Assessment for GMO products

- The release of vector DNA into the environment is detectable by PCR at the injection site and/or in excreta
- Replication competent impurity may cause an active infection in the patient or study participant capable of disseminating to others. ⇒ These variants may arise during manufacture or after product administration because of mutations, or recombination events.
- A super-coiled plasmid may still retain the ability to transfer genetic material (such as antibiotic resistance genes) to other bacteria even after limited degradation.



Levy et al: Quantitation of supercoiled circular content in plasmid DNA solution using fluorescence based method. NAR 28, e57, 2000

FDA: Design and Analysis of Shedding Studies for Virus or Bacteria–Based Gene Therapy and Oncolytic Products

1. **Why this guideline is published?**

–> The possibility that the shed viral vector for gene therapy or oncolytic product may be infectious raises safety concerns related to the risk of transmission to untreated individuals..

–> There are many product-specific factors and patient-specific factors that can influence the design of a shedding study.

2. **Purpose of the viral shedding guideline** ?

–>Recommendations on how to conduct shedding studies during preclinical and clinical development

How and when shedding data should be collected ?

–> How shedding data can be used to assess the potential for transmission to untreated individuals.

3. What is shedding-

–> Excreta (feces); secreta (urine, saliva, etc); or through the skin (pustules, sores, wounds)

–> Shedding is distinct from biodistribution, and signal in blood is not shedding

4. Design of Shedding Studies: Guiding Principles ?

–> Choice of samples, Frequency of sample collection, Duration of the monitoring period, Assay

–> VBGT Characteristics (Replication competence, Immunogenicity, Tropism) Route of Administration

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- Replication competence：Start from P-1 to P-2, Assess before P-3、
- Replication Incompetence：Start after the determination of dosing (P-2)
- Examples：sampling on the day, 1、3、7、10day then weekly. Continue to below LOD
- Samples should be determined in design of shedding studies
- Replication competence：**Infectivity Assay + PCR、incompetent：PCR** PCR (+) –> Infectivity (?)

According to shedding data, the sponsor should assess the risk of transmission to untreated individuals

EU Environmental Assessment: Law and Guideline

- EU and European nations have ratified the Cartagena Law
- EMA reviews the environmental risk of gene therapy product in submission of new drug approval centrally; Evironmental Risk Assessment + Control of Viral Shedding
- **Directive 2001/83/EC, as amended, and Regulation** 726/2004
- **Guideline on Scientific Requirements for The Environment Risk Assessment of Gene Therapy Medicinal Products** (EMEA/CHMP/GTWP/125491/2006)
- **ICH Considerations: general principles to address virus and vector shedding**

EU: Environmental Assess of GMO for IND

- For products containing genetically modified organisms (GMOs), an additional risk assessment step in the clinical trial authorisation (CTA) procedure is required in addition of IND.
- The application process for conducting clinical trials with an ATIMP consisting of or containing a GMO in the EU involves the need for differentiation between contained use and deliberate release review by different responsible authorities, with specific documents and procedures in addition to the standard CTA review by a competent health authority and the Ethics Committee. ➡ A multi-stakeholder meeting at EMA regarding the lack of harmonisation of the GMO requirements and the challenge to integrate the GMO assessment in the clinical trial process.
- The focus of Directive 2009/41/EC is on the assessment of the biosafety level classification of the GMO and the implementation of physical, chemical and biological barriers. All contained use procedures are classified based on the performed risk assessment into one of the following four categories:

Category	Risk Assessment	Viral Vector
Class 1	No or negligible risk	AAV（helper free)
Class 2	Low risk, level 2 containment	AAV (AdV helper), AdV, HSV
Class 3	Moderate risk, level 3 containment	Lentivirus
Class 4	High risk, level 4 containment	

GMO Contained use vs. Deliberate release

GMO –Contained use

- Contained use is defined as any activity with GMOs for which specific containment measures are used to limit their contact with the environment.
- The focus of Directive 2009/41/EC is on the assessment of the biosafety level classification of the GMO and the implementation of physical, chemical and biological barriers. The risk classification has consequences for the procedure and review period of the application

