PDA Global Headquarters
Bethesda Towers
4350 East West Highway
Suite 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (240) 482-1659
www.pda.org

January 7, 2009

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

Reference: Draft Guidance for Industry on Potency Tests for Cellular and Gene Therapy Products; Federal Dockets Management System Docket FDA-2008-D-0520

Dear Sir/Madam:

PDA is pleased to offer comments on the FDA Draft "Guidance for Industry on Potency Tests for Cellular and Gene Therapy Products". PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in cell and gene therapy and potency assays including members representing our Regulatory Affairs and Quality Committee and our Biotechnology Advisory Board. PDA appreciates the opportunity to offer comments on this Draft Guidance and wishes to thank FDA for the opportunity to do so.

PDA endorses the need to maintain regulatory guidance documents in a state that emphasizes current technology, science and best practices. We also acknowledge the effort made by FDA in the publication for comments of FDA's Draft "Guidance for Industry on Potency Tests for Cellular and Gene Therapy Products". PDA welcomes this Guidance document as it provides more detailed information on the application of the general rules, as laid down in 21 CFR, for cellular and gene therapy (CGT) products. The guidance provided helps sponsors in the development of an appropriate strategy for the production and control of these products.

With regard to the draft guidance document on potency assays for CGT products, we have provided detailed comments identified by section, paragraph and sentence and have included a supporting rationale in the accompanying table. The following is a brief overview of the major points that PDA believes are most important to highlight to strengthen this guidance document:

- The terminology used in the development and validation of potency assays as well as in CGT products often has multiple meanings. PDA has spent considerable effort trying to clarify wording and/or to highlight instances where wording is confusing or has multiple meanings. Some terms are used in a different way than previous use in 21CFR or other guidance documents, (e.g. "reproducibility",

and “sensitivity”), or terms are used which are not defined in this or other documents, (e.g. ‘reliable’ assay appropriate for lot release; strength vs. potency). Some clarification about the use of specific terms in this Guidance document are provided in footnotes, however it is proposed to add a Section ‘Glossary’ to collect all definitions in a single place (rather than in footnotes) and to clarify the intended meaning of terms in relation to CGT potency assays.

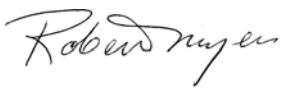
- The term “reproducibility” is used several times in 21CFR and those uses are referred to in this Guidance, but the term is never defined. PDA feels it would help the reader of this document to define “reproducibility” as it pertains to uses in this document, especially where it varies from the definition provided in ICH Q2(R1); i.e. with regard to qualitative assays. Because Q2(R1) refers to reproducibility as one of three aspects for characterizing assay precision, PDA recommends careful use of the term in accordance with Q2(R1). Where it seemed appropriate, PDA substituted the words “intermediate precision” for “reproducibility”.

- PDA feels that it is important for FDA guidance documents to be consistent with ICH documents and supports the efforts of regulators and industry to harmonize these documents. We urge the FDA not to ask for validation of parameters not called for in ICH Q2(R1), e.g. sensitivity in IV.C.1 and IV.C.3.

Again, PDA appreciates the opportunity to comment on this draft Guidance document and provides these recommendations for your consideration. PDA believes that these comments will clarify and strengthen the Guidance document to better serve the needs of both regulators and industry.

We would be pleased to offer our expertise in a public discussion and/or meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely



Robert B. Myers
President, PDA

Enc: Detailed Comment Spreadsheet; version eight (8)/December 22, 2008

FDA's Draft Guidance for Industry on *Potency Testing of Cellular and Gene Therapy Products*

