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November 21, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

**RE: Federal Register Document 05-16629 Draft Guidance for Industry
on Gene Therapy Clinical Trials---Docket No. 2005D-0310**

REQUEST TO EXTEND DEADLINE FOR COMMENT ON DOCKET:

The International Center for Technology Assessment (ICTA) appreciates the opportunity to comment on the FDA Draft Guidance for Gene Therapy Clinical Trials. We are engaged in a project to review the risk and efficacy of gene therapy clinical trials. We are submitting comments to comply with the November 21, 2005 deadline, but wish to also request that the Docket remain open for another 90 days.

The International Center for Technology Assessment is reviewing the NIH Recombinant DNA Advisory Committee (RAC) "Data Management Reports," which list adverse events that are of significant interest and concern to be discussed by the RAC at their quarterly meetings.¹ Until June of 2004 these reports were regularly posted on the NIH website and made available for public review. However, from June 2004 until November 2005, the reports were not posted. ICTA wished to incorporate the recent data into its review of the questions in the Document, but received the relevant material from NIH only on November 9. To adequately review approximately 93 new adverse events before your November 21 deadline is not possible. Along with the Data Management Reports, we were also sent over 2,000 pages of related information that we would like to glean for insight for our comments. So we request that the Docket No. 2005D-0310 remain open for another 90 days.

¹ See the NIH/RAC website: "Protocols that raise novel or particularly important scientific, safety or ethical considerations are discussed by the RAC at one of its quarterly public meetings."
<http://www4.od.nih.gov/oba/rac/aboutrdagt.htm>

2005D-0310

EXT 1



INTERIM COMMENTS FOR NOVEMBER 21, 2005 DEADLINE:

We are submitting the following comments to comply with the Nov. 21 deadline.

Re: IV. A. Criteria to Assess Potential Delayed Risks of Gene Therapy

The Criteria need to address the possibility of inadvertent germ-line effects.

The criteria as presented exclude further guidance from the FDA related to the possibility of inadvertent germ-line effects as a result of gene therapy trials. Guidance related to inadvertent germ-line modification should be added to the guidelines. As the age of participants in the gene trials has increased and many trials include persons of reproductive age, or include participants that have now reached reproductive age, the possibility of inadvertent germ-line effects increases.

As it is difficult to study inadvertent germ-line transfer in human trials, the first choice is to change the approach to gene therapy such that germ-line effects are avoided. The US Recombinant DNA Advisory Committee has not approved any direct germ-line therapy, but the British Fertilisation and Embryology Authority has recently approved a human embryo experiment involving mitochondrial genetic engineering, despite British law that prohibits embryo experiments that change the genetics of the embryo.² Moreover, because some prominent geneticists are arguing for germ-line therapy as a way around some of the more difficult problems in gene therapy, it is all the more important to monitor trials for inadvertent germ-line effects and possibly anticipated germ-line effects.³

The Food and Drug Administration and the RAC have addressed the issue of inadvertent germ-line line effects previously.⁴ Those reviews, in effect, concluded that while inadvertent germ-line effects are possible, they have not been witnessed yet. And this is a difficult phenomenon to study given that the precise outcome cannot be known for years and would depend on the vector, since different vectors integrate at different sites and affect the functioning of surrounding genes differently. Moreover, the social costs of preventing a serious, but low likelihood event like germ-line alteration are high in that this would require an expectation that trial participants not reproduce or would consent to a lifetime of monitoring. Even if the subjects did consent to be monitored, they could not bind the consent of their offspring into reproductive ages. No study should have such a level of coercion. Even so, to the extent possible, human subjects of

² See Human Fertilisation & Embryology Authority, Press Release 8/9/05, "HFEA grants licence to Newcastle Centre at LIFE for Mitochondrial Research," accessed at <http://www.hfea.gov.uk/PressOffice/Archive/1126195581>

