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	R & D	
Subject: Infrastructure Assurance	Eng.	

**Submission to FDA Docket 03D-0060
25 APR 2003
The Hollis Group, Inc.**

1. Purpose:

In the Federal Register / Vol. 68, No. 37 / Tuesday, February 25, 2003, the Food and Drug Administration (FDA) announced the availability of the draft guidance for industry entitled “*Part 11, Electronic Records; Electronic Signatures—Scope and Application.*” (0060 Draft Guidance) The 0060 Draft Guidance included a solicitation of comments from individuals, groups, and companies regarding the 0060 Draft Guidance to Docket 03D-0060. This document is such a comment.

2. Recommendations

1. The authors recommend that all references *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4* (ISPE/GAMP Forum, 2001) be removed from the 0060 Guidance
2. The authors recommend that the 0060 Guidance refer to the Final Guidance, General Principles of Software Validation; Final Guidance for Industry and FDA Staff, issued on January 11, 2002 as a source for suggested computer system and software validation methods.
3. The authors recommend that the 0060 Guidance include the risk analysis references listed in Section 4 of this document.

3. Rationale

At line 214 and at line 311, Reference 6, the 0060 Draft Guidance cites *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4* (ISPE/GAMP Forum, 2001) as an “Industry Reference” for further guidance on the validation of computerized systems. These are the only industry references to software or systems validation or quality assurance methods in the Guidance. Because GAMP 4 is exclusively mentioned, this reference could be interpreted as FDA’s endorsement of the methodology.

The authors recommend that this reference be removed from the 0060 Draft Guidance in order to avoid a presumption of such an endorsement. The authors urge this care because we have observed that GAMP 4 generally does not include objectives and methods that support current FDA software validation philosophy. Two examples of GAMP 4’s substantive diversion from FDA recommendations are:

1. GAMP 4’s exclusive dependence upon the IQ / OQ / PQ paradigm, and
2. GAMP 4’s exclusion of a human safety risk-based approach

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3.1. Current FDA Philosophy vs. IQ / OQ /PQ

The 0060 Draft Guidance withdraws the 1538 Draft Guidance, (Federal Register: September 24, 2001 (Volume 66, Number 185) Draft Guidance for Industry; Electronic Records; Electronic Signatures, Validation). This leaves only one current and in-force Final Guidance that deals with software and systems validation and quality assurance methods; this is the Final Guidance, General Principles of Software Validation; Final Guidance for Industry and FDA Staff, issued on January 11, 2002.

In the 2002 Final Guidance, at Section 3.1.3 IQ/OQ/PQ, FDA states

“While IQ/OQ/PQ terminology has served its purpose well and is one of many legitimate ways to organize software validation tasks at the user site, this terminology may not be well understood among many software professionals, and it is not used elsewhere in this document. However, both FDA personnel and device manufacturers need to be aware of these differences in terminology as they ask for and provide information regarding software validation.”

The 2002 Final Guidance includes in excess of 80 references to international, cross-industry standards, methods, and guides to software and system integration quality that do not use the IQ/OQ/PQ paradigm. The 2002 Final Guidance also includes three references to pharmaceutical, process control specific trade papers and standards that do refer to IQ/OQ/PQ. When reviewing this reference list, the authors are pre-disposed to treat the IQ/OQ/PQ references as being included as representative examples of “what not to do” as opposed to recommendations of proper procedure.

In support of a practice of providing clear and consistent recommendations, and noting FDA’s movement away from the IQ/OQ/PQ paradigm, the authors recommend that FDA remove the GAMP 4 references in the 0060 Guidance (Recommendation 1) and refer to the reference section of the 2002 Final guidance as a “how to do it” guide (Recommendation 2).

3.2. Public Health and Safety Risk Approach

On 21 August 2002 FDA announced a significant initiative entitled:

cGMPs for the 21st Century: A Risk Based Approach

In the announcement of this new initiative, FDA describes a focus upon several new approaches to product quality regulation. The first one listed is:

“Risk-based orientation: *In order to provide the most effective public health protection, FDA must match its level of effort against the magnitude of risk. Resource limitations prevent uniformly intensive coverage of all pharmaceutical products and production. Although the agency has been implementing risk-based programs, a more systematic and rigorous risk-based approach will be developed.”*

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The authors observe that the above-proposed method does not include a specific definition of the independent variable of the formal risk analyses that will be required to reasonably claim a “systematic and rigorous risk-based approach.” In other words, there is no explicit declaration of “Risk to what?” by the FDA.