Comments due to docket January 7, 2009

Line No.	Current Text	Proposed Change	Rationale
General Remark: Some terms are used in a different way as in other guidance documents, e.g. reproducibility in relation to Q2(R1), or terms are used which are not defined in this or other documents, e.g. 'reliable' assay appropriate for lot release; strength vs. potency. Some clarification about the use of specific terms in this Guidance document is provided in footnotes. PDA recommends addition of a Glossary to define these terms, rather than the use of footnotes throughout the Guidance.			
II. Background			
p.2; Footnote 7	Footnote 7: For purposes of this guidance, strength is the equivalent of potency.	Recommend that Footnote 7 belongs in the glossary	Use of a Glossary rather than footnotes.
p. 3; 6th bullet:	Establish and document the accuracy, sensitivity, specificity and reproducibility of the test methods employed through validation (21 CFR 211.165(e) and 211.194(a)(2));	Reproducibility as used in the CFR does not appear to comply with the formal definition provided in ICH Q2(R1). Please insert a footnote that reproducibility as used in the CFR does not have the same definition as used in ICH Q2 (R1) and clarify how the CFR use of "reproducibility" pertains to this particular guidance in the glossary.	Proposal to follow ICH definitions & guidelines with regards to "reproducibility"; or, when there is a deviation from this accepted definition, that this be clarified.
p. 4; Table 1, Line 2, 3rd bullet under examples	Error-Prone Replicating Virus	Please clarify the terms "error-prone replicating viruses". Which classes of virus/viral vector does the FDA consider to be error-prone? If error prone virus includes retroviruses, this would be inconsistent with the use of retroviruses in gene therapy as replication incompetent vectors. We suggest a definition of the terms virus and vector, as consistent use of these terms may aid in clarity. Please clarify why the example is limited only to replicating viruses since this refers to starting material used in manufacturing and thus virus or vector does not need to be replicating in vivo.	Eliminate this example or clarify. It is not a given that all replicating viruses are error prone What exactly (specifically) is meant by "replication"? {requires further clarification and reference; explain the types of variety, e.g., mutation/replication.

Line No.	Current Text	Proposed Change	Rationale
p. 4; Table 1: Challenges to potency assay development for CGT	Complex mechanism of action(s).	Proposed wording in left column: *"Complex mechanism of action(s) or not fully characterized systems"* Add 4th bullet in right-hand column: • *Intended effect occurs within a complex and not fully characterized system such as the immune system*	Added reference to" not fully characterized" is consistent with suggested wording in paragraph in III.A, third paragraph., second sentence, page 5 and highlights the fact that often MoA is not known especially during clinical trials and development of potency assays.
	None	Add another row to Table with the following in the left-hand column: *Dynamics of Potency assay* Examples to be listed in the right-hand column: • *Gene therapy products may require the expression of the vector in one cell line and the readout of the expressed vector product in another cell line.* • *Biologic-device combinations (ex: cells and scaffold) or other products where it is not possible/feasible to directly put the cells/gene therapy in the test system*	These are not discussed in Table but are common issues
III. Recommendations for Potency Measurements			
p. 5; 2nd para, last sentence	Although some of the assays….most properly designed assays (see Section IV.A) have the potential…., or both.	*Although some of the assays….a properly designed assay (see Section IV.A) has the potential…., or both.*	Readability
p. 5; 3rd paragraph, 2nd sentence	CGT products often have complex and/or poorly defined mechanism(s) of action…	*CGT products often have complex and/or* ***not fully characterized*** *mechanism(s) of action*	Consistency with proposed changes for Table 1
p.5; 3rd paragraph, end of second sentence	…which product attribute is most relevant to measuring potency.	"*…which product attribute(s) are most relevant to measuring potency*."	More consistent with rest of section; many developers think they should only explore one potency assay as they need to find THE mode of action; most efficacious products have multiple modes of action.