Contained use –risk classification

- All contained use procedures are based on classification of risk –as decided by appropriate agency / authority
  - Class 1: No or negligible risk, level 1containment
  - Class 2: Low risk, level 2containment
  - Class 3: Moderate risk, level 3containment
  - Class 4: High risk, level 4containment
- Classification is dependent upon strength of argument / data contained in a risk assessment / biosafety dossier
- Class 3 / 4 GMOs require prior consent from the competent authority but most ATMPs should be Class 1 / 2
- Contained use often requires clinical site–specific notifications and / or submissions to authorities

GMO –Deliberate release

Deliberate release is defined as any activity with GMOs that is not contained use.

Directive 2001/18/EC is based on a environmental risk assessment (ERA) covering effects on human health or the environment.

The ERA should be carried out in accordance with the principles set out in Annex II of this Directive. 5 steps:

i) identification of potential adverse effects,

ii) estimation of the likelihood,

iii) risk estimation,

iv) risk management

v) assessment of the overall environmental impact.

Contained use vs deliberate release

Generally, GMOs regulated under deliberate release come under greater scrutiny from competent authorities

Contained use has a greater administrative burden (requiring both clinical site submissions and sponsor submissions) which may slow approvals

However, lower classification equates to lighter regulatory touch and once approved, there are less likely to be conditions applied

Deliberate release or high risk contained use may require significant safety data / risk mitigations prior to or during the trial

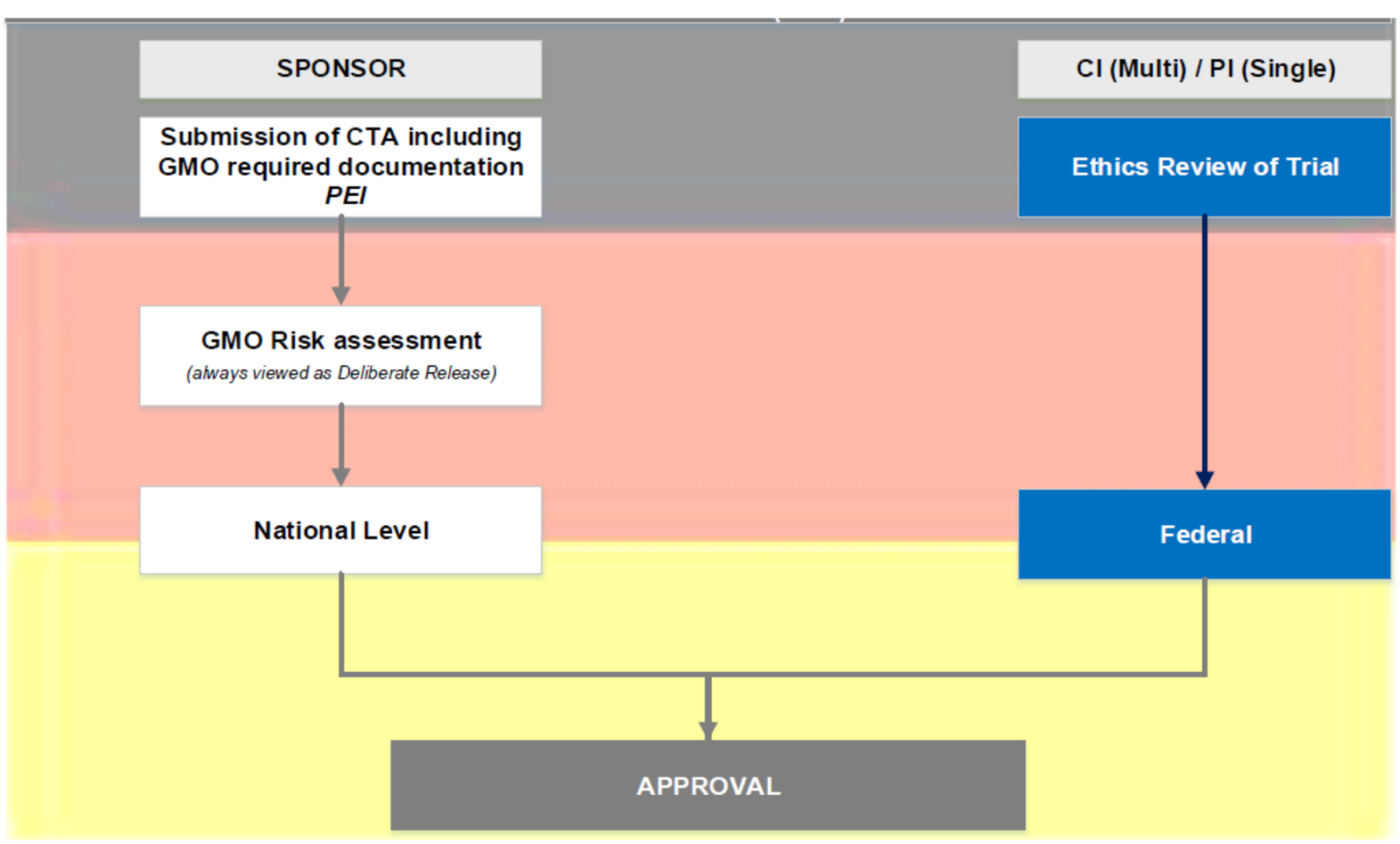
Clinical trials using GMOs classified as contained use or deliberate release for selected EU member states

