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To: Directors of Health Departments (Bureaus),
Prefectural Governments

From: Director of Compliance and Narcotics Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Questions and Answers (Q and A) regarding "Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-drugs"

Q1
Please give concrete examples of "other appropriate alternative approaches" of the stipulation "The computerized systems which have been developed or in operation prior to the effective date of this guideline, but have not been developed, validated nor operated in accordance with 'Guidelines on Control of Computerized Systems in Drug Manufacturing' or other appropriate alternative approaches shall be qualified" in Section 1.2 of the guideline.

A1
"Appropriate alternative approaches," includes guidelines equivalent to the major guidelines in Western countries, such as ISPE "GAMP guide" and PIC/S "Good Practices for Computerized Systems in Regulated "GXP" Environments." Other approaches are also applicable as long as their appropriateness is assured.

Q2
The guideline stipulates that the computerized systems which were developed or started operation prior to the effective date of this guideline, but was not developed, validated nor operated in accordance with "Guideline on Control of Computerized Systems in Drug Manufacturing" or other appropriate alternative approaches, shall be qualified in Section 1-2 "Computerized system under regulations". Please explain how we could conduct this validation.

A2

The validation methods include several approaches, such as confirmation of past records or documents including specifications prepared at the system development phase. Accordance with the User Requirement Specification or other quasi-documents of present use is also confirmed for the records and documents. Current operational records and results of periodical review may also be used for the validation.

Relevant Standard Operating Procedures and manufacturing instruction, etc. are included in the User Requirement Specification or other quasi-documents of present use. When you conduct a validation based on the above documents, it is required to make sure the validation items are decided by thorough review of both documents.

Reflecting on the in-house quality assurance policy and risk assessment results, Marketing Authorization Holders, etc. are required to describe basic ideas of validation scope, methods and items, etc. in the "Administrative Policy and Rules for Computerized Systems," etc., and validation needs to be conducted in accordance with the policy.

Q3

Section 1.2 of this guideline stipulates that when "Use of Electronic Records and Electronic Signatures in Submission for Approvals, Licenses of Medical Products"(PFSB/ELD Notification No. 0401022 dated April 1, 2005) or "Enactment and Revision/Disposition for Ministerial Ordinances and Notifications Pertaining to the Manufacturing Controls and Quality Controls (GMP/QMS) of Drugs, Medical Devices, etc. Accompanied by the Enforcement of the Law on Revising Partially the Pharmaceutical Affairs Law and the Law on Blood Collection and Donation Services Control" (PFSB/CND Notification No. 0330001, dated March 30, 2005) Title 3, Part3, Section 35. "Others (regarding Electromagnetic Records, etc.)" is applicable to the computerized systems that are covered by this guideline, the computerized systems should also meet the requirements stipulated in the above notifications. Please tell us if there is any other requirement other than ones stipulated above.

A3

It is necessary to set down requirements of each system by considering operations to be performed by the system and observation matters stipulated in laws and regulations, such as GQP Ministerial Ordinance and GMP Ministerial Ordinance, etc.

For example, requirements to ensure security, business continuity, countermeasure for the system failure, data backup, access privilege, and access records, etc, as well as the

operational procedure, necessary functions and performance (data processing capability, etc.) to implement relevant operations, and installation requirements, etc. need to be documented. It is preferable to determine requirements for the backup media and the media retention methods in advance.

Q4

Please give concrete examples of "business continuity" in 3 and possible measures to ensure the continuity.

A4

In this guideline, the "business continuity" is to avoid system failure or system trouble, which may cause disruption of the operations, by implementing appropriate countermeasures. It also refers to the prepared measures that will secure business operations in case of system failure or trouble.

Necessity of business continuity will be determined after consideration of risk assessment results, etc. of the relevant operations.

Concrete measures to secure the continuity is to set up of installation conditions and data backup methods (backup and retention methods, etc.) by factoring in possible natural disaster, such as earthquakes, or to prepare alternative computerized system for system failure and trouble as well as establishment of procedures. Furthermore, it also includes establishment of the procedures for system recovery or periodical data backup, etc.