Line No.	Current Text	Proposed Change	Rationale
p. 5; third paragraph	For example, a gene therapy vector should rely on at least two biological activities for its potency; the ability to transfer a genetic sequence to a cell and the biological effect of the expressed genetic sequence. Therefore, the potency assay should incorporate both a measure of the gene transfer frequency and the biological effect of the transferred gene.	Add the following statement: *If possible, measurement of the biological effect of the transferred gene should be quantitative. However, a qualitative measurement may be sufficient given the complex nature of these types of assays.*	While there are two biological activities required to deliver the necessary action of the gene vector example (transfer the genetic sequence and express the genetic sequence) it seems that only one of the two inter-related, biological activities would be needed for a routine potency assessment to assure lot to lot consistency as long as appropriate characterization of the other biological activity was performed.
	Not addressed	Testing of biologic-device combinations (ex: cells and scaffold) or other products where it is not possible/feasible to directly put the cells/gene therapy in the test system was not discussed in the document. Please include a comment in the guidance clarifying acceptable approaches for establishing potency in those situations.	For example, is indirect testing (metabolite secretion in culture media) considered a reasonable surrogate? Some of these cell-constructs have a structural aspect in addition to a metabolic one. Would potency only have to be addressed for the 'biologic' component of the cell-scaffold or is potency applicable to the entire construct (cells-scaffold)? If potency is to be applied to the entire construct, it is difficult to see how an in vitro test is feasible.
p. 6; section B.2, 3rd sentence	For example, you may need to use an analytical assay(s) that is practical and reliable for lot release.	*For example, you may need to use an analytical assay(s) that is practical and demonstrates adequate performance characteristics for lot release.*	Reliable is a subjective term.
p. 6; Footnote 11	Furthermore we acknowledge that in other contexts a bioassay may be considered an analytical assay	*However, we acknowledge…*	Clarity. The use of however makes clear that a bioassay is an analytical assay and that the guidance has used an artificial distinction.
p. 7; Section B.3 bullet	Product has complex mechanism of action	*Product has a complex and/or a not fully characterized mechanism of action*	Consistent wording in the document.

Line No.	Current Text	Proposed Change	Rationale
p. 7; III B 3 Multiple Assays (matrix) Sentence before last	The assay matrix may include assays that give a quantitative readout (e.g., units of activity) or qualitative readout (e.g., pass/fail).	*The assay matrix may include assays that give a quantitative readout (e.g., units of activity) and/or qualitative readout (e.g., pass/fail).*	Clarity: addition of "and" reads better with final sentence that requires quantitative assay if qualitative also used
p. 8; III C last sentence	If you intend to demonstrate potency by correlating a surrogate assay(s) to a relevant biological activity, you should start collecting product and assay characterization data during early investigational phases.	Revise as follows: *As with any potency assay, you should start collecting product and assay characterization data to support your choice of assay during early investigational phases.*	The sentence might be interpreted as suggesting that for a direct biological assay there is no need to collect product and assay characterization data during early investigational phases.
p. 8; III, E, last para 1st sentence	For some products in pre-clinical, Phase 1, and early Phase 2 studies, limited quantitative information on bioactivity may be sufficient.	*For some products in pre-clinical, Phase 1, and early Phase 2 studies, limited quantitative information on relevant biological attributes may be sufficient.*	"Bioactivity" is not clear and not defined. Recommended text is consistent with characterization of potency assays on page 5.
p. 9; E2 Later Phase Product Develop-ment	In addition, you should use a well-characterized potency assay with established limits during stability testing of conformance lots used to establish expiry dating for licensure (see 21 CFR 610.53; Ref. 7)	*In addition, you should use a well-characterized potency assay demonstrated to be stability indicating, or an assay matrix that includes complementary stability-indicating assays, with established limits during stability testing….*	Clarity and emphasize the need for a stability indicating method particularly at a later phase of development
IV. Assay Design and Validation			
p.9; IVA, second sentence	…using sample randomization…	add "to the extent that it is practical" so it reads: *… using sample randomization to the extent that it is practical…*	Unless the assay is well developed and computer aided systems exist, true random placement of the different doses in the response curve for a sample can lead to truly random results.
p. 10; IVA top of page	General principles for reducing variability include using well-defined reagents, well-calibrated equipment, and adequately trained operators.	*General principles for reducing variability including using qualified reagents, qualified equipment and adequately trained and qualified operators*	Clarity: delete "well" and "adequate" and use generally accepted terms.

