Panel Discussion: Regulatory Perspective for Pathology Data

(Transcript)

In the 25th JSTP annual meeting at Hamamatsu on 28 January 2009

The Japanese Society of Toxicologic Pathology (JSTP) held a symposium entitled “Panel Discussion: Regulatory Perspective for Pathology Data” on Jan 28, 2009 during the 25th JSTP annual meeting at Hamamatsu (Jan 27–28, 2009) (Meeting President: Dr. Sunao Manabe, Daiichi Sankyo Co., Ltd., Medicinal Safety Research Labs). The purpose of the panel discussion was to clarify differences between USA, EU and Japan of 1) definition of pathological data and 2) peer review process, and subsequently trigger their harmonization, by briefly introducing the results of questionnaire survey conducted beforehand thanks to the cooperation of Japanese pharmaceutical companies and contract research organizations. (This survey was conducted in cooperation with International Federation of Societies of Toxicologic Pathologists/Regulatory Interaction Committee (IFSTP/RIC) and Japanese Society of Toxicologic Pathology.)

The panel discussion was co-chaired by Dr. Yuji Oishi (Astellas Pharma Inc.) and Dr. Kazutoshi Tamura (Bozo Research Center). Panelists were Dr. Frédéric Schorsch (IFSTP/RIC, Bayer CropScience), Dr. Klaus Weber (Harlan Laboratories, Inc.), Dr. Jerry Hardisty (Experimental Pathology Laboratories, Inc.), and Mr. Jun-ichi Kuranami (the Japan Society of Quality Assurance, Kyowa Hakko Kirin). During the panel discussion, simultaneous interpretation -Japanese/English- was provided.

This transcript of the panel discussion is published in the Journal of Toxicologic Pathology with the approval of the 25th JSTP Meeting President and the board of directors of JSTP.

Moderator: Before we start the panel discussion, please listen carefully to the instructions on the use of the simultaneous interpretation receiver. Please place the earphone on your ear and adjust the dial at the top of the equipment to the channel of your preference. Channel 1 is Japanese and channel 2 is English. Please use the orange button on the side to adjust the volume. And now, we would like to start the panel discussion, “Regulatory perspective for pathology data.” Chairpersons Dr. Oishi and Dr. Tamura, I leave the floor to you.

Dr. Yuji Oishi, Astellas Pharma Inc.: We would like to start the panel discussion, “Regulatory perspective of pathology data” of the last session of the 25th meeting of the Japanese Society of Toxicologic Pathology. Allow me to first introduce the panelists to you. Dr. Frédéric Schorsch is the treasurer of the International Federation of Societies of Toxicologic Pathologists (IFSTP) and member of the Regulatory Interaction Committee. He is also the president of the French Society of Toxicologic Pathology and is the leader of the pathology group at Bayer CropScience in France. Dr. Klaus Weber is the head pathologist at the Harlan Laboratories in Switzerland. Dr. Jerry Hardisty has joined us today from the Experimental Pathology Laboratories, Inc. (EPL) of the United States. Last but not least, our Japanese panelist is Dr. Junichi Kuranami from JSQA, the Japan Society of Quality Assurance. We would like to proceed with the discussion with the above four panelists, myself, Oishi, and Dr. Tamura. (Slide 1–1)

There are two main topics to this panel discussion. First, on the handling and use of digital data including those taken
with digital cameras which are used quite frequently in recent years. In particular, the discussion will focus on how the digital image data are handled. The second topic of the panel discussion is the peer reviews on pathology data, especially given that there is great confusion in how they are perceived in Japan. (Slide 1–2)

This discussion on pathology data images originated as the position paper of the Society of Toxicologic Pathology (STP) of the US, which was reprinted in the Journal of Toxicologic Pathology at the beginning of this year. As those of you who read the article already know, the position paper itself was issued in 2007 with a statement that the American College of Veterinary Pathologists (ACVP) and the British Society of Toxicological Pathologists at the time gave their full support and agreed with the general perspective of the position paper. The Japanese Society of Toxicologic Pathology (JSTP) would have followed suit and joined others in expressing its agreement regarding the perspective of the position paper as consensus for full support was obtained at our board meeting in 2007, but did not meet the deadline for publication. As such, we took the liberty to state our full agreement and support regarding the position paper in the latest issue of our Journal of Toxicologic Pathology under the name of the President of the Japanese Society of Toxicologic Pathology Dr. Tatematsu. (Slide 1–3)

Now, I would like to hand the floor over to Dr. Tamura for a brief explanation on its content. Dr. Tamura, please. (Slide 1–4)

Dr. Kazutoshi Tamura, Bozo Research Center Inc.: As part of my role today, I would like to introduce the view of STP regarding pathological image data as well as that in Japan, while taking into consideration the results of the questionnaire survey conducted by JSTP. First of all, I would like to point out that the article partly quotes the basic perspective of the position paper of STP. In the position paper of STP, it describes what pathological image data and their raw data entail. It is described in the position paper that basically the pathological image data which are used as the base for data generation are recognized as raw data, while other data which are not used for data generation are merely illustrative images and not raw data. (Slide 1–5) Furthermore, it also defines the requirements of the raw data and the raw data of the pathological images which were used as the base for data generation. As there is a need to ensure the integrity of the data in compliance with the GLP, one of the requirements is to establish SOP. In addition, it describes adding appropriate labels and signs, as well as determining a standard storage method. When storing digital images, authentication of the data must be conducted in compliance with the electronic signature and part 11, and printed images may be used. (Slide 1–6)

