Questions for the Committee:

1. The Code of Federal Regulations (CFR) Part 312.42 defines the bases for FDA to place a study on clinical hold. CFR 312.42(b)(iv) ("insufficient information") was cited previously as a basis for placing INDs on clinical hold in response to the development of leukemia in subjects of X-SCID clinical trials. However, we note CFR 312.42(b)(i) that states FDA may place a study on hold if it finds that "Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury". With this requirement in mind, please discuss the current incidence of leukemia (3/12) and death of one subject from leukemia reported in the clinical trial in France relative to the potential benefit of retroviral vector-mediated gene transfer in X-SCID. Consider in your discussion:
    a. The risk/benefit issues for gene therapy vs. haploidentical bone marrow transplantation.
    b. The incidence of leukemia associated with retroviral vector administration that would make clinical trials of this therapy unacceptable in X-SCID. Would this advice differ if a subject in another clinical trial develops leukemia? Would another subject death due to leukemia influence your recommendations?

2. Please comment on what changes, if any, would reduce the risk to subjects in clinical trials using retroviral vector-mediated gene transfer in X-SCID. Please consider the following:
    a. Limit the dose based on total vector copy number in the transduced cells.
    b. Limit the dose based on total number of transduced cells.
    c. Alteration of retroviral vector design.

3. Please discuss the impact, if any, of the SAEs in X-SCID, combined with the development of myeloid sarcoma in the single monkey administered hematopoietic stem cells after ex vivo transduction with a retroviral vector, on the use of retroviral vectors in other clinical indications. Please comment specifically on the risk/benefit considerations:
    a. In ADA-SCID relative to X-SCID.
    b. In other clinical indications.

4. Given the increased efficiency of lentiviral vectors to transduce cells, often resulting in multiple vector copies per cell (up to 10 have been reported), please discuss whether restrictions on vector copy number per cell are warranted for the use of lentiviral vectors in ex vivo transduction clinical protocols, and if so, what limit would you advise?

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Appendix 3. Press Release from AFSSAPS

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Press release

24 janvier 2005

3rd complication case in DICS X gene therapy clinical trial

In May 2004, the French Health Product Safety Agency (Afssaps) authorised the restart of the gene therapy clinical trial conducted by Prof. Alain Fischer and Marina Cavazzana-Calvo, in Necker-Enfants-Malades hospital in Paris. The clinical trial is aimed at assessing efficacy of a gene therapy approach in the treatment of X-linked severe combined Immuno-deficiency (X-SCID), an inherited genetic disease.
This clinical trial, which included 11 patients, was put on hold in October 2002 (see press release October 3rd 2002), after a first notification of a complication in one of the patients had been observed, consisting in an uncontrolled T-lymphocyte proliferation. The same complication has been reported for a second patient at the end of 2002 (see Afssaps Press release dated 15 January 2003). The hold was maintained until analysis and identification of the mechanism(s) responsible. One of the patients died last October, the other is progressively recovering.

The clinical trial has been authorised to resume after the investigators proposed several protocol modifications (number of administrated cells, inclusion criteria, age of the patients to be enrolled, etc.) aimed at reducing the risk of insertional oncogenesis. Since the restart of the clinical trial, one new patient has been treated.

On January 18th, 2005, a new complication was notified to Afssaps. It concerns a third child who was 9 months old when receiving the treatment in April 2002. This complication is also a T-lymphocytes proliferation, which characteristics are still under investigation.

Following this information, and in agreement with Afssaps, the investigators and promoter decided to put on hold the clinical trial again, and wait for further investigations in an attempt to better explain the mechanism of the adverse event.

Appendix 4.

Table 1. Comparison of X-SCID Retroviral Vector-Mediated Gene Transfer

Characteristic	**Fischer [1]**	**Thrasher [2]**	**Weinberg***	**Malech***
Cell Source	Bone Marrow	Bone Marrow	Bone Marrow	Bone Marrow
$CD34^+$ Selection	Miltenyi Biotec	CliniMACS	Isolex 300 I	Isolex 300I
Media	X-Vivo-10	X-Vivo-10	X-vivo-15	X-Vivo 10
Serum/Other	4% FCS	1% HSA	None	1% HSA
Cytokines (Source):				
1. Flt-3 ligand	300 ng/ml (Immunex)	300 ng/ml (R&D)	300 ng/ml (Immunex)	50 ng/ml (R&D)
2. IL-3	60 ng/ml (Novartis)	20 ng/ml (R&D)	----------	5 ng/ml (R&D)
3. TPO	----------	100 ng/ml (R&D)	50 ng/ml (R&D)	50 ng/ml (R&D)
4. MGDF	100 ng/ml (Amgen)	----------	----------	----------
5. SCF	300 ng/ml (Amgen)	300 ng/ml (R&D)	50 ng/ml (R&D)	50 ng/ml (R&D)
6. IL-6	----------	----------	----------	25 ng/ml (R&D)
Hrs Prestim.	24	40	40	18
Transduction				
1. Fibronectin	Yes	Yes	Yes	Yes
2. Exposures	Three	Three	Three	Four
3. Time	72 hours	56 hours	72 hours	78 hours
Vector Backbone (LTR)	MFG (MoMLV LTR)	MFG (MoMLV LTR)	MND (MPSV LTR)	MFG (MoMLV LTR)
Vector Envelope (Packaging Line)	A-MuLV (Psi-CRIP)	GaLV (PG-13)	GaLV (PG-13)	GaLV (PG13)