Line No.	Current Text	Proposed Change	Rationale
p.10; IVB, 1st paragraph	As with all well designed experiments, developing a potency assay should include appropriate controls and a comparison to an appropriate reference material, when available. Running a reference material and/or control samples in parallel with the product helps ensure that the assay is performing as expected. In addition, controls help establish that the equipment and reagents are working within established limits. A well designed set of control samples can substantially increase confidence that results are meaningful and reproducible.	*As with all well designed experiments, developing a potency assay should include appropriate assay controls and a comparison to an appropriate product-specific reference material, when available. Running a product-specific reference material and/or control samples in parallel with the product helps ensure that the assay is performing as expected. In addition, controls help establish that the equipment and reagents are working within established limits. A well designed set of control samples can substantially increase confidence that results are meaningful and reproducible.*	All potency assays are relative potency assays which means that the reference material/standard and test sample have to be run in each and every assay. The potency of the test sample is reported relative to the reference standard only after it is shown that the two have similar response curves. Even if a reference material as described in the now third paragraph exists, you should develop an "in house" reference material as the general standards described in the third paragraph will not have product specific functionality needed for a potency assay.
p.10; IVB, 2nd paragraph	Reference materials and standards can help with assay development and can be used to develop and qualify more relevant "in house" reference materials and/or controls. A number of reference materials, standards, and controls are available or are being developed for characterizing biologics. For instance, there are fluorescent bead/antibodies and particle size standards[13] and guidelines[14] available to help calibrate equipment and help define acceptable parameters for quantitative flow cytometry analysis (Ref. 18). Reference materials are also currently available for adenovirus type 5 (Ref. 19)[15] and retrovirus[16] vectors. A reference material for adeno-associated virus type 2 vectors[17] is under development. Standard materials and controls for lentivirus vectors have also been described (Ref. 20).	*You should develop your own "in house" product-specific reference material(s) (Refs. 9 through 11). These may include well characterized clinical lots or other well characterized materials prepared by you or another resource (e.g., a well characterized cell line with a profile similar to your product). There should be a clear rationale for how and why the reference material (including "in house" product-specific reference material/control) was developed. We encourage you to consult with your CBER review team when developing or obtaining reference materials.*	Switched the order of 2nd and 3rd paragraphs to continue the discussion of product-specific reference materials (introduced in the first paragraph) before the discussion of general, non-product-specific reference materials. General standards described in the draft guidance's second paragraph will not have product specific functionality needed for a potency assay. Even for novel recombinant proteins one has to develop in house standards; i.e. one should develop in-house reference materials along with assay development regardless whether or not there is universal standard or reference material available.

Line No.	Current Text	Proposed Change	Rationale
p.10; IVB, 2nd paragraph	In the event that a universal standard or reference material is not available, you should develop your own "in house" reference material(s) (Refs. 9 through 11). These may include well characterized clinical lots or other well characterized materials prepared by you or another resource (e.g., a well characterized cell line with a profile similar to your product). There should be a clear rationale for how and why the reference material consult with your CBER review team when developing or obtaining reference materials.	*Other reference materials and standards can help with assay development and can be used to develop and qualify more relevant "in house" reference materials and/or controls. A number of reference materials, standards, and controls are available or are being developed for characterizing biologics or the "read-out" system for a potency assay. For instance, there are fluorescent bead/antibodies and particle size standards[13] and guidelines[14] available to help calibrate equipment and help define acceptable parameters for quantitative flow cytometry analysis (Ref. 18). Reference materials are also currently available for adenovirus type 5 (Ref. 19)[15] and retrovirus[16] vectors. A reference material for adeno-associated virus type 2 vectors[17] is under development. Standard materials and controls for lentivirus vectors hace also been described (Ref 20).*	Switched the order of 2nd and 3rd paragraphs to emphasize the typical chronological order; i.e. one should develop in-house reference materials along with assay development regardless whether or not there is universal standard or reference material available.
p.10; IVB, 2nd paragraph	Because you will use reference materials at various stages of product development and characterization, you should subject them to stability studies in parallel with your product stability studies (Ref. 7). Moreover, you should appropriately characterize each new batch of reference material, compare it with the original, and establish appropriate procedures to qualify and eventually validate new reference materials. When possible, you should retain samples (Refs. 6 through 8) of each lot of reference material for comparison with newly manufactured reference material and prepare in advance for depletion or expiration of reference materials.	*Because you will use in-house reference materials at various stages of product development and characterization, you should subject them to stability studies in parallel with your product stability studies (Ref. 7). Moreover, you should appropriately characterize each new batch of in-house reference material, compare it with the original (in-house and/or external reference materials), and establish appropriate procedures to qualify and eventually validate new in-house reference materials. When possible, you should retain samples (Refs. 6 through 8) of each lot of in-house reference material for comparison with newly manufactured in-house reference material and prepare in advance for depletion or expiration of in-house reference materials.*	Changes to add clarity.