In order to maintain the validated status of computerized systems, these measures should also be validated in advance.

Q5

"2. Scope of Application" stipulates "This guideline is applicable to the Marketing Authorization Holders, etc., who conduct their operations under GQP Ministerial Ordinance and/or GMP Ministerial Ordinance by using a computerized system." When development and operations of computerized system, etc. are outsourced to external contractors, are the contractors subject to this guideline as well?

A5

When the Marketing Authorization Holders, etc. outsource development and operations of computerized system to external contractors, the Marketing Authorization Holders, etc. are required to ensure that operations are conducted in accordance with this

guideline. The contractors are also required to conduct their operations under the appropriate quality system. It is recommended to stipulate these conditions in the written agreement, etc.

Q6

Please give concrete examples of the "(1) Systems to make decisions on market release of drugs and quasi-drugs and to create and retain market distribution records" in the "2. Scope of Application," of the guideline.

A6

It includes a system to control market release by input of the market release judgment results or a system to prepare, issue and retain market release records.

Q7

Please give concrete examples of the "Systems to create and retain manufacturing orders and manufacturing records, in the "2. Scope of Application,"

A7

Followings are examples of the above:

- A system to create manufacturing orders based on the production schedule
- A system to create and retain manufacturing records based on the data from manufacturing equipment of finished products and active pharmaceutical ingredients

Q8

Please give concrete examples of the"(3) Systems to control/manage manufacturing processes and to retain relevant data" in the "2. Scope of Application," of the guideline.

A8

Followings are examples of the above:

- A system to control granulators, tablet presses and coating machines at the finished product site and reaction and fermentation vessels at active pharmaceutical ingredient sites, as well as a system to manage those operations
- A system to support weighing operations

Q9

Please give concrete examples of the "(4) Systems to manage storage and inventory, etc. of raw materials and products (including intermediates; the same shall apply hereinafter) in "2. Scope of Application," of this guideline.

A9

Followings are examples of the above:

- A system to control receipt and release of raw materials and products (including intermediates which are produced during the manufacturing processes; the same shall apply hereinafter) in an automated warehouse
- A system to control stocks, etc.
- A system to prepare inventory or storage records, etc. of raw materials and finished products
- An automated transfer system to carry raw materials and finished products, such as automated guided vehicles

Q10

Regarding the automated warehouse in the answer to question 9, if the system only provides pallet racking functions, is it still included in the scope of this guideline?

A10

Yes, the function of the system needs to be validated and controlled by this guideline.

Q11

Please give concrete examples of "(5) Systems to control/manage laboratory instruments used for QC tests and systems to retain QC test results and relevant data" in Section 2"Scope of Application," of the guideline.

A11

Followings are examples of the above:

- An integrated system to control and manage the testing instruments (HPLC, GC, etc.) used in the manufacturing unit or quality unit (Laboratory Information Management System; LIMS),
- A system to verify the quality (collation with each specification value) of raw materials and packaging materials and product quality based on the data from the testing analytical instruments (HPLC, GC, etc.) in the manufacturing

unit or quality unit,

・A system to collect and store data from the testing instruments in the manufacturing unit or QC unit

・A system to prepare records relating to the testing based on the data from the testing analytical instruments,

・A system to issue the Certificate of Analysis.

Q12

When the supplier of the hardware (including machines and equipment to be controlled by a computer) only set general-purpose functions in a system for its limited purpose and the functions are fulfilled by setting up of the parameters, the system used to be classified as a firmware or PLC (Programmable Logic Controller). Is the above system also included in the scope of this guideline?

A12

A firmware and PLC are still subject to this guideline. Appropriate procedures need to be taken depending on the system risks by referring to the Appendix 2 “Categorization and Corresponding Examples” of this guideline.

Q13

When one part of the designed computerized system falls into the scope this guideline and the other part does not, please explain how it should be handled.

