Document Title: System Validation Statement for the IBM Clinical Development (ICD) Offering		
Document No.: QA-7083	**Document Version: 03**	
Area: Quality and Compliance	**Document Type: Statement**	

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Introduction

Development of the IBM Clinical Development (ICD) product occurs by the policies and procedures that are in place within Watson Health Systems (WHS). The established Quality Management System (QMS) documents address all stages of software development, validation, deployment, maintenance, and support. Validation of ICD (previously known as "eCOS" or "eClinicalOS") establishes verification of the reliability, accuracy, and consistency by using defined functional requirements, which are available for review by customers upon request as part of an audit.

When applicable, the following set of guidelines, regulations, and frameworks were implemented into the software development process for the ICD product:

- Food and Drug Administration (FDA) 'Title 21 CFR Part 11: Electronic Records; Electronic Signatures"
- Food and Drug Administration (FDA) "Guidance for Industry: Computerized Systems Used in Clinical Investigations"(May 2007)
- Food and Drug Administration (FDA) "General Principles of Software Validation: Final Guidance for Industry and Staff'
- International Conference on Harmonisation (ICH) Topic E6(R2): "Guideline for Good Clinical Practice"
- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guidance: "Good Practices for Computerized Systems in Regulated 'GxP Environments"
- Good Automated Manufacturing Practice (GAMP 5)
- Annex 11
- General Data Protection Regulation (GDPR - EU)
- Lei Geral de Protecao de Dados Pessoais (LGPD – Brazil)
- California Citizens Privacy Act 2018 (CCPA - California, USA)

Further, as part of the maintenance and retirement portion of the System Lifecycle within IBM Watson Health, additional policies and procedures have been created to ensure the confidentiality, reliability, and integrity of the Regulatory Data generated by the ICD product and stored within IBM Watson Health.

The ICH E6 R2 guideline was evaluated for applicability to the ICD Product. Although the guideline is intended for three distinct audiences (Investigators, Sponsors, and CROs), the updated guidance document does identify certain standards related to the systems that support the clinical trial. It is our position that the responsibility for verifying that ICD product and supporting activities comply with the standards of the ICH E6 (R2) guideline belongs to the Sponsor or Contract Research Organization (CRO), based on how that entity chooses to use the product. However, we do have a standard within our QMS that identifies how ICD has incorporated controls into our processes to address applicable sections of the ICH E6 (R2) guidance. Selected applicable sections and the IBM WHS response are described below in the document.

21 CFR Part 11 Compliance

The WHS QMS, as part of its documented system development life cycle, designed the ICD product so that it can be configured by a Sponsor or CRO to be compliant with the requirements of 21 CFR Part 11.

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A traceable mapping of the ICD requirements to the components of 21 CFR Part 11 and Annex 11 is available for client review.

Please note that while WHS designed the ICD product to comply with the requirements of 21 CFR Part 11 through the implementation of features that meet the regulation, it is ultimately the responsibility of the Sponsor and/or CRO to ensure that they have the ICD product and its functionality configured to comply with the 21 CFR Part 11 regulation as they have defined it within their organization.

Additionally, the ICD product is developed to ensure that the records created during the design, development and deployment of the application meet applicable 21 CFR Part 11 standards as we have defined them as captured in our 21 CFR Part 11 Interpretation and Implementation SOP.

Validation. ICD product is validated by documented and approved life cycle development methodologies. These methodologies are included as part of the WHS QMS. In 4th quarter of 2015, WHS implemented quarterly regression testing for 21 CFR Part 11 requirements as part of the regular validation testing of the ICD product.

Training. Training on the development, configuration, maintenance, and operation of the WHS QMS is a requirement for all appropriate staff. Training is required for all permanent and contract staff on 21 CFR Part 11, Annex 11, and Good Clinical Practices including ICH E6 (R2).

Access Control. WHS has established system functionality and internal procedures to control access to clinical study databases and related documentation for the ICD product. User IDs and passwords are required to be unique and not used by anyone other than their intended owners. User IDs and passwords are not able to be re-assigned or re-used. Each user is granted a Role, which determines the level of access within the system. ICD includes a timeout feature after a period of inactivity.