There are other pathological image data which may not be used for data generation. Among those are illustrative images which are required by the protocol and illustrative images which are attached in the final report. These images are not raw data, but they should be stored as documentation of an action required by the protocol and preserved as the illustrative images attached to the final report. Furthermore, illustrative images submitted in a regulatory response are not raw data, but these images are usually archived for convenience. As for film photograph, authentication of the data by printout used for data generation is thought to be
more appropriate than by negative films. (Slide 1–7)

In response to this, I have quoted the GLP Guidebook 2008 for the general view in Japan. Various types of image data are taken, but currently the observation form is defined as raw data at many facilities, thus the photographs are considered as reference materials. As such, it is said that images taken by digital camera are considered as reference materials. However, while considered as reference materials, it says to enhance the procedures and records, conduct thorough training and demonstrate the validity of the process while following all procedures. At the same time, assure the credibility of the image data, in particular its non-falsification property. (Slide 1–8)

In recent years, various image data in addition to the pathological data have been collected. When digital images listed here are defined as data, it is said that one method for securing their authenticity is to retain the data in media with an electronic record and signature which is difficult to modify. As well, another method to secure non-falsification is to strengthen the system set out in the SOP, the records of photographs taken, and the operations and staff training, as well as retaining the digital images as read-only data with a password. In any case, the method of securing non-falsification depends largely on the technical advancement of digital cameras and related peripheral devices. Even at this moment, by strengthening the system to secure a non-falsification process in terms of computer software, staff training and adequate records, it is feasible to regard digital images as raw data. If digital cameras are used, each facility should consider the GLP compliance on their own. (Slide 1–9)
In front of you, to the question “which photographs do you use in the pathological examination?” most answered that the materials they use are film cameras, and the use of digital cameras is restricted to only a few institutions. (Slide 1–11) When further asked, “Which photographs do you take with a digital camera?” the response was that while they were mainly for macroscopic images, they were also used for microscopic data, in addition to electronic microscopic data and image analysis. Nevertheless, they are still not all that common. (Slide 1–12)

Let us now consider the position of “raw data” photographs acquired with these digital cameras. As you can see, the use of such data is very low and the use of those raw data acquired with digital cameras is limited to certain institutions at present. In particular, there are a few institutions which only use digital data. (Slide 1–13) In addition, in response to the question on the use of digital cameras, “What digital image data do you define as raw data?” there was a response that, “The morphometric analysis data including the images as the base for generating the data are at times recognized as raw data at certain institutions as well as those data recording other representative illustrative images of changes.” (Slide 1–14)

Actually, more detailed questionnaires are being conducted, but I believe that you now have a general picture of the current status of pathological image data in Japan and their usage. Other points I have described now are direct quotes of the opinions and requests regarding the pathological image data. (Slide 1–15)
I have given you a brief outline of the perspectives of the STP position paper and the Japanese government, as well as the current usage of the digital data such as those taken by digital camera in Japan. Therefore, I would like to ask Mr. Kuranami to further elaborate on the view of JSQA as well as on the various discussions on image data which have been conducted over quite some time now in Japan. Please, I hand the floor over to you now, Mr. Kuranami.

Mr. Junichi Kuranami, JSQA; Kyowa Hakko Kirin Co., Ltd.: As you can see before you, I would like to talk about the use of digital images in the GLP study, as well as the instructions from the authorities and the view of JSQA. As has been introduced by both chairpersons just now, I have been invited to this conference today as an executive member of the group that is studying the GLP pharmaceutical drugs at the JSQA. It is my great pleasure to be invited here today. Thank you very much. (Slide 2–1)

Now, let me begin. Firstly, I would like to speak about the instructions of the authorities, including the Pharmaceuticals and Medical Devices Agency (PMDA), and the involvement of JSQA until now. In front of you now is the chronological outline of its history. As for digital images, PMDA issued an instruction manual for the first time in 2001 and digital cameras were practically not permitted for use from that point. Since then, JSQA has been working to obtain the permission for the use of digital cameras. We have made a proposal for their use in May 2007. Discussions have been held continuously with PMDA around the time, and the use of digital cameras was conditionally permitted later in September 2007 at the GLP training course. In the GLP Guidebook 2008 that was issued the following year, it provides a more detailed description on what makes raw data. (Slide 2–2)

I would like to go into detail on the use of the digital camera data which was first banned in 2001. Three points were given by the authorities with a note “at present”. As you can see before you, this was the general idea given by PMDA. As such, it is difficult to define digital images as raw data. It is also stated that they shall not be used in the final report or even as a reference material. They all came with the condition, “at present.” (Slide 2–3)

This led to the practical banning of the use of digital cameras. Two major issues were raised by PMDA on the report at the time, the major one being that digital images are...
extremely easy to edit on computers. The other problem was that this modification procedure may be conducted without leaving any trace. These two are extremely crucial issues, which put in more sophisticated terms can be referred to as the lack of authenticity, inadequate audit trail, etc. As such, the trend led to the thinking of such data as basically not being adequate for use.