A13

Only relevant functions need to be validated. However, if non-existence of mutual affection between the functions within and outside of this guideline is not proved, the entire system needs to be validated for its compliance to the guideline.

For example, the integrated-type software such as Enterprise Resources Planning (ERP) constitutes various kinds of modules including accounting management, personnel management and sales management as well as production control and quality control. However, this guideline applies only to the functions to execute operations under control of GQP and GMP, such as production control and quality control. But, when the operations under GQP and GMP are conducted by using other modules, for example, the personal allocation is controlled together with the personnel management module, the relevant modules are also included in the scope of this guideline.

Q14
However small the scale of the system is, is the system still subject to the guideline?

A14
Since the purpose of this guideline is to ensure proper system operations in accordance with GQP and GMP, this guideline is applicable to systems regardless of their scale. Accordingly, when the systems fall under the scope of "2. Scope of Application," those are subject to this guideline.
However, as to a system with relatively small scale (for example, stand-alone type HPLC/GC system) or a system software of which is not complex (for example, software to monitor the temperature), it is allowable to omit the preparation of an individual plan, as long as the contents of the individual plan, such as IQ, OQ and PQ plan are described in the validation plan collectively.

Q15
In the case of using leased computers, is the system still subject to this guideline?

A15
Even when you use leased computers, the system to control the computers is still subject to this guideline. When the system falls under the scope of this guideline, compliance with this guideline is required regardless of its ownership.

Q16
When a Japanese subsidy use a computerized system which was developed and is supposed to be modified by foreign parent firm, is the system still subject to this guideline?

A16
Since a parent company and its subsidy are separate cooperate bodies, the above example is considered to be an entrustment of system development from a Japanese subsidy to the parent company. Accordingly, this guideline shall apply to the system development and modification. Furthermore, relevant documents for domestic use are required to be prepared in Japanese except for cases with rational reasons.

Q17
When new terminal equipment alone is added to the existing computer system which

has been validated appropriately, and if the extension has already been planned at the original system design, how far is this guideline applied to the system?

A17
In principle, “6. Activities on Operations Management” and “6.7 Change Management” of the guideline is applicable to this case. However, if the system test and qualification are completed for the equipment, only Installation Qualification is required in general.

Q18
If it is confirmed that the change will not make any impact on the quality of system at the planning phase, does the guideline still apply to the change?

A18
The change is to be made in according with “6.7 Change Management” of “6. Activities on Operations Management”, but validation is not required.

Q19
Are the following sub-systems under the computerized system relating to production control subject to this guideline?
Issuance of manufacturing orders, Inventory control of raw materials, Product Inventory control, Manufacturing cost control

A19
The computerized system relating to the issuance of manufacturing orders, the inventory control of raw materials, and the product inventory control are subject to the guideline. However, in the case where the product inventory control systems cover the inventory to be managed by the Marketing Authorization Holders at the post-marketing phase, relevant parts are not subject to the guideline. Furthermore, the computerized systems for the manufacturing cost control is supposed to be outside of the scope of the guideline, nevertheless if it controls cost of GQP / GMP related operations, the system is also subject to the guideline.

Q20
Are the computerized systems to control manufacturing equipment (e.g., water and steam supplying equipment for HAVC), which will not have direct impact on the quality of pharmaceuticals, subject to this guideline?

A20
Computerized systems to control manufacturing equipment which will not have any impact on the product quality, such as water supply system for VAC water, are not subject to this guideline.

Q21
When the data controlled by other system is utilized for GQP, GMP system, such as personnel database controlled by Personnel Affairs System to be used for the manufacturing record preparation system, to what extent should the system be covered by the guideline?

A21
Systems which are not co-related to GQP and GMP (systems for personnel and accounting, etc.) are not subject to the guideline.
However, when such systems are connected to the system under this guideline to utilize stored data and their functions, this guideline becomes applicable to the area which has impact on the GQP or GMP related system.

Q22
I would like to know what a system inventory is like. Please specify its purpose, matters to be described, and registration timing, etc.