Even without this explicit declaration, the authors maintain that it is reasonable, considering a.) the FDA’s warrant by the US Congress, b.) the proximity of the proposal to FDA’s stated intent of improved product quality, and c.) a combination of optimism and common sense, that one independent variable in any risk analyses associated with pharmaceutical information systems should be “risk to product quality” and, by inference, “risk to public health and safety.” In other words, the first obligation of any computer systems validation effort must be to demonstrate, through rigorous and systematic risk analysis, how the computer system improves public health and safety (or at least does not compromise them), most likely by validating how the system improves or demonstrates pharmaceutical product quality.

The GAMP 4 methodology does not support the FDA’s risk-based direction. GAMP 4 includes, as one of its basic, early phase evaluation techniques, the assignment of a “Software Category” (Category) to software that is to be validated. The assigned Category is represented by a numerical classification from 1 through 5. This Category number corresponds to the rigor, complexity, and extent of the documentation and testing that must accompany the validation of the software. The greater the classification number, the more documentation and testing are required.

Because the Category numbers correspond directly to testing and documentation levels, the Category Number functions as a Criticality Level, and the Categorization process serves the function of a Criticality Assessment.

GAMP 4, Appendix M4, *Guideline for Categories of Software and Hardware*, describes the types of software that are to be included in each Category. In the text of the GAMP 4 specification, no evaluation, assessment, or justification criteria are specified for the types of software that are included in the various Categories.

The authors have reviewed the Software Categories listed in GAMP 4 Appendix M4, and have attempted to infer inclusion criteria that correspond to the Category Levels. After careful consideration, the only criterion that the authors can ascribe to the Category Levels is “Difficulty in Obtaining Verification and Validation Documentation and Cooperation from the Vendor,” which the authors will abbreviate to “V&V Hassle.”

In the authors’ opinion, it is very poor engineering and quality assurance practice to correlate testing and documentation requirements for human-safety grade information systems with the “V&V Hassle,” instead of correlating testing and documentation requirements with the results of rigorous and systematic analysis of the risk to product quality and public health and safety associated with the information system. Because of the lack of any criticality assessment criteria other than those listed in the Appendix M4 software Categories, GAMP 4 has the effect of causing an inappropriate “safety vs. difficulty” correlation. Because the entire GAMP 4 methodology

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depends upon this flawed categorization process at its start, the methodology effectively obscures product quality and public health risks.

Therefore, because the GAMP 4 methodology has the effect of making it more difficult to evaluate the product quality and public health risks of information systems validated using this method, the authors recommend that FDA remove the GAMP 4 reference from the 0060 Guidance (Recommendation 1) and add the risk analysis references listed in Section 4 to the 0060 Guidance (Recommendation 3).

4. Risk Analysis Methods:

Numerous standards and texts are available that describe methods that can be used to assess risk that is directly associated with stated independent variables. It is a straightforward task to apply these methods and correlate product quality and public health risk with information systems used for pharmaceutical research, development, manufacturing, labeling, testing, and distribution. The authors recommend, as a start:

IEEE Standard for Software Life Cycle Processes--Risk Management
IEEE, 2001; Softcover; 2001; ISBN 0-7381-2834-1;
IEEE Product No.: SH94925-TBR; IEEE Standard No.: 1540-2001

NASA Document # 19980120589A
"Combined analysis approach to assessing requirements for safety critical real-time control systems", Goddard, Peter L., Hughes Aircraft Co., USA; 1996, pp. 110–115; In English;
Copyright; Avail: Aeroplus Dispatch

Instrument Society of America
Proceedings, ISA EXPO 2000
Tolerable Risk Guidelines
Edward M. Marszal, P.E.
Product ISBN/ID: TP00ISA6014