On the other hand, however, I would first like to note that the situation started changing around 2005. The Electronic Records and Electronic Signature Guideline (ER/ES Guideline) was starting to be established and the camera market was becoming very active. At the time, there were news that single-lens reflex camera for film will no longer be manufactured. As for the basic medium, there was a market trend to shift over to digital for all filming methods. As for actual medical equipment, the cameras on the medical equipment are all digital cameras now; thus such a change in environment called for reconsideration of the policy. We shared the same concerns as PMDA over the three points: non-falsification cannot be assured, preservative quality cannot be secured and the audit trail must be enhanced one way or another. As such, we reviewed and discussed in search of a solution to these issues. (Slide 2–4)

The conclusion we drew was as follows: development of the procedures, enhancement of the records and provision of thorough training. After all, what we came up with was in general the same as what was written in the position paper. We planned to cover for the disadvantage of digital images which lacks GLP through taking this approach. In any case, as digital cameras are not allowed for use in GLP studies, our objective is first and foremost to obtain the approval for their use. The ultimate goal, however, is to use them as raw data, and a proposal has been made as such. (Slide 2–5)

In response to this, the policy issued by PMDA that same year aimed to prove the validity of the process by having well-trained employees keep the operation records according to set procedures. The intention of PMDA was that the non-falsification property of the data should be ensured through such measures. Being able to ensure the non-falsification property means that editing and modification of the digital images after filming can be denied; thus, it was thought that this should resolve the aforementioned issues. Regarding this point, it was thought that the same procedures must be effective for all raw data, therefore applicable to both reference materials and raw data. That is how the use of digital cameras practically became permitted. (Slide 2–6)

I would like to once again state the basic perspective of JSQA I introduced so far. The focus is placed on the thorough training of the personnel in charge, such as the development of the procedures and the SOP. Furthermore, audit trail is enhanced through taking records, as well as its validity being ensured through such an approach. As such, digital images now may be defined not only as reference data but as raw data, signifying that digital images could most likely be considered as being like the so-called “paper data” at this point, and thus accepted as such. (Slide 2–7)

And now, in the square at the very bottom of the screen you will see the message that has been discussed ever since the ministerial ordinance was revised last year. It states the need to determine appropriate response measures at each facility, operate based on their own decision and be able to give adequate explanations. The message states that GLP is not something that is imposed but instead something we
create with our own hands. In short, we decide what we want to do first, and then brainstorm what kind of approach we should take. At the same time, it also states that while it is extremely problematic if the plan is merely self-approving, there is no need to be worried if an adequate explanation can be made. As such, we consider it as something we create ourselves. (Slide 2–7) That is all, thank you.

**Dr. Tamura:** Thank you very much, Mr. Kuranami. I believe we were able to deepen our understanding of the current situation with the explanation given by Mr. Kuranami, as he broke down and described the details in chronological order. In contrast to such a situation in Japan, I would like to ask the opinions of the panelists who have joined our conference today. Please share with us the views of your country and from your professional standpoint. First of all, it would be our great pleasure if Dr. Schorsch of the IFSTP could give us a brief overview of the situation in your country. Dr. Schorsch, please.

**Dr. Frédéric Schorsch, IFSTP, Bayer CropScience:** Thank you. Concerning the digital images, we all share the same difficulties. We have in Europe a discussion similar to the one you have in Japan. For us, what is difficult today in our different companies is to secure the electronic file and its archiving according to GLP requirements. I think this is the most difficult issue, because digital cameras and associated software do not fulfill GLP requirements. The difficulty concerns mainly the process of archiving. There are still discussions to have such a system in place in our different companies, and there is no standard defined by IT, QA or our companies to deal with electronic data and electronic images. There are different solutions, but the archiving of raw data on paper is often the final choice. But is it acceptable with images? As it was said in this meeting, the local and company policies have to define how we have to deal with the images.

**Dr. Tamura:** Thank you very much. Dr. Schorsch has kindly described to us now that the biggest problem probably is ensuring the quality of the data preserved. And now, I would like to ask Dr. Weber of Harlan Laboratories for some comments. Dr. Weber, please.

**Dr. Klaus Weber, Harlan Laboratories, Inc.:** The major problem that we encounter with archiving is that when we have digital pictures we have to find a way to control if these pictures are still running after two years or three years, or something like this. We are especially asked from the Swiss Medic to check our electronic data recordings every two years, so this would increase tremendously the amount of work that you are doing. We consider currently pictures only as raw data when we use them for measurements and all other pictures we do not consider as raw data; also, we store them all in the same way.

**Dr. Tamura:** Thank you very much. Dr. Weber’s comments just now, on how various data are checked every two years, I believe that it certainly comes with great effort and presents a real problem in reality. Next, I would like to ask Dr. Hardisty of EPL of the United States for his input. Dr. Hardisty, please.

**Dr. Jerry Hardisty, EPL:** Thank you. It seems to me that there is not a lot of difference between the US position in handling digital images as compared to the Japanese position. The one area where there may be some differences is whether illustrative images are considered raw data or not. The STP position is that illustrative images are not considered raw data; only those images, as Dr. Weber said, where we obtain measurements are considered raw data. When we do electron microscopy at EPL, even though the image is taken with a digital camera we print a photomicrograph, and that is the image that we use to generate the data, so in that case the printed photomicrograph would be raw data and not the digital file. That is not necessarily true of morphometry. When you are generating morphometry data, you do have to treat the digital data as raw data. Some of the problems that we run into is Part 11 compliance with some of the hardware and software that is available in the United States. It is difficult to assure that it is Part 11-compliant. The way we do that is exactly the same way you do it in Japan, by ensuring that we have well trained personnel, that we have SOP procedural methods to assure that there is no possibility of falsifying the data, and have an audit trail so that we maintain the original image as well as any image that we may generate where we change that image. We always keep the original image and an audit trail, so I don’t really see too much difference between the different areas (Europe and the United States and Japan) in how digital images are being handled today, except with illustrative images.