A22
Purpose of the system inventory is to clarify systems to be controlled by this guideline in principle; Name of the system, registration number, whether it is a subject of validation (category of the software), and the name of the person in charge of the system, etc., are included in the registration items. If necessity, it could be an option to illustrate registration items, such as risk assessment results (high/medium/low) and complex system composition, with a diagram.
New computerized system is needed to be registered in the system inventory by the time of its operations. If there are any items, the details of which have not been determined at the time of registration, it is necessary to register those items right after the settlement.
A responsible person to manage the system inventory needs to be specified and the system needs to be updated regularly.
Furthermore, necessary rules such as registration procedure or approval matters, etc.,

need to be specified in the Operations Management Standard Code, etc.

Q23
Are there any things to be considered over the designation of Development Project Manager, Validation Project Manager, Operation Manager and responsible persons in the GQP and GMP Ministerial Ordinances? Please explain qualifications of Development Project Manager, Validation Project Manager and Operation Manager.

A23
Designation of responsible persons needs to be stipulated in the "Administrative Policy and Rules for Computerized Systems" etc. in line with the policy and actual situation of the Marketing Authorization Holders. People who are capable of fulfilling responsibilities in this guideline need to be selected by each organization.

Q24
Is it allowed for one person to hold the position ofthe Development Project Manager and the Validation Project Manager concurrently?

A24
When your firm develops your own systems, one person is not allowed to hold both positions of the Development Project Manager and the Validation Project Manager at the same time. However, when a part of the development operations is entrusted to a contract supplier, and if reasonable operation is possible by one person from the development phase to validation phase, it becomes acceptable.

Q25
Could you clarify differences between "4.3 (3) Supplier Assessment" and "5.1 Supplier Audit"?

A25
In this guideline, the supplier assessment is conducted for selecting an appropriate supplier at the initial phase of system development. On the other hand, the supplier audit is a part of the validation as to whether the selected supplier executes the entrusted activities appropriately.
The supplier assessment is to mainly assess the scale, production history, and Quality Management System (QMS), etc. of a supplier, and in the case of a packaged product,

the product history and product specifications, etc., are assessed for the selection of the supplier. As assessment methods are either written inquiries or on-site assessments, however the pamphlets and the website information on the internet, etc. may also be used for assessment.
On the other hand, the main purpose of the supplier audit is to confirm that development of the computerized system has been controlled under the adequate quality management system. Supplier audit may be conducted by document or on-site audit.
This guideline defines supplier assessment and supplier audit separately, however the past supplier audit results could be utilized for a supplier assessment for new system.

Q26
Is it possible to utilize supplier's system test result for the acceptance test?

A26
An acceptance test is conducted to demonstrate specification, functions and performances of the system upon its delivery. The Marketing Authorization Holders, etc. shall confirm if the delivered system satisfies quality of their order. On the other hand, a system test is conducted to confirm if the program works as designed. The test is conducted during the development phase. Since purpose and contents of the system test is different from the acceptance test, it is not allowed to utilize the system tests results for the acceptance test.
However, if a system test (integrated test) is conducted as a combined test of each module and conducted at the final stage of the development and if the reliability is proved to be equal level to an acceptance test, for example test plans are approved and its records are properly stored, etc, the test result may be utilized for the Factory Acceptance Test (FAT) in some cases.

Q27
Is it allowed to use some other terms to describe "validation" in this guideline?

A27
Other term may be used as long as concept of the word is in line with this guideline or it can be explained as the "an appropriate alternative method" in the Section 1.2 of the guideline.

Q28
Duplication is found in the validation items of system test and the OQ and PQ. Since it is described in this guideline that the result of an acceptance test can be utilized for the OQ and PQ, I would like to know if system test results can also be utilized for the OQ and PQ as well.

A28
Since the system test is conducted by suppliers at the development phases, it is basically not allowed to utilize its result for the OQ and PQ, which are conducted during the validation stage. However, if the system test is a integrated test of all modules at the final stage, and the reliability is equal to the validation activities, for example, the test is conducted in accordance with the plan approved by the Validation Project Manager and all the records are retained, it could be allowed to utilize the test results for the OQ. On the other hand, since PQ is a validation under operational conditions, it is not allowed to utilize the test results for PQ.