Member State	Contained use or Deliberate release
Germany	Deliberate release
UK	Either (most studies are considered contained use)
France	Either(until recently all studies considered contained use but deliberate release also applicable)
Sweden	Clinical studies are now normally considered as deliberate release
Spain	Either
The Netherlands	Deliberate release
Belgium	Either

Gene Therapy Legislation in Germany

Gene therapy trials require authorization by the Paul-Ehrlich-Institut (www.pei.de), residing with the Ministry of Health (Bundesministerium für Gesundheit), and approval by the local ethics committee of the principal investigator. Guidance on the submission of clinical trial applications is provided by the 3rd Notification on the Clinical Trial of Medicinal Products for human Use. Germany generally considers clinical trials with medicinal products containing genetically modified organisms (GMOs) as deliberate release and requires an environmental risk assessment (ERA) in accordance with Annex II and based on information as per Annex III to the Directive 2001/18/EC.

The deliberate release of a GMO within a clinical trial is authorised by the Paul-Ehrlich-Institut in consultation with the German GMO competent authority, the Federal Office of Consumer Protection and Food Safety (BVL). Any handling of the GMO-containing medicinal product outside the clinical trial falls within contained use which is regulated by the Genetic Engineering Act (GenTG).



Database are published in GMOinfo-GMOregister of European Commission

Deliberate Release and Placing on the EU Market of GMOs - GMO Register

Home

Deliberate release into the environment of other than plants GMOs for any other purposes than placing on the market (experimental releases)

List of SNIFs submitted to the Member State's Competent Authorities under Directive 2001/18/EC (after 17 October 2002)

Click here for an historic overview of all data since 1991e 1991

Notification Number	*Member State*	*Publication*	*Name of the Institutes or Companies*	*Project title*	*Final report*
B/DE/18/PEI3279	Germany	01/10/2018	CRISPR Therapeutics AG	Clinical study CTX001-111 titled: "A Phase 1/2 Study of the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) in subjects with Transfusion-Dependent β-Thalassemia"	
B/DE/18/PEI3341	Germany	01/10/2018	Universitätsklinikum Carl Gustav Carus an der TU DresdenUniversitätsklinikum EssenUniversitätsklinikum Würzburg	Testing the safety and efficacy of KTE-C19 in patients with refractory or relapsed B cell malignancies. KTE-C19 is a novel adoptive cellular immunotherapy for cancer whereby autologous T cells are genetically modified/transduced ex vivo by a replication-deficient retroviral vector to express anti-CD19 chimeric antigen receptors (CAR) on the surface of T cells to target malignant B cells expressing CD19 antigens.	