**Dr. Tamura:** Thank you very much. As Dr. Hardisty has mentioned just now, the question is what kind of digital images may be defined as raw data. As I have explained
briefly earlier and just as STP and JSTP have supported, and thus in accordance with the basic stance of JSTP, raw data are those used as a base for data generation. As for the treatment of the illustrative images, however, the stipulated range seems to vary slightly. In particular, my personal impression is that common understanding on the range for its use as reference material has not yet been fully established in Japan. I would like to ask for a few words from our chairperson, Dr. Oishi, regarding another situation in Japan today, the current status of pharmaceutical firms in Japan. I think this will give us a wider perspective. Dr. Oishi, please.

**Dr. Oishi:** As we are engaged in morphology, it goes without saying that we collect various images as part of our daily routine. Fundamentally, these data should just be stored with a report, but it requires a lot of energy when storing the raw data in accordance with the regulations we have been discussing so far. In addition, the photographs are not taken as a direct material used in studies but merely as reference, and in most cases photographs are merely taken as so-called “typical examples.” As explained earlier, an instruction to “save reference data just like any raw data for GLP” is very abstract and vague in Japan has been caused a very serious problem in reality. That is where we feel that digital cameras are extremely difficult to use in GLP studies. It seems that such regulations are hindering the digital camera images from being used as a material for supplementary data to improve the quality of the study.

On the contrary, for example, the electronic microscopes that we use at our facility have a digital camera and a digital television installed, but we are observing the television and directly recording our findings. Normally, photographs are taken first and then findings recorded while observations are made from these photographs, but there are some cases where photographs are not taken (due to the regulation regarding digital data). In general, it is best to photograph the findings, but the various procedures stated before to fulfill the regulations of the digital data are extremely complicated and require a lot of energy. The problem that Japan is faced with currently, therefore, is that the standard for which data must be actually stored and the cutoff line from where they do not need to be stored is very obscure. I feel that the border is extremely ill-defined as to what should be stored, and as a result the cutoff line seems to be established at a lower level because of accepting compromise plans. That is all, thank you.

**Dr. Tamura:** Thank you very much. As discussed just now, I would like to ask a few words from Dr. Hardisty on how to handle data as the so-called “reference data.” How are those image data attached to a final report handled? And also, how are they stored, or are they not stored at all? It is briefly mentioned in the position paper, but I would like Dr. Hardisty to give us a few words on the current situation on this point.

**Dr. Hardisty:** I was not involved directly in the drafting of this document by STP, but I think that STP proposes that those illustrative images that are included in the final report are not raw data. They are just illustrations of a particular lesion, and no data is generated from those. It is a photograph used to demonstrate what something looks like, but it is not actually considered raw data so it would not be handled as raw data.

**Dr. Tamura:** Thank you very much. In other words, could we take you to mean that there is no need to store the object itself?

**Dr. Hardisty:** I think that they are archived along with the final report, but they are not required to meet the Part 11 compliance process, but the image would be archived with the final report in the raw data.

**Dr. Tamura:** Thank you very much. I believe that point is very easy to understand for us on the Japanese side as well. Dr. Weber and Dr. Schorsch, are there any points that you find different between your countries and Japan in particular? If you do, please share them with us. Dr. Schorsch, how about you?

**Dr. Schorsch:** I think that the position explained by Dr. Hardisty is exactly the one we face in our different companies. The illustrative photographs are not considered to be raw data. What has to be considered as raw data is the diagnosis and the final conclusion made by the study pathologist after his evaluation. Illustrative photographs can help and support this conclusion. But there are few toxicologists who can really interpret such photographs. You must have the skill of a pathologist to interpret such photographs and there are few pathologists within the different authorities. Furthermore you know that it is impossible to make a complete evaluation based only on pictures which reflect only a small part of the slide and do not take into consideration the whole animal and all the observations found in all animals belonging to one group. Clearly, illustrative photographs are not very useful from the pathologist point of view. What is important is the conclusion written and signed by the study pathologist. Concerning the electron microscopy or the cell proliferation studies, it is clear that those photographs are raw data, and we have to store and to archive them. As I said before, the problem we have today in our different companies is how we can guarantee the security of these files for a long period of time. I am working in the agrochemical industry and we have to keep this data as long as possible, and of course during the life time of the compound, and today IT systems do not guarantee that we can open this file again after a long period of time. This is why we are not completely clear with electronic data.

**Dr. Weber:** I can just support this opinion, because we are using the photographs as a type of explanation in a report; this is something as we would write a sentence in a report.
We sign the report and this report is the original raw data along with the slide used for taking the photograph. We consider the slide as an original subject and we can make another photograph if necessary, so it would not make a lot of sense to use these illustrative images as raw data.

**Dr. Tamura:** Thank you very much. That was very interesting. I believe raw data is actually clearly defined at each facility. As mentioned earlier, even when some data are actually used as raw data, I believe the issues we have discussed thus far are something we must continue to tackle instead of trying to study and uncover the relation between raw data and its preservation quality right now. While I feel this issue is something that should not call for such a big debate, I believe that through various opportunities the vague boundaries will be determined through discussions, such as among those institutions in Japan in particular that are responsible for handling reference data. I believe that the way these digital data should be handled is starting to take concrete form through the various opinions shared today by Dr. Schorsch, Dr. Weber, Dr. Hardisty, Mr. Kuranami and Dr. Oishi. As we have two topics scheduled to discuss today, we would like to end the discussion on the digital data issue for now. Let us now move onto the session on peer review. Dr. Oishi, please.