Q29
Does the person in charge of maintenance, etc. in the Section 6.3 (1), need to be selected from the Marketing Authorization Holders, etc.?

A29
People from external contractors may work as the person in charge of maintenance, as long as the maintenance operations are conducted in accordance with this guideline.

Q30
When we use a computerized system which is developed and operated overseas, is it acceptable to have the Standard Operating Procedures, characters on the screen and ledger sheets written in foreign language?

A30
It is acceptable, as long as people in charge of the operations management, such as operators, people in charge of system maintenance, and the Operation Manager, could understand the written language and proper operations are ensured.

Q31
Please show your basic ideas of the system retirement.

A31

System retirement is not as same as disposal. Primary purpose of the retirement is to ensure authenticity, readability and preservation of the data that are prepared by and stored in the computer(ized) system during the storage period stipulated in the GQP Ministerial Ordinance and GMP Ministerial Ordinance. Secondary purpose is to ensure its information security. The system, security of which is controlled throughout their life cycle, still needs to maintain the same level of data security upon its retirement.
Time capsule approach which saves a part or all of the data in the old system as Read-Only File to secure readability is also system retirement.

Q32

This guideline indicates that the retirement plan is to be prepared as necessary. Please give us concrete examples of unnecessary cases.

A32

Systems which do not have the electromagnetic record and do not require its readability, such as systems to control manufacturing equipment or manufacture-supporting equipment, etc., come under the unnecessary cases.

Q33

Please tell us which category in the guideline is applicable to the case, where the Distributed Control Systems (DCS) is used in order to control manufacturing processes.

A33

DCS is a system, in which several modulated programs are combined to execute targeted functions, therefore the functions of which vary depending on how those programs are combined. Accordingly, either category 4 or 5 is applicable to the DCS depending on its contents.

Q34

Which category is applicable to the computerized systems to control manufacturing process water, such as deionized water and distilled water, etc.?

A34

When you install commercially available system and use it alone, the Category 3 is applicable. If purposes of the usage are limited and the system is controlled only by a

few kinds of parameters such as temperature, pressure, electric conductivity rate, etc., and the functions are validated by the supplier, validation may be conducted during equipment qualification. In this case, the suppliers are required to prove that the system has been adequately validated at any time.

Q35

Which category is applicable to the computerized systems such as a system to control commercially available high pressure steam sterilizer, temperature and time of which are set by the user and the system of which is controlled by the embedded general-purpose program?

A35

When commercially available and versatile systems are used without any revision to the program, it is classified as Category 3. Validation of the program may be conducted during the equipment qualifications, if appropriate.

Q36

Which category is applicable to the blister package machines equipped with computerized systems with following functions?

- Function to identify lack of tablets in the blister pack by optical sensor and to remove the relevant pack in the subsequent process
- Function to calculate ratio of output of optical sensor to the tablet surface area and find tablets which lacks defined surface area and judge them as defective tablets
- Function to manage data of number of manufactured sheets (quality/defective products), etc.

The driving part is controlled by Programmable logic controller (PLC).

A36

When a blister package machine is operated on its own and performs its functions just by setting operational condition, it is classified into Category 3. Therefore, validation of the program can be conducted during the equipment validation if all of the program can be validated. However, when interface, etc. is established to connect each machine and other equipment etc. with other controlling computer, Category 5 is applied to the blister packaging machines in principle.

Q37
If the PC loaded with newly developed program is connected with a instrument to determine quality attributes of an in-process product (an intermediate for API) for process control (the data will be accumulated in a database of PC at all times), which category is applied to this system?

A37
If the obtained data are saved in the database of PC as required and utilized as manufacturing controlling information of GMP, and various quality attributes of the in-process products are processed by the newly developed program, the system needs to be validated by Category 5. However, when it is not a newly developed program and is commercially available software, Category 3 is applicable to the system.

