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Submitted by:

Jeffrey A. Green, Pharm.D, FCP
President & Chief Executive Officer

The following comments and position statements are respectfully submitted for consideration in the drafting and/or revision of future regulations in 21 CFR Part 11, specifically pertaining to Audit Trail functionality in electronic data collection systems. Our current recommendations are consistent with our previously stated positions that can be found in the 2001 White Paper, "*Does Your EDC Product Complete Its Case Report Form in Pencil?*" that was posted on the FDA Dockets website at the following address:

<http://www.fda.gov/ohrms/dockets/dockets/00d1541/00d1541.htm>.

We are aware of the current Regulations regarding specifications for Audit Trail functionality for electronic systems. We are also aware and emphasize the importance of the Predicate Rules of conduct in clinical research as itemized in Good Clinical Practices (GCPs) Guidelines diligently followed by this industry for several decades.

Our position on this critically important issue of Audit Trail tracking with electronic systems is built on these summary statements:

1. The Predicate Rules of conduct in clinical research as defined in GCPs should be followed no less diligently and, in fact, more stringently with technology than they are with paper methodologies.
2. Regulations should drive technology, not the other way around.
3. Strict adherence to Regulations should be "built-in" to technological solutions allowing for guaranteed compliance with aspects such as identity and time stamping pertaining to information entry.

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Our specific recommendations that appear at the end of this brief communication are based on this reasoning.

A handwritten signature in black ink, appearing to read "Jeffrey A. Green".

Jeffrey A. Green, Pharm.D, FCP,
President and CEO, DATATRAK INTERNATIONAL

The Predicate Rules of GCP Should Be Followed No Less Diligently and Even More Closely With Technology Than With Paper

Regulation 21 CFR Part 11 does not require tracking of every backspace or deletion within an electronic field. We agree with this specific exclusion in Audit Trail tracking, as this is similar to penmanship or handwriting corrections in a paper model of data collection. It represents a transitory state prior to the finalization of a complete entry. When changes to data entry in a paper process are of insufficient magnitude to make the data entry illegible or ambiguous, stipulated corrections to the field with incumbent identity marks or dates are not required. Hence, in the electronic model, Audit Trail tracking would also be unnecessary in this situation.

However, such latitude in 21 CFR Part 11 should not be utilized as a loophole allowing for less diligence in the electronic tracking of Audit Trails in comparison to that of paper methods. A penmanship overwrite in the paper process is in no way equivalent to a complete **change** to a data field. They are two distinctly different actions in paper models of data entry and should likewise be considered separately when electronic systems are used.

In the paper process, the determinant of entry clarification is a matter of subjective evaluation and is usually left up to the reviewer or monitor when the magnitude of the change so dictates. A complete change to a data field in the paper model requires the drawing of a single line through the entry with a clarified re-entry in close proximity to that field, accompanied by the date and initials of the individual making the alteration.

However, the current language in 21 CFR Part 11 actually allows for backspaces and complete re-entries of data to be treated synonymously, since the determinant for characterizing both in an Audit Trail exists "when the information is committed to the database". When compared with the GCP-acceptable, everyday process used with paper described in the paragraph above, presumably an infinite quantity of entries can be made into a data field when using some technologies and that **only the final entry** would be available in an Audit Trail.

This level of information tracking is clearly far below the high level of diligence dictated by GCPs with paper and, perhaps most importantly, far below the level of performance possible with some EDC technologies. What can be the rationale of allowing for less diligent Audit Trail tracking with technology than with paper methods, especially when far higher levels of electronic Audit tracking are currently available?

In analyzing the potential impact of decreased diligence in electronic Audit Trail tracking, please consider the following scenario:

Some electronic data capture technologies cache data on a client (local) machine through the use of JAVA script or Active X applets that provide edit checks at the time of data entry. These edit checks can be used for field entries (such as for blood pressure, as an

example) in order to ascertain if data within certain boundary conditions is allowed in a specific study.