**Dr. Oishi:** Now I would like to start our discussion on pathological peer review. (Slide 3–1) First of all, I would like to describe briefly the basic perspective of the position paper that has been brought up quite often so far. The basic perspective of the position paper on reviews, whether official or unofficial, which includes those that are sometimes referred to as “sponsor reviews” in Japan, is that it is to be conducted before the data has been finalized. I believe this is the most different point from the procedures practiced in Japan. The position paper provides that the records and explanatory notes regarding the review are all part of the intermediary notes of the personnel in charge of pathological findings; thus these notes need not be stored. In case of an official review, differences in the interpretation of the findings among the pathologists are resolved first, and then written down in the statement of the peer review that the review has reached an overall agreement. This statement is normally then included in the final report. This is the basic procedure outlined in the position paper. (Slide 3–2)

The view in Japan is that basically its definition of raw data practically meets the international standard described in the position paper. The understanding is that raw data is something that is finalized after the pathologists make decisions, fiddle the information around in his/her head or change the findings. As for the changes made after the data has been finalized as raw data, it states that all changes must be recorded. I feel that this part of the procedure is mostly consistent around the world. (Slide 3–3)

The biggest difference between the Japanese practice and the international standard is regarding the “sponsor review.” While “sponsor review” is a name used which is unique to Japan, example procedures were found in the GLP inspection conducted for a Contract Research Organization (CRO) in 2006. The inspection revealed that a sponsor review was conducted upon drafting a final report on the pathological findings, where some of the findings were modified. Despite such modification, however, the places
that were modified and the reason for such changes were not recorded in the final report. Because of this, the aforementioned sponsor reviews on histopathological examination are now to be conducted after the findings have been finalized. Moreover, in case of conducting a sponsor review, all records must be kept, while the reason and content of the modification or change if any must be included in the final report. These instructions have been given in Japan, and the participants were advised to do so at the GLP training seminar in 2007. (Slide 3–4)

In Japan, histopathological data is finalized before the review. As for Europe and the United States, however, the reviews are basically viewed as a process conducted to finalize their findings in reports, including the position paper. In short, the timing of the review differs. Furthermore, as mentioned by Dr. Weber just now, the pathological report exists in Europe and the United States. This in Japan again is slightly different. According to the instructions given by the Japanese authority, the general understanding is that reports shall be written by SD and those written by someone other than SD are not considered as a report. It is also not a common practice in Japan to attach signed pathological reports to the final reports. (Slide 3–5)

As for the questionnaire results regarding the question whether they are conducting a peer review of any form, including external sponsors and/or internal parties, the majority of the people responded that they are conducting peer reviews. (Slide 3–6) As for the type of reviews, the most common response was internal peer review. As it will amount to an immense number of reviews when conducting both reviews (internal and external), therefore, pathologists in the same laboratories are made to conduct reviews on each other first. The responses also revealed that most studies are constantly under internal review, and also that most of the cases are external review when only a partial review is being conducted. Sponsor review is the next most common type of review conducted according to the responses we received. (Slide 3–7)

The next question was on what kinds of studies the reviews are conducted on. The responses showed a similar pattern for studies between three to six months. Basically the most common type of review conducted was internal reviews as mentioned earlier, followed by sponsor reviews. Cases of external reviews are very minor. On the other hand, the responses stated that reviews of most carcinogenicity studies are conducted as external reviews. The second most
common type of review is the sponsor review, which proves that in any case sponsor reviews are actually conducted very frequently. (Slide 3–8)

Regarding the question on the timing when the reviews are conducted, the results of the responses were reflective of the administrative instruction. In case of internal reviews, conducting it prior to fixing the findings is the most commonly practiced style. In case of sponsor reviews and external reviews, however, responses showed that the majority of the people follow the guidelines of PMDA, and they are conducted after the findings are fixed. (Slide 3–9)

As for the question as to whether they are saving the pathological reports when revisions are made, there were unexpectedly many who answered “only those after revisions.” Many responded that, “Only a revision record after has been saved”, while PMDA instruct record to be made every step, we only record after a revision has been made.” There are, however, people who keep records both before and after a revision. (Slide 3–10)

Another question asked was in case of a revision being made to a finding, where will the reason to the modification be recorded. The responses we received were, “basically on the raw data,” while the PMDA instructs records to be included in the final report. Basically it is most common that the records are kept on the raw data. The next common place was the ledger sheet (Table/Appendix), followed by the final report. There were responses that stated they do not keep any record. (Slide 3–11)

Next, to the question of whether they attach the statement of a peer review as it used in Europe and the United States, there were many cases where these statements were attached in external reviews. In some cases, however, there were responses that they do not attach such statement. (Slide 3–12)

Then the next question was whether they record and attach a list of all changes made to the final report. The most common response we received again was that they do not practice this procedure. The result was the history of changes are hardly ever recorded for external, sponsor or internal reviews. (Slide 3–12)

Other comments left in the blank space provided in the questionnaire included the following. The principle provided by the institutions was not actually to reflect the history of changes and other revisions in the final report but to clarify the history of modification made by a peer review. As such, there were cases where modified parts were marked in the
Another comment said that an internal review was not the equivalent of a peer review. However, there was also a comment that conducting a sponsor review prior to fixing the pathological findings is inappropriate. There is an instruction that a sponsor review shall be conducted after all findings have been fixed. The above is the situation in Japan.

I would now like to ask Mr. Kuranami to share with us the views of QA.