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

Title of the project: Oncolytic adenovirus therapy using a prostate-specific conditionally replication-competent adenovirus as an adjuvant treatment for localized prostate cancer.
GMO named: Genus Mastadenovirus, species human Adenovirus subgenus C, serotype 5.

Summary of the potential environmental impact of the release of the GMOs

The environmental risks associated with the use of the GMO are negligible. The GMO is a strongly attenuated derivative from a commonly occurring cold virus with an unmodified tropism, and adverse effects are limited to the prostate only. There is a risk of transmission of this virus in case of an accident during administration, resulting in the potential exposure of pharmacy or trial personnel to high amounts of virus, and in case of exposure of third persons by transmission of virus that is shed via excreta, predominantly semen. Harmful effects of transmission of virus or recombinants to third persons are not to be expected due to the strongly attenuated pathogenicity of the GMO, which is restricted to prostate cells only, and the negligible level of potential recombinants.

Identity of the vector,
Host range of the vector
] Description of identification and detection methods
(a) Techniques used to detect the GMO in the environment
(b) Techniques used to identify the GMO
4. Method and amount of release
(a) Quantities of GMOs to be released:
(b) (c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site

Summary of GMO regulation in EU Nations

- GMO requirements are implemented very differently across Europe and can require regional interactions with numerous bodies / authorities
- Admin burden can be great for small companies and lack of clarity with procedures can be frustrating
- Benefits of using contained use procedures depends upon MS but generally seen to be less burdensome in terms of negating risk to humans and environment
- Deliberate release or higher risk contained use (Class 3/4) may require significant safety data / risk mitigations prior to, or during the trial
- Its not about contained use vs deliberate release –just need the approval!

UKにおけるContained Useの考え方

- CU：GMOが環境中に放出される可能性がほとんどない場合
  - 物理的バリア（入院管理）
  - 生物的バリア（十分弱毒化されている場合、感染性、増殖性、外界での生存性を失っている場合）
  - Sheddingがほとんどない場合

✓ 入院管理はCUだが、入院しなければDRとは限らない
✓ ワクシニアワクチンでは密封包帯を使用すればCU
✓ 長期間排出が予測される場合はDRとして扱い、sheddingのモニタリングを実施

CUの場合、治験前の環境影響評価は不要で承認申請時に実施

EMA 審査報告書
Strimvelis（ADA導入自己CD34細胞）

環境毒性＆環境リスク評価

- 対象は第三者及び動植物を含む環境全般
- 評価結果は非臨床の毒性の項に記載
- 遺伝子導入された細胞（Strimvelis)とADA retrovirusの特性を考慮
- 医療従事者への影響を避けるため治療場所を限定した使用
- 投与部位からの漏出を防ぐ非開放系での使用により環境への伝播を防止
- 20年近くにわたる使用経験から環境へのリスクが少ないことを確認
- 増殖性ウイルス（RCR)の出現リスクについても考察：
  ➡臨床試験でRCRの検出がないこと、患者体内で野生型のレトロウイルスと組換えが起こりにくい設計となっている（ホモロジーをできる限り低減化）

EMA 審査報告書
Zalmoxis (HSV-TK導入同種T細胞)

環境毒性＆環境リスク評価

- ✓ 対象は第三者、動植物を含む環境全般
- ✓ 評価結果は非臨床の毒性の項に記載
- ✓ 遺伝子導入された細胞(Zalmoxis)とγ-retrovirusの特性を考慮したリスク評価
- ✓ 医療従事者への影響を避けるため治療場所を限定した使用
- ✓ Phase I/IIとPhase IIIで2つのベクターを使用
- ✓ ベクターの伝播リスクは、ベクターそのもの又はプロウイルスが生殖細胞に入ったときのみ起こりうると推定
- ✓ Viral-sheddingに関する解析は実施されていない(遺伝子組換えT細胞にはフリーのウイルスベクターは含まれていない)
- ✓ 生殖細胞へのベクター分布のリスクはないと判断(3箇所の変異を導入したベクターのためRCR出現のリスクはほぼない、T細胞系のみ増幅する条件etc.)