Backup and Restore of Regulated Data. Regulated data generated by the ICD product that is hosted by IBM WHS is backed-up by documented and approved internal WHS QMS IT procedures. Likewise, IBM WHS requirements relating to data integrity, confidentiality, and accuracy are in place, as well as being suitable for housing regulated data.

Disaster Recovery. IBM WHS has an approved Disaster Recovery Plan that includes the ICD product, which is periodically tested following internal procedures. This is done to ensure that the ICD product has appropriate system failovers in place to prevent the loss of any regulated data derived from the ICD product.

System Documentation and Record Retention. ICD product documentation is produced following a version-controlled validation process described within the WHS QMS. Documents are retained for the longer of the Record Retention SOP retention period or the customer's defined retention period.

Electronic Systems with Electronic Signatures. IBM WHS evaluates and validates internal applicable electronic systems, including the ICD product, for 21 CFR Part 11 compliance, risk and impact. This includes electronic systems used by IBM WHS for the creation or storage of quality records.

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ICH E6 Compliance

IBM WHS software and practices adhere to applicable portions of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use per the (ICH) Harmonised Tripartite Guideline for Good Clinical Practice E6(R2). While much of the ICH E6 guidance is directed toward Sponsors, Investigators and Review Boards, ICH E6(R2) Section 5.5.3 is concerned with "electronic trial data handling and/or remote electronic trial data systems" and as such applies to the ICD product. IBM WHS responses to these specific guidelines are provided below.

For a complete list of ICH E6(R2) Sections deemed applicable to ICD, please review the WHS Standard, QA-6922 Applicability of ICH GCP E6 (R2).

Section 5.5.3
When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance.

IBM WHS Response: The WHS control for this section is QA-170, External Audits, which governs the response of WHS to external audits performed by clients consistent with the contractual agreements.

(b) Maintain SOPs and WIs for using these systems.

IBM WHS Response: The WHS control for this section is QA-170, External Audits, which governs the response of WHS to external audits performed by clients consistent with the contractual agreements .

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data.

IBM WHS Response: The WHS control for this section is QA-1356, QA-150, or QA-2927 which govern the identification of requirements, design, development, and release of validated offerings to support the conduct of a clinical trial and requirements per 21 CFR Part 11, including the blinding of the study data and data integrity.

(d) Maintain a security system that prevents unauthorized access to the data.

IBM WHS Response: The WHS control for this section is QA-1356, QA-150, or QA-2927 which govern the identification of requirements, design, development, and release of validated offerings to support the conduct of a clinical trial and requirements per 21 CFR Part 11, including the blinding of the study data and data integrity.

(e) Maintain a list of the individuals who are authorized to make data changes.

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IBM WHS Response: The WHS control for this section is QA-1356, QA-150, or QA-2927 which govern the identification of requirements, design, development, and release of validated offerings to support the conduct of a clinical trial and requirements per 21 CFR Part 11, including the blinding of the study data and data integrity.

(f) Maintain an adequate backup of the data.

IBM WHS Response: The WHS control for backup of the data is QA-166 Backup and Restore SOP

(g) Safeguard the blinding, if any.

IBM WHS Response: The WHS control for this section is QA-1356, QA-150, or QA-2927 which govern the identification of requirements, design, development, and release of validated offerings to support the conduct of a clinical trial and requirements per 21 CFR Part 11, including the blinding of the study data and data integrity.

Note: WHS is committed to safeguarding study blinding where we able to do so. However, ultimately it is the Sponsor who is accountable for and has the final responsibility to ensure that only those persons who are in a role within the study that requires un-blinding are granted un-blinding permissions.

Position on GAMP 5

The intent of GAMP 5 is to assist in the development of computerized systems that are fit for purpose and meet current regulatory requirements by building upon industry good practice efficiently and effectively. GAMP 5 is neither a prescriptive method nor a standard but a collection of approaches and toolsets to offer a robust, cost-effective approach to computer system development.