Q38
When the system is programmed to transmit the obtained data from instruments to the connected PC or when those data are manually inputted into PC and evaluated by the built-in program, which category is applicable to the system?

A38
When the built-in program is newly developed for this system, it is subject to Category 5 of the guideline. If the program is the existing system and only some parameters in which are modified, Category 3 or 4 of the guideline is applicable.

Q39
Which category is applied to the spread-sheets software, formula or macros?

A39
When commercially available general-purpose software such as spread-sheet software, is used for the operations under the GQP and GMP Ministerial Ordinance, etc., it is recommended to follow necessary steps such as registration of the version number into the system inventory, etc.
The created formula of the spread-sheet needs to be validated by the Category 3 or 4 of the guideline depending on how it was created and their complexity. The concrete category is determined based on the corporate fundamental policy and risk assessment results, etc. written in the “Administrative Policy and Rules for Computerized systems.”
Furthermore, as macro is thought to be one kind of programs, when the macro is created,

the macro's performance needs to be validated by Category 5 of the guideline.
The spread-sheet software used for the macro needs to be validated by Category 1 with the version number, etc.

Q40
I would like to know which category of the guideline is applicable to the integrated system, which collects data from various analytical instruments and send the data into the superior computer. By using this integrated system, Certificate of analysis is printed out by the accumulated data as well as data by keyboard input.

A40
When each analytical instrument is connected to the superior computer where the compiled data are controlled by the original system, the entire system needs to be validated by Category 5 of the guideline.

Q41
When configuration alone is set in the package software, Category 4 is applicable.

A41
When the package software can be utilized without customization, Category 3 of the guideline is applicable.
Which category of the guideline is applicable, when we use general-purpose marketed integrator for an analytical instrument without modification?
When an integrator is combined with an analytical instrument, it is subject to Category 3 of the guideline. When the program function can be verified by the instrument qualification, the validation may be included in the instrument validation.

Q42
Which category is applicable to the following manufacturing equipment and analytical instruments, which are loaded with the computer developed by hardware supplier?

High pressure steam sterilizer	HPLC
Tablet press	GC
Fluid- bed dryer	UV
Filling machine	IR
Lyophilizer	Other analytical instruments
Coating machine	

Other manufacturing equipment

A42
When each manufacturing machine or analytical equipment is operated separately and the function can be fulfilled only by the setting of operation condition, etc., each of them is classified as Category 3 of the guideline. The validation of which may be included in the equipment validation if appropriate. However, when each equipment requires composition setting, validation in line with Category 4 of the guideline becomes necessary. If program supplied by a hardware vendor is modified, the validation by Category 5 is to be conducted for entire system.

Q43
Which category is applicable to the system which controls all the HVAC in the facility?

A43
When a system functions by composition setting, such as registration of various conditions of a room and selection of control function, in addition to the setting of parameters (temperature, humidity and pressure difference, etc.), the system is classified as Category 4. When a system is prepared or added for your in-house operations, the affected area is classified as Category 5.

Q44
When some other functions are added to a general purpose program developed by the supplier or the program is modified, to what extent is the guideline applied?

A44
The validation needs to be implemented by Category 5 of the guideline within the affected area.

Q45
It is described that “4, Establishment of Functional Specification or the Design Specification may not be omitted if function is simple and system can be designed by the User Requirement Specification” in the remark column of Category 5 of the Table. Please give concrete examples of the functions that do not require either Functional Specification or Design Specification.

A45

The description applies to the case where a macro-program is used for relatively simple arithmetic processing at a laboratory. When all the functions are described in the User Requirement Specification and contents of the macro-program are easily available in print, preparation of the Functional Specification or the Design Specification may be omitted.

Q46

Please explain handling of the legacy systems, such as firmware and PLC, etc., which came to be included in the validation scope by this guideline.

A46

When validation of the relevant equipment is completed, the validation of the computer system is not required. However, in the case where any system trouble is likely to occur at the time of actual operations, the validation of the computer system becomes necessary.