EMA 審査報告書
Imlygic（腫瘍溶解性ウイルス）

環境毒性＆環境リスク評価

- ✓ 遺伝子組換え制限増殖性ウイルス（HSV-1由来）の開放系での使用
- ✓ 神経毒性や病原性は1/100～1/1000に減弱されており、また、がん細胞でのみ増幅し正常細胞では増幅しない設計（ベクターの安全設計）
- ✓ 最も伝播の起こりやすい第三者は医療従事者と近親者と想定
- ✓ 投与部位からの排出が最もハイリスク
- ✓ 対象疾患を成人のメラノーマに限定することにより、環境中への排出によるリスクを低減化
- ✓ Imlygicは患者から排出されると急速に感染性を失うことから、環境影響リスクは少ないと考えられる
- ✓ しかし、免疫抑制状態にある患者や妊婦へ暴露された場合のリスクは健常人に比べて高いと考えられる

Environmental Risk of Replication Competent Virus and Viral Vector

- Recombinant Oncolytic Virus Vector
- Wild and Attenuated Oncolytic Virus
- Attenuated Viral Vaccine expressing recombinant Antigen (Ebola, MERS antigen etc.)

- Imlygic, recombinant oncolytic HSV-1 virus has a risk on immune-compromised patients, new-born children.
- The sponsor was required to mitigate the risk on transmission of Imlygic to intimate 3rd party and HCW.
- To prevent the 3rd party transmission, the sponsor provides the medication-guide and the education program to patients

Sponsor is required to prevent the transmission of vectors from patients to 3rd parties in clinical use of gene therapy products (ICH Consideration, viral shedding).
免疫状態の正常なヒトに対しては安全性上問題はなくても、免疫不全の人に対しては重篤な副作用を及ぼす可能性がある。そのリスクを低減する方策が必要。

Comparison of GMO Regulation about Gene Therapy Products between EU, USA and Japan

	Japan	USA	EU
Cartagena Law	Adapt	No	Adapt
Environment Assessment GL	None	Adapt	Adapt
Focus	Recombinant Virus	Gene Therapy Products include Plasmid	Gene Therapy Products include Plasmid
Review Timing	Before Clinical Study	At Approval for Market Authrization (MA) (except for replication competent virus or etc)	Before Clinical Study by each Regulatory Agency At Approval for MA (EMA)
Viral Shedding	ICH Consideration	Viral Shedding GL	ICH Considration
Shedding Data		Submit with Approval for MA	Submit with Approval for MA
When collect shedding data	Phase 1:	Replication Competent Virus: Phase I Non-replication : Phase II	England : Phase I
Control Pts	In hospital (isolated room)	In or out hospital	In or out hospital

*Cartagena law

✓ Japanese Cartagena Law may correspond EU and USA environmental Assessment.

遺伝子治療薬開発ステージと環境影響評価、カルタヘナ申請

R&D

Clinical Trial

Market

日本

CMC

Non-clinical

Ph-I

Ph-II

Ph-III

Approval for Market Authrization

RMP

RS consul.

第2種使用

第1種使用

治験届

承認時の評価と承認後の使用条件？

米国

基礎研究

非臨床試験

IND

治験（第一相）

治験（前期第二相）

治験（後期第二相）

治験（第三相）

申請と承

RMP

治験初期に緻密なデータ収集

Consultation

Pre-Pre IND meeting

Pre IND meeting

viral shedding Dataの収集

EA治験でのViral sheddingデータ

EU

基礎研究

非臨床試験

IND

治験（第一相

治験（前期第二相）

治験（後期第二相）

治験（第三相）

申請と承

RMP

各国でのGMO規制国による審査対応の違い

viral shedding Dataの収集

ERA治験でのViral sheddingデータ

Summary

Thank you !
Any question?

Library Center In KIT