Mr. Kuranami: As has been discussed so far, I would like to talk about the instructions given by the authorities and the views of JSQA on sponsor reviews. (Slide 4–1) I will be talking in chronological order just like earlier, but just to give you an outline, I would like to state the following. It is rather a relatively old topic, but when looking back at its history, the definition of raw data in pathology started to form its outline in 1997. In response to this development, the definition of raw data of pathological examination was first determined in what is known as an instruction manual, GLP Handbook of Pharmaceuticals and Chemicals 1997, which has been around for quite some time. Its content is as how Dr. Oishi has explained just now. I will go into details later. The instruction manual GLP Handbook of Pharmaceuticals and Chemicals was renewed in 2002, while its content virtually remained the same as the 1997 edition.

The next development was, as explained earlier by my fellow panelist, the prohibition of conducting sponsor reviews which was brought up at the GLP training course in September 2005. After that, we come back to the following. GLP Handbook of Pharmaceuticals and Medical Devices, Vol.1 was published in October 2008, but basically the contents of all three editions are the same. That means that even after sponsor reviews were prohibited in 2005, the definition of raw data has remained the same as that in 1997. At the very end of the list, there is a question mark printed after March of this year where volume 2 of the publication is scheduled to be released. I have been told that its content would most likely be what sounds like a collection of Q&As. I am hoping that a new description on how sponsor reviews are to be handled will be provided in this new publication. (Slide 4–2)

Let us now look at the details in chronological order. As we had Dr. Mitsumori kindly share with us about the raw data of the pathological examination in 1997, the raw data of pathological examination is different from those of other examinations. As for the pathological data, they are the...
finalized data and was clearly stated that these are to be defined as raw data. There were two other messages he has shared with us which were: data are to be finalized as raw data first in the case of requesting an opinion of someone outside of the GLP; and, there are possibilities of the findings being altered drastically by the sponsor in extreme cases when opinions are requested to a third party before the said data are finalized. (Slide 4–3) In the GLP Handbook of Pharmaceuticals published the following year in 1997, however, five points were listed as the main messages in the manual. These points included that one may get closer to the truth after examining all slides microscopically and re-examining the findings. Another point mentioned was that conclusions are most appropriate to be drawn not from the initial findings but from the finalized findings. As such, procedures for modification in the raw data are necessary in making the changes in the finalized findings. Obviously, the procedures for modification are required to be followed appropriately. (Slide 4–4)

Although a topic of a slightly different tone, it comes down to predetermining who will hold responsibility for the finalized findings. I believe this is being commonly practiced now. On a different note, or rather a slightly different subject, there are opinions that it is preferable to record all the procedures up until the finalization of the findings. As “preferable” in Japanese legal terms can be interpreted as “pretty much do it,” thus realizing something that is written as “basically preferable” could be extremely difficult. Actually, however, I believe that keeping records of such procedures is hardly ever practiced at present.

For a while new pathological views were not shown, but the topic of sponsor review as discussed by Dr. Oishi just now was brought up in 2005. That is when conducting sponsor reviews after the pathological findings have been finalized became a huge topic of interest. It was also stated that records must be kept that a sponsor review was conducted and that its reason and contents be recorded in the final report if a pathological finding was to be revised as a result of conducting the sponsor review. In short, the instructions were to conduct a sponsor review on the finalized pathological findings, as well as to keep records of all changes in the sponsor review and to write them down in the report. Behind this or rather at the core of these instructions was the concern over a space for reasonable doubt that the sponsors may have changed the findings given that the record of changes made to the pathological findings are not kept prior to its finalization. It is called “sponsor power,” and it is understood that these instructions were given as the possibility of such power intervention cannot be denied. (Slide 4–5)

And as for the perspective of JSQA, we have indicated our view to PMDA last September. What I mean by that is, in light of the second volume of the instruction manual we are planning to publish this March which I mentioned earlier about, we have reviewed over 350 Q&As in total in the guidebooks published between 2003 and 2008, and have added necessary comments upon submitting it to PMDA. Sponsor review was one of the topics we covered.

The problems concerning sponsor reviews are as I described earlier, that no records are kept until the findings are finalized and the possibility of the sponsor power working cannot be denied. We also recognize that the problem also lies in the possibility that changes are unintentionally made as a result of such factor. There are,
The view of JSQA regarding the sponsor review and its nature is that there should be no problem in conducting them prior to finalizing the findings. However, the point is this. The findings become raw data only after they have been finalized, but we believe that it might be better to record all findings and changes made from before they are finalized. Through such practice, we believe we can alleviate some of the concerns we now face. We have submitted this view to PMDA so far and have expressed our wish for the prohibition on the sponsor review which has been in place for some years now to be lifted. However, we have not yet received an official or public response from PMDA on this point, so we do not know if our opinion will be accepted or denied. I would like to state that this is the view of JSQA. (Slide 4–6) That is all, thank you.

**Dr. Oishi:** Thank you very much. And now, I would like to ask Dr. Schorsch of the IFSTP to discuss about matters in this area next. Dr. Schorsch, please.

**Dr. Schorsch:** Thank you very much. I would like to thank Dr. Manabe for his kind invitation. It is a pleasure for me to be here in your fascinating country. We have a lot of experience to share. I would like to thank the Japanese Society of Toxicology Pathology, for having addressed this issue at the international level. As an IFSTP representative and officer, we were pleased that we were contacted to deal with this topic and we have organized a group with one representative for the United States, with Jenny Mackay, one representative for the Japanese with Dr. Manabe, and one representative for Europe with Dr. Catherine George. I would present some results of our understanding of what it is done at least in Europe and the United States. (Slide 5–1)

I think that there is a clear understanding of what we do, because we are all pathologists, and we do daily the same job.