[10]Hacein-Bey-Abina, S., et al., *Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy.* New England Journal of Medicine, 2002. **346**(16): p. 1185-1193.

[11]Gaspar, H.B., et al., *Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector.* Lancet, 2004. 364(9452): p. 2181-7.

* Details provided with kind permission from Drs. Weinberg and Podsakoff of The Saban Research Institute of Childrens Hospital Los Angeles, and Dr. Malech of NIH/NIAID.

Table 2. Clinical Summary of X-SCID Trials

Investigator	Previous BMT?	Previous infectious or other complications	Max Dose transplanted gamma-c^{+} cells/kg	Longest time from treatment to last follow-up
Fischer [1]	No	Yes (except 1)	20 x 10^6	5 years
Thrasher [2]	No	Yes	9.62 x 10^6	29 months
Weinberg#	Previous BMT not excluded.	Yes	NA	NA
Malech*	Yes, haploidentical with low or no evidence of engraftment	Yes	32 x 10^6	9 months

[10] Hacein-Bey-Abina, S., et al., *Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy.* New England Journal of Medicine, 2002. **346**(16): p. 1185-1193.

[11] Gaspar, H.B., et al., *Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector.* Lancet, 2004. 364(9452): p. 2181-7.

* Details provided with kind permission from Dr. Malech of NIH/NIAID.

Details provided with kind permission from Drs. Weinberg and Podsakoff of The Saban Research Institute of Children's Hospital Los Angeles; no subjects treated to date.

Table 3. Comparison of ADA-SCID Retroviral Vector-Mediated Gene Transfer

Characteristic	**Bordignon[3]**	**Kohn***
Cell Source	Bone Marrow	Bone marrow
$CD34^+$ Selection	CliniMACS	Isolex300I
Media	X-Vivo10	X-Vivo15
Serum/Other	4% FCS	None
Cytokines (Source):		
1. Flt-3 ligand	300 ng/ml (Immunex)	300 ng/ml (Immunex)
2. IL-3	60 ng/ml (Novartis)	----------
3. TPO	100 ng/ml (Glaxo SmithKline)	----------
4. MGDF	----------	50 ng/ml (Amgen)
5. SCF	300 ng/ml (Amgen)	50 ng/ml (Amgen)
Hrs Prestim.	24 hours	40 hours
Transduction		
1. Fibronectin	Yes	Yes
2. Exposures	Three	Three
3. Time	72 hours	72 hours
Vector Backbone (LTR)	LXSN (MoMLV LTR)	MND (MPSV LTR) GCSAP (MPSV LTR)
Vector Envelope (Packaging Line)	A-MuLV (GP+Am12)	GALV (PG13)

[9] Aiuti, A., et al., *Gene therapy for adenosine deaminase deficiency.* Curr Opin Allergy Clin Immunol, 2003. **3**(6): p. 461-6.

*Details provided with kind permission from Drs. Kohn and Podsakoff of The Saban Research Institute of Children's Hospital Los Angeles. Conditions reflect methods used since 2001, not previously.

Table 4. Clinical Summary of ADA-SCID Trials

Investigator	Previous BMT/ Conditioning	Previous infectious or other complications	Max Dose transplanted ADA$^+$ cells/kg	Longest time from treatment
Bordignon[3]	1 of 2 subjects Busulfan conditioning	Yes	2.15 x 10^6	Approx 3.5 years
Kohn*	1 of 4 subjects No conditioning	No	6.67 x 10^6	Approx 40 months

[9] Aiuti, A., et al., *Gene therapy for adenosine deaminase deficiency.* Curr Opin Allergy Clin Immunol, 2003. **3**(6): p. 461-6.

*Details provided with kind permission from Drs. Kohn and Podsakoff of The Saban Research Institute of Children's Hospital Los Angeles. Conditions reflect methods used since 2001, not previously.

1. Hacein-Bey-Abina, S., et al., *Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy.* New England Journal of Medicine, 2002. **346**(16): p. 1185-1193.
2. Gaspar, H.B., et al., *Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector.* Lancet, 2004. **364**(9452): p. 2181-7.
3. Aiuti, A., et al., *Gene therapy for adenosine deaminase deficiency.* Curr Opin Allergy Clin Immunol, 2003. **3**(6): p. 461-6.