Boehringer Ingelheim

Boehringer Ingelheim Corporation

Division of Dockets Management HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Docket No. 2004N-0133

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**Submittal of Comments to Docket 2004N-0133**

To the Food and Drug Administration,

In response to the publishing of Docket 2004N-0133 in the Federal Register on April 8th 2004, Boehringer Ingelheim Pharmaceuticals respectfully submits for your review and consideration input from our global organization, as requested in the aforementioned docket. A response has been provided in each case found in the above docket where the Agency has requested input. The following table provides this input in the order of which the request for input is found in the docket.

While we feel that all responses we have provided to the Agency are worthy of consideration and discussion, we would like to emphasize for the Agency's consideration 5 key points that we feel are most in need of reform and or further clarification.

- Part 11 must be revised and include the FDA's interpretation of the narrow scope of Part 11 in order for Industry to comply with it.

- Part 11 should identify which records required by predicate rule fall under the scope of Part 11, and clarify which activities required by predicate rule, and which records generated to substantiate that those activities took place, do not fall under the scope of Part 11(e.g. training records).

- A risk based approach should be acceptable for all attributes of Part 11 and the Agency should accept a level of compliance with the ruling that is in direct relationship to the risk a record poses to product quality and public safety.

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- Part 11 must make it clear that electronically submitted data generated by systems not impacted by predicate rule requirement (pharmacology systems as an example) would not be subject to Part 11; only the electronic submission records containing that data would be subject to Part 11 requirements.

- The Agency must make it clear that if a system was in use prior to August 1997, and that system has been updated since, whether or not it falls under the scope of Part 11. FDA should consider permanently extending "enforcement discretion" for all legacy systems.

We applaud the Food and Drug Administration for its recognition of the need to re-examine 21 CFR Part 11 and we look forward to further information regarding the progression of this matter.

Regards,

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| A. 1. Part 11 Subpart A - General Provisions | We are interested in comments on FDA's interpretation of the narrow scope of part 11 as discussed in the part 11guidance and whether part 11 should be revised to implement the narrow interpretation described in the guidance. | Yes, we feel that Part 11 must be revised, including the FDA's interpretation of the narrow scope of Part 11, in order for Industry to comply with it. Also, the revised approach should be risk-based. This should allow for compliance levels that are directly related to the risk the record poses to product and human safety. |
| A. 2. Part 11 Subpart A - General Provisions | We are interested in comments on whether revisions to definitions in part 11 would help clarify a narrow approach and suggestions for any such revisions. | Definitions should be revised to support the FDA position that Part 11 should only apply to electronic records created to satisfy predicate rule requirements or electronic records submitted to the Agency. For example the current definition of an electronic record (*any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system*) is indicative of the original perception of a broad based application of Part 11. In addition other pertinent definitions are not included, such as legacy system, part 11 records, audit trail etc. While the current guidance document may not fall under the FDA request for input, we feel it is important to reflect that the indication of "enforcement discretion" is somewhat unclear and may be left to the discretion of one particular inspector. |

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| A. 3. Part 11 Subpart A - General Provisions | We are interested in comments on the need for clarification in part 11 regarding which records are required by predicate rules and are therefore required to be part 11 compliant? | Our feeling is that the actual number of records that are created in the Industry that are specifically required by a predicate rule is small compared to the overall number of quality related records. However, there is a clear expectation that required activities shall take place, while predicate rules do not require that records be maintained. Therefore, Part 11 should identify what predicate rule required records fall under the scope of Part 11 and clarify that activities required by predicate rule and records generated to substantiate that the activity took place do not fall under the scope of Part 11. |
| B. 1. Part 11 Sub Part B - Electronic Records | We are interested in comments on whether there are other areas of part 11 that should incorporate the concept of a risk-based approach detailed in the part 11 guidance (e.g., those that require operational system and device checks). | Our feeling is that a risk based approach should be acceptable for all attributes of Part 11 and the Agency should accept the level of compliance with the ruling in direct relationship to the risk the record poses to product quality and public safety. |
| B. 2. Part 11 Sub Part B - Electronic Records | Is additional clarity needed regarding how predicate rule requirements related to subpart B can be fulfilled? | We feel moreover it should be clearer within Part 11 exactly where within the predicate rules one can find these requirements related to subpart B. For example, how many predicate rules actually require that an audit trail be maintained or a signature be provided? |

