Tentative translation as of February 20, 2012

Administrative notice
February 1, 2012

To Heads of the Prefectural Health Department (Bureau)

Compliance and Narcotics Division
Pharmaceuticals and Food Safety Bureau
Ministry of Health, Labour and Welfare

Q and A on "Application of PIC/s GMP Guide"

Administrative notice entitled "Application of PIC/s GMP Guide" dated February 2, 2012 provides basic concept on utilization of PIC/s GMP Guide. We hereby issue Q and A on the notification in order to help resolve specific issues at actual operations.

This Q and A involves significant information concerning how to proceed with GMP inspections based on the PIC/s GMP Guide. Therefore, you are requested to thoroughly inform all the related parties and cooperate for smooth implementation.

Please note that copies of this notification are to be sent to the related organizations listed in the attachment.

Appendix

Q1 What benefits can pharmaceutical companies expect from utilization of PIC/s GMP Guide?

A1 PIC/s aims to promote international cooperation between competent authorities, provide framework for information exchange and to promote quality assurance of inspections. When a company produces quality products in accordance with globally harmonized PIC/s standards, this will lead to the enhancement of quality of their products. Then the company will eventually win confidence and support from patients.

Q2 Where does PIC/s Guide stand under Japanese legal framework?

A2 In Japan, Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs" (MHLW Ministerial OrdinaneNo.179, 2004, hereinafter referred to as "GMP Ordinance"), etc is the legal provision of Japanese GMP.
PIC/s GMP Guide will be utilized as a guidance of quality assurance based upon GMP Ordinance, similarly to other existing guidelines, such as administrative notices, administrative notices, etc.

Q3 Will Japanese regulations be revised in response to the introduction of PIC/s GMP Guide?

No, since no major discrepancies have been admitted between PIC/s GMP Guide and current Japanese regulations and administrative notices, etc., it is not necessary to change our current regulations.
However, there are still some items, which need to be adjusted to PIC/s Guide. This adjustment will be notified by revision of administrative notification, PFSB/CND No.0330001 "Establishment, revision and abolition of ministerial ordinance and public notices of GMP/QMS upon enforcement of the Pharmaceutical Affairs Act" dated March 30, 2005 or "Case study of GMP/QMS" (hereinafter referred to as "Case study"), office memorandum dated October 13, 2006.

Q4 How are existing Japanese regulations and administrative notices going to be made further compatible with PIC/s Guide?

A4

For the time being, just like existing administrative notices, office memorandums, PIC/s GMP Guide will serve as a guidance of quality assurance based on GMP Ordinance.

However, in order to facilitate further global harmonization, existing regulations are going to be replaced with PIC/s GMP Guide in the future. Also, as to items unique to Japan, new guidance will be provided by revision of notifications or office memorandums.

Q5 Some terminologies in PIC/s Guide are not found in Japanese regulations. Are clear definitions of those words going to be provided?

A5 Clarification or definition of such words will be addressed by revised version of Q and A, etc.

Q6 Japanese translation of PIC/s GMP Guide was published. Is there any plan to amend the text to comply with Japanese regulations?

A6 No, there is no plan for amendment. Translation of PIC/s GMP Guide was published in Japan in order to harmonize our quality assurance system to the international standards. And also, it aims to respond to the need of international cooperation of GMP inspections , such as information exchange. Amendment of text is not consistent with these objectives.

To explain how to interpret the text of PIC/s GMP Guide, it will be addressed by revised version of Q and A, etc.

Q7 If there is any discrepancy between the scope of PIC/s GMP Guide and GMP Ordinance, how should it be treated?

A7

As for manufacturers of investigational medicines, medicinal gasses or manufacturers undertaking powdering and subdividing process of herbal medicinal products, scope of GMP is different between PIC/s GMP and GMP Ordinance. However, with regard to investigational medicinal products, “Ministerial Ordinance on Good Clinical Practices” Ministerial Ordinance, No.28, 1997 will cover this area. Also, new administrative notice will be issued to address quality assurance of medicinal

gasses and manufacturers undertaking powdering and subdividing herbal medicinal products.
To seek further accordance to the international standards, additional adjustment should be made to the entire Japanese system. However, for the time being, PIC/s Guide will be utilized within the scope of current GMP Ordinance.