³ At the June 2000 press conference on the announcement that a New Jersey fertility laboratory had inadvertently made germ-line changes in an IVF embryo, a Nation Magazine reporter asked James Watson what he thought of his friend Eric Lander's proposal for a statutory ban on germ-line engineering. "Disaster," he spat back without hesitation. "It's germline, if anything, that one day will save us." Save us from what? "Oh, something like AIDS," he suggested (Ralph Brave in "Governing the Genome", Nation, Dec. 10, 2001)

⁴ See minutes of the March 1999 RAC meeting, www4.od.nih.gov/oba/RAC/meeting.html. See the same site for minutes of the December 2001 RAC meeting and minutes of the March 2002 meeting.

experiments should be urged to participate in long-term follow-up to determine possible germ-line effects of their treatments. Though vector DNA has not been detected in germ cells, it has been detected in the semen of a human subject up to ten weeks after administration of an adeno-associated viral vector.⁵ The presence of such DNA in human semen should give gene therapy researchers pause, and argues for continued, vigilant monitoring for germ-line effects. Additionally, subjects should be offered the option of having an autopsy performed after they die.

The challenges discussed for human follow-up make animal studies of inadvertent germ-line effects all the more important. These studies should include studies of possible germ-line effects on offspring. Animal studies should review the effect of varying doses and methods of administration of gene therapy vectors on inadvertent germ-line modification. Then the offspring of subject animals should be monitored as well.

In summary, we recommend: 1. That trials be designed to avoid germ-line effects; 2. That the studies of the long-term effects on human subjects include possible germ-line changes in the subjects and their offspring; and 3. That animal studies include study of possible germ-line effects in both study animals and their offspring.

Viruses not believed to be susceptible to integration in the genome should be studied more thoroughly.

Like inadvertent germ-line modification, the integration of viruses like adenoviruses is believed to happen infrequently, but modifications of large genes in order to fit them into the space of a viruses, or the modification of the gene to encourage it to reside in a different organ as is being done with adeno-associated viruses may change the likelihood of integration or the location of integration in the human genome. The modification of genes to allow them to fit into a particular viral vector may also pose additional risks. As viruses are genetically altered they may develop properties hitherto unknown. Finally, vectors are now being intentionally modified to increase their persistence in the patient, since persistence may be desired for therapeutic effect. Guidelines for follow-up that are structured around vector type (see Table 1 in Document) are likely to be insufficient. All viral vectors should be subject to testing for integration, other mechanisms of persistence, and delayed adverse effects.

Adeno-Associated Virus (AAV) vectors

A 2004 paper by Douglas M. McCarty, et al. points out that adeno-associated virus has the potential for mutation and oncogenesis due to random integration. The authors note *“the evaluation of the frequency of rAAV vector integration and its propensity for targeting transcriptionally active regions of the genome is therefore an area of research being pursued with some sense of urgency....many novel gene delivery systems are being devised to take advantage of the targeted integration properties of the AAV Rep protein. These include hybrid viral vectors as well as non-viral systems for*

⁵ See RAC Meeting Minutes, Dec. 6, 2001. Accessed at: <http://www4.od.nih.gov/oba/rac/minutes/Dec01minutes.pdf>

delivering Rep protein and naked plasmids...All of these issues are certain to have an impact on the safety and efficacy of rAAV mediated gene therapy.”⁶

Our review of gene therapy trials suggests that 14 of 28 human gene therapy trials using AAV vectors have begun in the last two and a half years.⁷ As more trials are begun, use of this vector may increase still more. Its potential for random integration when lacking the Rep protein gene should make trials involving modified AAV strong candidates for long term monitoring.

Adenovirus vectors

As presently worded the guidelines suggest that in most cases there are fewer long term concerns with adenovirus vectors than retroviruses, herpes viruses, and some other viral vectors. A major limitation of adenovirus vectors for gene therapy has indeed been the instability of adenovirus-mediated therapy to maintain the transgene through reproduction and integration. Still, there have been many attempts to develop strategies including extra-chromosomal mechanisms for assuring transgene persistence. Given that much work is being done to devise ways of improving transgene persistence in adenovirus vectors,⁸ we believe that the burden of proof for researchers should be to demonstrate that their use of a modified adenovirus vector carries no likelihood of long term effects. The high rate of adverse events and mortality in trials using adenoviruses argues for long term monitoring of adenovirus trial subjects.⁹

Length of Follow-up and other issues

We agree with the FDA recommendations on length of follow-up with subjects, but as noted above believe the children of subjects should also be followed to the extent possible to monitor for the possibility of long term effects. Finally, given the substantial number of unanticipated adverse events in gene therapy clinical trials,¹⁰ it is clear that the actions and effects of gene therapy agents are not entirely understood. Therefore, all studies where subjects are expected to live beyond the immediate period of the study should include provisions for long-term follow-up at least once a year.