First we have a consensus for the need of a pathologic peer review. The study pathologist is the unique scientist who has to create his own data in the toxicology study. He has to be helped. The goal of the peer review is to add the experience of one’s peer pathologist, to secure the data, and to add some expertise to this first analysis. Furthermore, the peer review process has to bring some standardization, harmonization if needed, and of course some training, but the main goal is to give security, accuracy to the conclusion of the study and expertise on the pathological data. We are well aware that there is potential influence on the data, but for us, since the peer review is done by one’s peer who is a true pathologist, bringing his own expertise, we do not question the need of such process. (Slide 5–2)

Secondly, there is a consensus on how the peer review must be conducted. There are a lot of papers explaining how it has to be done. Dr. Hardisty and other colleagues have published a long time ago a very detailed paper with best practices, explaining how a peer review has to be conducted. We can make the difference between different types of peer review: In some papers we speak about “formal,” “informal,” “sponsor,” but for us there is one type of review, the peer review done by a pathologist for adding accuracy to the produced data by the study pathologist. (Slide 5–3)

Then there has to be a consensus on interim notes for pathology data: the interim notes (that the study pathologist needs to build his interpretation) are not raw data. It is well recognized by US authorities, the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and it is clearly stated—and it is the same in Europe—that we need some interim notes to construct our study. We can change our data until finalization. The changes we do during the peer review are included into this process, because the peer review is to help, again, to give more accuracy to the data we generate. (Slide 5–4)

There is a clear consensus of the workflow for the generation of the pathology data, there are first some interim notes. The data are not finalized, the data are not locked at this stage. We do the peer review, whatever the type of peer review you want: informal, formal, sponsor peer review. During the discussion you can change your data, and afterwards you finalize the data. Then you can produce a report, a pathology report which has to be signed, or the whole toxicology report, both of them have to be signed by the study pathologist. If changes come after this signature,
then all changes have to be audited of course, as it has been described before. (Slide 5–5)

For us, there is again a clear consensus of what is a pathology peer review. It is not an audit. It is a discussion, a discussion between two pathologists, as we do daily when we show some slides to our colleagues. The second pathologist must normally be more experienced, and since a discussion is always positive, it must be considered as an external help. If there is some discussion or problem with interpretation, this face to face discussion will help to resolve the issue. If there are still some difficulties, you can ask for a third party, a third pathologist, or a pathology working group whatever you call it. You can lock the data before or after. But if they are locked, you must justify the changes. If not, it means that the discussion process is not finished and that you are still working on interim notes. (Slide 5–6)

So in conclusion, for us the peer review has to be conducted before finalization of the data, and since these changes or discussion are considered to be interim notes, they are not considered to be raw data; they can be documented and kept. They are not considered to be raw data, and they have not to be presented to the auditors. (Slide 5–7) For me, I think that there is a problem of definition. Thank you very much.

Dr. Oishi: Thank you very much. There is a difference in opinion at an international level between the Japanese agency and the Society of Toxicologic Pathology, but first of all, I must say that “sponsor review” is not a term used in other countries. Nonetheless, I would like to know how
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1. It is not an audit.
2. It must be considered as an external help for one individual. A face to face discussion will help to resolve differences.
3. If differences exist between the SP and PR, they should be resolvable. If not, a pathology working group (PWG) with expert consultants should be organized for resolution.

CONCLUSION on pathology raw data and PR

• PR conducted before the finalization of the study report is considered as "interim notes" which the SP uses for finalizing the data.
• These interim notes must not considered to be raw data when the PR is conducted before the finalization of pathology data.
• A consensus statement reporting that differences of opinion were resolved must be included in the raw data and in the final study report.

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much they are conducted. Could Dr. Klaus Weber from the CRO in Europe kindly share with us the situation in Europe? How much sponsor reviews are actually conducted?

Dr. Weber: We have quite a lot of peer reviews performed by sponsors. How we handle the situation is, within our pathology department I take care that every study of four weeks and longer will be peer reviewed internally. In Europe, we have a guideline that is asking us specifically for a peer review for carcinogenicity studies performed in pharmaceuticals. This guide is from the EMEA. EMEA expect that we do such a peer review in such a type of studies. But this is the only regulation we have. This regulation is dealing with a minimum of what you have to do. It is telling you at least 10% of the tumors, and at least 10% of the animals per group. But this is a recommendation. We are able to make more of these things. Again, a sponsor peer review in the CROs as in Japan is in Europe, a common situation.

Dr. Oishi: Thank you very much. How about in the United States, Dr. Hardisty?

Dr. Hardisty: I think the situation in the United States is very much like the situation is in Europe. The study pathologist has a very strong position in the generation of pathology data. In the United States I understand the study director in Japan is the one who writes the report, but in the United States, the study pathologist has to write the pathology report. The study pathologist is the only one that
can finalize the pathology data. When we do peer review in the United States, we always do it on draft data. We do it before the study pathologist finalizes the data, and we act as consultants with the study pathologist to come up with the most accurate data that we can for this study. In a formal peer review, we are trying to achieve two things. One is to increase the accuracy, but also to increase the confidence that a study sponsor or a regulatory agency has in the data. We also approach it in a manner where we are trying to make sure that all target tissues have been identified, that the data is using current nomenclature and diagnostic criteria, and that the correct no adverse effect level (NOAEL) has been identified. So a peer review, a formal peer review, is a very involved process where you are working with the study pathologist to finalize the data. The study pathologist though is the only person who can actually change the data. The peer review pathologist acts as a consultant to advise the study pathologist.