Line No.	Current Text	Proposed Change	Rationale
p. 11; end of section IVB	None	*Suggest inserting:* *"The use of statistical control charts to map the ongoing performance and stability of reference material during routine assays can be a useful quality control tool allowing for early detection of adverse trends. "*	Control charts for reference material are often used by companies, providing an early indication of degradation of the reference material.
p. 11; C1	You should perform analysis and validation of all relevant assay parameters (Ref 9 through 11) including : • Accuracy • Precision (repeatability, ***Reproducibility)*** • ***Sensitivity (Limit Of Detection/ Quantitation)*** • Specificity • Linearity and Range • System Suitability • Robustness/Ruggedness	Remove reference to reproducibility and sensitivity. Revised wording: *You should perform analysis and validation of all relevant assay parameters (Ref 9 through 11) including :* • *Accuracy* • *Precision (repeatability, Intermediate precision)* • *Specificity* • *Linearity and Range* • *System Suitability* • *Robustness/Ruggedness*	Per ICHQ2(R1): While intermediate precision is part of the precision parameter for validation, reproducibility (precision between laboratories) is not. LOD/LOQ are not normally evaluated for content/potency assay (see table 1 of ICH Q2(R1)
p. 11; IV. C.2 5th sentence	These descriptions should be sufficiently clear to permit independent statistical analysis and evaluation of the results presented in the study reports. Data collected from potency assay validation studies, when provided in electronic format, can facilitate statistical evaluation by the CBER review committee.	Delete reference to providing assay validation data in electronic format, or provide further clarification of the circumstances under which this data might be required.	If electronic data of this sort is deemed a requirement, instructions should be provided for how the data is to be formatted, organized and the extent of data that should be provided. It is not clear what the CBER review committee would do with the data or the value of that action, nor is it clear when in the development process such electronic data might be requested or why.
p.12; IVC.3, 1st paragraph, last sentence	…should be used to characterize the assay for specificity and sensitivity as well as for other features of acceptable performance (e.g., robustness, system suitability).	delete "sensitivity"	It's not clear why sensitivity would be important in a qualitative assay for potency when it is not for a quantitative potency assay.

Line No.	Current Text	Proposed Change	Rationale
p.12; IVC.3, 2nd paragraph, first sentence	Without quantitative data, demonstrating accuracy and precision could be challenging; however, with proper assay design (e.g., sufficient replicates), you might be able to demonstrate reproducibility.	Please clarify what is meant by the term "reproducibility" within a qualitative assay.	As written, the meaning of "reproducibility" is not clear.
p.12; IVC.3, 2nd paragraph, third sentence	Also, limits of detection and/or quantitation may be built into the assay design suitability criteria.	Delete	It is not clear why limits of detection and/or quantitation would be important in a qualitative assay for potency when it is not for a quantitative potency assay.
p.12; IVC.3, 2nd paragraph, 4th sentence	For example, if a reasonable amount of the control or reference material does not exhibit the desired activity with sufficient statistical justification, the assay would not generally be considered acceptable.	Replace 3rd and 4th sentences of this paragraph with: "You should establish acceptance criteria for the control and/or reference materials in your qualitative assay to determine if each assay is acceptable. If the controls fail in many of the individual assays the assay would not be considered to be acceptable."	References to statistical justification are not applicable for qualitative assays.
p.12; IVC.4,	4. Assay evaluation and modification	Replace by adding a new section D with the heading "**How Do I Maintain and Manage Change in my Assay**?"	The activities listed under IV, C, 4 are not solely validation activities.
p. 12; Section 4	Insert new sentence before last sentence on page 12	Insert new sentence before last sentence on page 12: *"In addition, a statistically designed study to demonstrate comparability between the modified and/or new assay, and the original assay should be conducted. The study plan should include pre-determined acceptance criteria to demonstrate equivalence between the assays."*	Assessment of equivalence between original and modified or new assay was not discussed.