⁶ Douglas M. McCarty, et al in “Integration of Adeno-Associated Virus (AAV) and recombinant AAV Vectors” in Annual Review of Genetics, Palo Alto: 2004, Volume 38, p.819-845

⁷ See below for trials w/ AAV vectors 1996-2005 (partial year). This was derived from a database kept by the Journal of Gene Therapy (<http://82.182.180.141/trials/index.html>)

Vector	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total
Adeno-associated virus	0	1	1	2	4	5	1	3	8	3	28

⁸ See for example, Valeri Krougliak, et al, “Stabilization of transgenes delivered by recombinant adenovirus vectors through extrachromosomal replication,” in The Journal of Gene Medicine, 2001, Vol.3: pgs. 51-58

⁹ See Tables at end of this comment.

¹⁰ For instance, according to NIH/RAC Data Management Reports, there were approximately 100 “serious, possibly associated, and unexpected” adverse events in gene therapy clinical trials discussed by RAC from March 2001 through September of 2002.

Thank you for this opportunity to comment

We wish to thank you for this opportunity to comment on the guidance document. However, we wish to reiterate our request that the comment period be extended for an additional 90 days so that ICTA and others might have adequate opportunity to review the new postings of adverse event data related to gene therapy trials.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Andrew Kimbrell', written in a cursive style.

Andrew Kimbrell
Executive Director

Table 1: NIH/RAC reported adverse events and deaths by vector, 1996 to present¹¹

Vector Type	Reported adverse events		Reported deaths	
	#	%	#	%
Retrovirus	99	19.9	16	30.8
Adenovirus	262	52.6	23	44.2
Adeno-associated virus	13	2.6	0	0.0
Herpes virus	9	1.8	0	0.0
Pox virus	39	7.8	6	11.5
Plasmid DNA and other non-viral vectors	76	15.3	7	13.5
TOTAL	498	100.0	52	100.0

Table 2: Total trials by vector-type, 1996 to present¹²

Vector Type	Approx. trials	
	#	%
Retrovirus	229	32.4
Adenovirus	176	24.9
Adeno-associated virus	25	3.5
Herpes virus	10	1.4
Pox virus	84	11.9
Plasmid DNA and other non-viral vectors	182	25.8
TOTAL	706	100.0

¹¹ This information was compiled from the NIH RAC "Data Management Reports" posted on the RAC website, <http://www4.od.nih.gov/oba/rac/documents1.htm>. These are the adverse events that were of significant interest to be reviewed by RAC, though the criteria for these events seem to have changed over time. Every effort was made to weed out follow-up reports or other reports that did not indicate new adverse events.

¹² Information in this table was compiled from GeMCRIS, the database of gene therapy clinical trials maintained jointly by FDA and NIH. Due to complications in the way vectors are listed in the database, this should be viewed as a rough estimate. Accessed at: <http://www.gemcris.od.nih.gov>.

Table 3: NIH/RAC reported adverse events by vector and year¹³

	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	Total
Retrovirus	0	6	6	11	61	1	3	0	2	9	99
Adenovirus	1	6	12	22	123	39	22	1	29	7	262
Adeno-associated virus	0	0	0	0	0	0	0	0	10	3	13
Herpes virus	0	0	0	0	3	0	4	0	0	2	9
Pox virus	0	0	0	0	9	3	0	4	8	15	39
Plasmid DNA and other non-viral vector	0	1	1	12	26	6	8	3	8	11	76
Total	1	13	19	45	222	49	37	8	57	47	498

¹³ See footnote #11 for source of this data.