Several of the key principles of GAMP 5 guidance include the following:

- Development and adherence to a defined system development life cycle that determines and controls system activities from the planning to the retirement stages.
- Progress and adherence to a project life cycle that defines how the organization's products are configured and released per customer requirements.
- Recognition that many systems used in the industry are configured systems supplied by key vendors, with the responsibility of the customer to ensure supplier integrity.
- Implementation and maintenance of a quality management system to provide repeatable operations and quality deliveries.
- Implementation of a risk-based approach that takes into consideration the impact of patient safety, product quality and data integrity on system development activities.

IBM WHS has implemented policies and procedures that are consistent with the principles listed above and integrated them into the development and management of the ICD product.

IBM WHS has defined controlled processes for system development and product life cycles. IBM WHS has a process for vendor management that includes periodic review and risk-based vendor monitoring

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activities. IBM WHS has implemented a QMS that includes controls over system and project delivery processes, as well as system administration, employee training, and auditing. As appropriate, these procedures include an assessment of risk in determining how development and change control are implemented, tested and released.

Position on Annex 11

Annex 11 was intended to allow for the European Commission (EC) to guide the industry regarding how to implement a risk-based approach to computerized systems while still meeting good manufacturing practices and GAMP standards for automated systems.

Annex 11 stresses that patient safety, data integrity and product quality must not be put in jeopardy, and that the extent of validation and data integrity controls that are required for a computerized system should be based on the use of a documented risk assessment. IBM WHS utilizes a risk-based approach in line with GAMP processes and is in harmonization with Annex 11 for its ICD product.

Annex 11 also addresses the handling of Electronic Records and Electronic Signatures (ERES) and closely parallels the US FDA's stance on this topic found in the 21 CFR Part 11 regulation, which is addressed elsewhere in this document. Due to the harmonization of 21 CFR Part 11 with Annex 11 regarding Electronic Records and Electronic Signatures, the IBM WHS position complies with both standards.

Position on PIC/S

The PIC/S guidance provides recommendations and background information for inspectors of GxP-regulated systems by detailing good practices for the implementation, validation, and operation of the GxP systems.

Like GAMP, PIC/S recognizes the industry trend toward the use of configurable/customizable off the shelf (COTS) systems and recommends that supplier management is included as an aspect of the validation process. This consists of the maintenance and assessment of an inventory of computerized systems and vendors that are used to develop and maintain internal operations.

Other aspects of PIC/S include:

- Implementation of a system development life cycle to guide system development.
- Implementation of a quality management system to ensure that quality is being built into the product and that the software engineering process is followed.
- Conduct of testing against formal specifications to ensure systems operate as intended.
- Generation of documentation and records to provide evidence of validation activities.

As stated above, IBM WHS QMS has defined controlled processes for the system development and product lifecycle for the ICD product.

IBM WHS QMS has an established process for vendor management that includes periodic reviews and risk- based vendor monitoring activities. IBM WHS has implemented a QMS that contains controls over system and project delivery processes, as well as employee training, and auditing, Also, IBM WHS,

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following its procedures, conducts testing of the ICD product, as well as the study applications configured within, and documents these activities through test plans, test evidence and test reports to prove that adequate testing was performed for the ICD product.

Position on Data Protection Regulations

(General Data Protection Regulation [GDPR-EU]; Lei Geral de Protecao de Dados Pessoais [LGPD-Brazil]; California Citizens Privacy Act 2018 [CCPA-California, USA].

The data protection regulations intent is to enhance the protection of the governing body's subject data, including strengthening the fundamental right to privacy and security of personal data. Except for the login information, IBM WHS is the data processor for all information entered into ICD. The execution of obligation that rests with the data controller is deferred to our customers as the data controllers. IBM WHS QMS has a process which will support the data controller.

For logon data, IBM WHS is considered the data controller. To meet the relevant requirements of Access, Rectification, Restricted Processing, Right to Object to Processing, Erasure, Data Portability and notifications of Third parties, IBM WH and WHS have defined processes, which are controlled and periodically reviewed.

The requirement for Data Security is met through Security and Privacy standards. IBM WHS follows IBM's process for breach notification which requires data breach plans at the application level. These plans allow for the notification data breach within the prescribed number of hours, based on the applicable regulation, of first notice for the data controllers.

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