Glossary (Definitions for the purpose of this document):

Active ingredient Active Pharmaceutical Ingredient (API) or Drug Substance	Component that is intended to furnish pharmacologic activity or other direct effects in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or any function of the body of man or *other* animals (21 CFR 210.3(b)(7)); (footnote, p. 5). Prefer ICH Q7 Definition: Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. (Section 20, Glossary)
Analytical assay	A method that measures the biological activity of the product outside a living system. Could be a cell-culture based assay or a biochemical assay method that measures immunochemical (e.g. quantitative flow cytometry, enzyme-linked immunosorbant assay), molecular (e.g. reverse transcription polymerase chain reaction, quantitative polymerase chain reaction, microarray) or biochemical (e.g. protein binding, enzymatic reactions) properties of the product outside of a living system. To distinguish traditional bioassay methods (performed in a living system) from non-bioassay methods (performed outside of living system), we use "analytical assay" to refer to methods that measure immunochemical (e.g., quantitative flow cytometry, enzyme-linked immunosorbant assay), molecular (e.g., reverse transcription polymerase chain reaction, quantitative polymerase chain reaction, microarray) or biochemical (e.g., protein binding, enzymatic reactions) properties of the product outside of a living system. Furthermore, we acknowledge that in other contexts a bioassay may be considered an analytical assay.
Biological activity	The specific ability or capacity of the product to achieve a defined biological effect. Potency is the quantitative measure of the biological activity (ICH Q6B).
Correlation	Statistical relationship between two or more variables such that systematic changes in the value of one variable are accompanied by systematic change in the other.
Potency	The measure of biological activity using a suitably quantitative biological assay (also called the potency assay or bioassay), based on the attribute of the product which is linked to the relevant biological properties (ICH Q6B) (Add both 21 CFR 600.3S)
Product characterization	A series of tests, including drug substance, in-process, and final product tests, that measure product attributes associated with product consistency and quality in order to assure identity, purity, strength (potency) and stability of products.
Pivotal study	Any clinical study where the data obtained from this study will be used to support a clinical efficacy claim for the biologics license application (BLA).
Replication	New synthesis of DNA by DNA-Replicase. The doubling of genomic DNA or RNA when used in the context of the reproductive cycle of cells or viruses
Replication - competent	Refers to the ability of the virus to make more of itself in humans, resulting in infectious particles.
Replication-incompetent vector	Vector or virus that cannot undergo a second round of replication outside of the manufacturing environment.

Repeatability	Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision (ICH Q2A(R1).
Reproducibility	Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology) (ICH Q2A(R1). We request that the FDA define what is meant by "reproducibility when used in 21 CFR. We believe it means "intermediate precision" as defined in ICH Q2A (R1).
Strength	Term used interchangeably with 'potency' to denote a measure of biological activity (footnote, p. 2).
Test	Term used interchangeably with 'assay' and 'measurement' to denote a procedure designed to quantitatively or qualitatively measure a specified parameter (footnote, p. 1)
Virus	Intracellular replicating infectious agents that are potentially pathogenic, possessing only a single type of nucleic acid (either RNA or DNA), are unable to grow and undergo binary fission, and multiply in the form of their genetic material. (ICH Q5A)
Vector	Vehicle used to transfer genetic material to a target cell; virus vector: a virus modified to deliver genetic material to a target cell. A virus vector can be replication competent or not. If not (e.g. adenovirus vectors), testing for absence of Replication Competent Virus (RCV) is required.
Vector sequences	Refers to specific sequences of nucleotides, either DNA or RNA, that have been introduced into a gene therapy vector. The sequence includes all components of the gene therapy vector, the vector backbone, transgene(s), and regulatory elements. [Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (28NOV06)]
Viral vector	A virus that has been modified to transfer genetic material. [Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (28NOV06)]