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| B. 3. Part 11 Sub Part B - Electronic Records | Should the requirements for electronic records submitted to FDA be separate from electronic records maintained to satisfy predicate rule requirements? | Requirements for electronic records should be identified case by case based on risk assessment. For example, it could be interpreted by the industry that the Agency is requesting that records not required by predicate rule (e.g. General Pharmacology) but possibly electronically submitted to the Agency be required to comply with all aspects of Part 11. Our input to this position would be the data generated by pharmacology systems (as an example) would not be subject to Part 11; only the electronic submission records containing that data would be subject to Part 11 requirements.<br><br>An additional example would be when preparing an electronic submission for the agency, a large series of small editing steps to attributes are required to fulfill the electronic submission guidelines (e.g. to provide appropriate bookmarks and hyperlinks as part of the PDF files submitted). FDA should not consider these attribute edits individually as changes applied to an electronic record. |
| B. 4. Part 11 Sub Part B - Electronic Records | Should part 11 continue to differentiate between open systems and closed systems? | Yes, but we suggest that a more robust definition be established for both. |
| B. 1. Part 11 Sub Part B - Electronic Records - Individual Controls | Should we retain the validation provision under Sec. 11.10(b) required to ensure that a system meets predicate rule requirements for validation? | We assume that the Agency is referring to section 11.10 (a) and not 11.10 (b). Regardless, we feel that Part 11 should indicate systems need to be validated as required by predicate rule, full stop. The requirement should be mentioned in the scope section of Part 11, so that it is clear it applies to electronic records and electronic signatures. We also feel strongly that current predicate rules are weak in identifying the requirements for validation of computer systems and those predicate rules should be updated. |

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| B. 2a. Part 11 Sub Part B - Electronic Records - Individual Controls | Are there any related predicate rule requirements that you believe are necessary to preserve the content and meaning of records with respect to record copying and record retention? | We feel that the current predicate rules describing the requirements for record retention are weak. This has led to Industry maintaining huge electronic document archives that come with equally huge costs. The value of these long term archives has been questioned throughout our organization. The agency should bear these factors in mind when reworking the records retention requirements of Part 11. In regard to record copying, the Agency should consider that technology may be the driving factor in our ability to meet this requirement and consider a broad range of options for industry, including storing data as images or PDF files or paper, providing data integrity can be maintained. |
| B. 2b. Part 11 Sub Part B - Electronic Records - Individual Controls | What requirements would preserve record security and integrity and ensure that records are suitable for inspection, review, and copying by the agency? | We feel that current requirements regarding record security and integrity are appropriate, but these requirements should be based on the system level, not the record level, and therefore found in a predicate rule regarding validation of computerized systems. These requirements would not only apply to the systems creating the records, but subsequently the system used to archive the record. |
| B. 3. Part 11 Sub Part B - Electronic Records - Individual Controls | Should audit trail requirements include safeguards designed and implemented to deter, prevent, and document unauthorized record creation, modification, and deletion? | Our feeling is no. The Agency should acknowledge that the current audit trail requirements are difficult enough to comply with and that appropriate security should eliminate activities by any unauthorized individual for any reason. Furthermore, the Agency should not attempt to impose audit trail requirements that would exceed those found in paper based records required by predicate rules. Doing so would only further support the avoidance of electronic record usage. |

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| B. 4. Part 11 Sub Part B - Electronic Records - Individual Controls | Section 11.10k requires appropriate controls over systems documentation. In light of how technology has developed since part 11 became effective, should part 11 be modified to incorporate concepts, such as configuration and document management, for all of a system's software and hardware? | No, although these subjects should be predicate rule requirements, they are more appropriately found in a predicate rule for computer systems validation than in Part 11. |
| C. 1. Part 11 Sub Part C - Electronic Signatures | Section 11.10(d) requires that system access be limited to authorized individuals, but it does not address the handling of security breaches where an unauthorized individual accesses the system. Should part 11 address investigations and follow up when these security breaches occur? | Our feeling is that security and access should be considered an element of predicate rule requirements for computer systems validation, not specifically Part 11. The activity of security breach investigation should be part of a quality management system approach that addresses deviations of predicate rule requirements. |
| D. 1. Additional Questions for Comment | What are the economic ramifications of modifying part 11 based on the issues raised in this document? | The economic effect of modifying Part 11 in such a way it is friendly to industry and acceptable to the Agency is that Industry can channel funds required to remediate systems into efforts for technological advances and encouraging innovation of new medical treatments. |