Q8 What if the requirements of Japanese regulations are different from those of PIC/s Guide, such as retention period of biological products or person in charge of manufacturing control on bio-derived products?

A8 Japanese guidelines will prevail.

Q9 I understand that PIC/s GMP Guide is continuously being amended. How should the appendix of the administrative notification “Application of PIC/s GMP Guide” be treated when the original PIC/s GMP Guide is revised?

A9
Yes, PIC/s GMP Guide is continuously amended for further improvement. When PIC/s GMP Guide is revised, revision will also be made in Japan to cope with the change. The revised contents will immediately be notified by administrative notices, etc.

Q10 Upon GMP inspection with PIC/s Guide as a guidance, is there transitional period granted to each manufacturer for adjusting to PIC/s GMP Guide?

A10 Similar to other administrative notifications and office memorandums, PIC/s GMP Guide is utilized as a guidance for GMP inspection based on the GMP Ordinance.
Therefore, transitional period, etc. is not set specially.

Q11 Do we need to start applying methods in PIC/s Guide immediately?

A11 Manufacturers are expected to utilize methods provided by PIC/s Guide after issuance of this notification. However, as long as equal or superior quality is assured for the products, other methods may be applied, as well.

Q12 In the “Application to the PIC/s GMP Guide”, there is an expression “any undeniable risks to

the quality of the products or to the public health". Please tell us how you judge the significance of the case and what actions we will be expected to take in such case.

A12
When a manufacturer adopts their own methods, risk assessment is conducted to see if the method poses any risks to the product quality or to the public health. At the same time, risk assessment is conducted based on scientific expertise and through assessment between the manufacturer and inspectorate. Also we check if equal quality is assured compared to the methods of PIC/s Guide.
When potential risk is detected, observations for corrective action will be made depending on the significance of the risk. The action may include manufacturing and quality control methods laid down in PIC/s GMP Guide.

Q13 When there is a discrepancy between manufacturer's and inspectorate's judgments on the case with undeniable risks, which judgment will prevail?

A13 Basically, risk is judged based on thorough assessment based on scientific wisdom. As for cases requiring special expertise for judgment of risk, such as risk assessment of new scientific methods, it will be discussed at the committee among representatives from MHLW, PMDA and prefectures and comments will be made by the committee.

Q14 Please elaborate on the sentence "whether or not to apply the methods in PIC/s Guide for the manufacturing process relies on the discretion of each manufacturing site".

A14 First, manufacturers are obliged to ensure quality of products based on the concept of administrative notifications and office memorandums. They are also expected to be aware well of potential risks associated with characteristics of products and manufacturing methods. When a method different from PIC/s Guide is applied, manufacturers should prove that it can achieve quality at equal or superior level to that of PIC/s Guide by showing sufficient grounds.
Only when the above condition is met, whether or not to apply PIC/s methods relies on the discretion of each manufacturing site.

Q15 How do you confirm "equality to PIC/s Guide" during GMP inspections?

A15 Upon GMP inspections, PIC/s Guide is utilized as a guidance, just like other domestic

guidelines, including administrative notifications, office memorandums, etc. When a method which is different from that of PIC/s Guide is applied at a site, inspectors will conduct inspection on science and risk based methods and scrutinize if the same or superior quality to the PIC/s level can be attained by the method.
In cases where the “equality” is not verified, the manufacturer is asked to justify the methods.

Q16 What will a manufacturing site be asked if manufacturing or quality control methods at the site is judged to be different from PIC/s GMP Guide?
A16 Mere difference in manufacturing or quality control method will not pose an immediate problem. However, when undeniable risks to the product quality or public health are detected, instruction to comply with PIC/s Guide may be made upon deliberations of characteristics of the product. The instruction is also based on the concept of notifications and office memorandums.