Under the current guidelines, investigative staff can make an unlimited number of field entries without being tracked on an Audit Trail **until the final entry is made** and the “information is committed to the database”. Such a situation can give rise to investigative personnel “fitting data into a study” with impunity knowing that such activities would never be tracked.

In fact, guidance from the existing edit checks on the client machine would actually assist less-than-scrupulous investigative staff in forcing the data to be compliant with written protocols. Therefore, the relaxing of the GCPs rules, done for the sake of “moving forward with technology” would actually contribute to the disguising of fraudulent data entries. Under the current manual methods adopted and used by this global industry for decades, an analogous lackadaisical approach would never be allowed.

It is our belief that allowing a less diligent tracking process for technology than that which exists with paper is a dangerous precedent to set in the global clinical trials industry. With improprieties and ethics violations apparently growing in frequency and magnitude in our society (e.g., Enron, Arthur Andersen, and recent financial scandals at Lehman Brothers, etc.), and with the clinical trials industry far from immune to similar occurrences we, as an industry, should shut the door tightly on any process that even allows the possibility of fraud.

We now have the opportunity to more diligently use technology to our benefit in the pursuit and tracking of information than ever before, but this requires that the correct guidelines be drafted to ensure that the process is as foolproof as possible.

Regulations Should Drive Technology

The relaxation of rules for the electronic collection of clinical trial data should not provide a crutch for inferior technical software and platforms. Technologies that currently exist provide capabilities now that far exceed those clinical trial methods associated with paper. Though the FDA does not approve electronic collection systems, per se, it has the opportunity now to efficiently guide the pharmaceutical and medical device industries in such a direction so as to save potentially immense amounts of time, expense, and risk from guidelines that are too lenient. It will be far easier to prevent the growth of unqualified technologies than to try to control a wayward market once it starts.

As this industry progresses toward the inevitable replacement of paper with computing technology, this is a particularly critical time in which Regulators should set the “bar of achievement” appropriately high. As was stated in the White Paper, “we cannot move forward with technology and fall behind in process”. How can we proclaim any advancement if we implement technology in such a way that it is inferior to the current

paper process? How can regulatory bodies ever consider an excess of information about clinical trial data to be undesirable or detrimental?

Some providers in this industry claim that the “commitment of data to a database” is the baseline from which efficiency, compliance and successful Audit Trail tracking is to be measured. We believe this is not the germane issue at all and it is quite possible this is being positioned in such a manner as to obscure consistency between current GCPs for paper and electronic systems secondary to limitations in current technical platforms. We believe that the **tracking** of data appropriately and consistently with established predicate rules should be used as the minimum acceptable standard for Audit Trails. The commitment of information to a database is the lowest possible baseline, is less diligent than paper methods and is akin in manual models to database entries subsequent to Query resolutions months after an investigator has seen a patient.

Recommendations for Future Guidance Requirements

1. Every data item in a clinical trial data system should have an Audit Trail.
2. Such an Audit Trail should contain **every** entry made into a particular field, just as is demanded by the Predicate Rules in GCPs used with paper methods. Without this level of tracking, it is impossible to determine an accurate sequence of events leading to data changes and would clearly be in conflict with GCPs for paper methodologies.
3. Such Audit Trail tracking should be involuntary, automated and not open to any potential for undisclosed modification in either content or timing by investigative or sponsor staff members.
4. The standard for Audit Trail tracking of data should be as high as is possible and limited only by the constraints of current proven technologies. Audit Trail tracking at the minimal level of “commitment to the database” is insufficient and far below the current capabilities of available technologies. The qualifier of tracking data in an Audit Trail after being committed to a database allows investigative staff to selectively determine what information is catalogued, simply by entering another “final” data item before the commission is performed.
5. Caching of data on a client machine for purposes of firing edit checks locally, combined with committing data to an Audit Trail **after** entry of a page (e.g., committing the information to the database), is not only less diligent than paper models of data collection and review, but is inviting future regulatory complications and concerns.