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| D. 2. Additional Questions for Comment | Is there a need to clarify in part 11 which records are required by predicate rules where those records are not specifically identified in predicate rules? If so, how could this distinction be made? | Yes, there is a strong need to clarify what predicate rule records are expected to meet the requirements of Part 11 when they are not specifically identified. Since these records are not identified in the CFR and the Agency is the ruling body, it is therefore up to the Agency to clearly identify those records by name if Industry is to be expected to understand they are within the legal scope of Part 11.<br><br>In addition, we would like the revised ruling to clearly indicate that when a computer generates a record that is subsequently printed, and the paper record is used to direct regulated activities, Part 11 does not apply. |
| D. 3. Additional Questions for Comment | In what ways can part 11 discourage innovation? | Part 11 imparts a huge financial burden on Industry because of the investments required for meeting compliance. Additionally, the resources being dedicated to Part 11 activities could otherwise be used to benefit both the Industry and health care. Part 11 has created an environment that is forced to foster the use of paper records and avoidance of technology that falls short of perfect Part 11 compliance that could otherwise benefit the organization. |
| D. 4. Additional Questions for Comment | What potential changes to part 11 would encourage innovation and technical advances consistent with the agency's need to safeguard public health? | We feel the Agency must implement a crystal clear requirement (that truly limits misinterpretation) for Part 11 so that Industry can understand what the short and long term commitments are for meeting requirements and avoiding regulatory actions. In addition the Agency must adopt a flexible approach which allows levels of compliance that are directly related to the risk level of the system and its record, as established by proper risk assessment. |

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| D. 5. Additional Questions for Comment | What risk-based approaches would help to ensure that electronic records have the appropriate levels of integrity and authenticity elements and that electronic signature are legally binding and authentic? | We feel this question is confusing as we fail to see the link between a risk-based approach to electronic record integrity and authenticity of electronic signatures. That being said, we feel that the integrity and authenticity issues related to electronic records are a direct relationship to good validation and security procedure. A risk-based approach to establish appropriate levels of testing and security should be made clearer by the agency as previously discussed. Regarding the issue of legally binding signatures, our feeling is that it should be acceptable to have employees sign an electronic signature certification that indicates any and all signatures executed by that employee are in fact the legally binding equivalent of that individual's handwritten signature. We feel no further requirements should be imposed. |
| D. 6a. Additional Questions for Comment | What are stakeholder concerns in regards to modifications made to legacy systems in use as of August 1997? | There are a number of major concerns that can be attributed to legacy systems, starting with the vague definition found in Part 11. For instance, the Agency is not clear if a system that was in use prior to August 1997, that has been updated since, falls under the scope of Part 11. The Agency does not address the issue of acknowledging that legacy system were implemented following predicate rules for computer systems validation, which have limited requirements (as previously stated) and would not potentially meet current computer systems validation standards (as defined in the FDA Guidance "General Principles of Software Validation" and/or GAMP4). Additionally, the FDA must acknowledge the huge costs associated with attempts to remediate legacy system from a technical viewpoint. The FDA should consider permanently extending "enforcement discretion" for all legacy systems. |
| D. 6b. Additional Questions for Comment | Can the use of risk mitigation and appropriate controls eliminate concerns regarding legacy systems? | Yes, but only if the FDA clearly defines what the expectations are for legacy systems. |

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| D. 7. Additional Questions for Comment | Should part 11 address record conversion? | We feel that record conversion should be allowed provided the integrity of the converted record is maintained |
| D. 8. Additional Questions for Comment | Are there provisions of part 11 that should be augmented, modified, or deleted as a result of new technologies that have become available since part 11 was issued? | We do not feel that technological advances that could benefit Part 11 have seen significant improvement since the ruling was established. |