I have never had a situation where I could not work with a study pathologist to come up with a consensus in the diagnosis, and we have never had to go to a pathology working group to resolve these. It has worked very well. I think that the quality of the data when we are done with peer review is excellent. In the United States, the FDA does not have a guideline for requiring peer review. They do not require peer review. But they do like to see studies submitted to them that have been peer reviewed, because it gives them extra confidence in the data. I do not think that there is a concern by our regulatory agencies over sponsor influence on the peer review, because I think they understand that it is two scientists working together to come up with the best set of data for the regulatory agencies to make their decisions on.

**Dr. Oishi:** Thank you very much. Have there been any discussions made regarding “sponsor power” at IFSTP?

**Dr. Schorsch:** No, I think it is exactly what was explained by Dr. Hardisty. We do not make such a difference, because for us, the peer reviewer must be an experienced pathologist, and his goal is to increase the accuracy of the data, and give his expertise. There is no problem, it can be internal, it can be external, it can be a sponsor peer review. What is important is that the peer review is conducted by a skilled pathologist, and that he gives an input and help to the initial pathologist. That is the goal of the peer review. Whatever you call it, it is to increase and make the evaluation better, and each company responsible for the data understands that. As Dr. Hardisty said, although I am a little bit younger but I have never seen difficulties to resolve the differences if they are there between two experienced pathologists. We understand that we do a difficult job; we know that. We understand that we have to prepare a unique set of data, of course. We have to be clear, and responsible. There is never a problem to finalize the data after the peer review.

**Dr. Oishi:** As Dr. Schorsch is also at the manufacturing firm of Bayer, how much review do you actually conduct as a sponsor? What is the general stance of the corporations in Europe?

**Dr. Schorsch:** Yes, we have occasionally some sponsor review, and there is no problem; it may be a problem if the pathologist mandated by the sponsor has limited experience. But it is the responsibility of the company to select the good expert, because we have to produce the correct data. In agrochemical industry, since the data generated during the development will serve for the risk assessment without studies in humans, it is necessary to trust the data we generate. For us and for me, it is clear: we have to select internally or externally, whatever we want, an experienced pathologist to do this task; and in the raw data, what is important is to include the name of the study pathologist. As you may know, at the IFSSTP level, we are now discussing an international system of recognition for study pathologists, because in this peer review process, it is very important to bring expertise. If you do not bring expertise, the peer review is not necessary, and I completely understand the US situation where it is not regulatory or mandatory. But if you do the process, you have to bring some additional expertise to your review.

**Dr. Oishi:** Thank you very much. As from this discussion now, I believe that you here are all under the impression that the sponsors do not pose that much pressure on the pathologists and are not a realistic threat. As we all practice pathology, I think we all believe in each other that none of our fellow pathologists will sell out our consciences and hearts, yielding to such power. To the contrary, as proposed by JSQA, the general stance is to practice a more open procedure if there is no such pressure from the sponsors. As stated by Mr. Kuranami on the standpoint of QA in Japan just now, I believe one of the proposals made by JSQA is to
keep records more in an open manner in the effort to prove that there is no forced modification of data or pressure from the sponsors. Any thoughts on the point discussed just now?

Mr. Kuranami: Speaking from a scientific point of view, sponsor reviews and reviews in general are indeed very important. When considering the factors that are impeding the reviews, I believe “sponsor power” is a factor that cannot be ignored. If this problem can be resolved and effective reviews may be conducted, then I believe it is in our best interest to consider what we can do to resolve this setback. And I think one of the proposals drawn from such thought is to start by keeping records as I have just mentioned. I would like to see this happen more now that I have heard you exchange your views today.

Dr. Oishi: On that point, Dr. Hardisty, what would you say if there was a proposal to practice procedures in a more open manner since the discussions in Europe and the United States have nothing to hide?

Dr. Hardisty: It is a different approach than we have in the United States. It varies. If we finalized our data, as you do in Japan before the peer review, then that is the way we would have to do it. Occasionally we do have peer reviews of finalized reports in the United States. When we do that, we have to keep the records, and the study pathologist then, though, has to prepare an amended report, so there are two reports now. That is what we are trying to avoid. We are trying to make this a streamlined process. The raw data is defined as the signed final report by the study pathologist, trying to make this a streamlined process. The raw data is now. That is what we are trying to avoid. We are responsible, we understand the issue and we want to do it also in this way. So it has nothing to do, in my opinion, with the peer review. On the other hand, as Tamura-san said, when someone is telling the young pathologist, and they could be becoming intimidated, the young pathologist has obviously also a head of pathology, and if my pathologist would become intimidating for my client, I would take this into my hands and then we would rule this out.

Dr. Oishi: Dr. Schorsch, any thoughts on that point? Do you have any thoughts or points to discuss regarding this?

Dr. Schorsch: I think that I understand the issue, but as you have said, we are all pathologists; we have the same difficulties, and we all agree that there is a need for discussion to improve our data. This discussion between two pathologists, which takes place during the peer review, has to be done, and the problem of the influence is again not a problem if it is a good influence. There is an influence; a peer review of course is a discussion and the peer reviewer will influence the data. But that is the role of the peer review. But the role has been clearly explained by Dr. Hardisty, this role is to be sure that we have detected the correct no adverse effect level, that we have not missed a target tissue. Since this is a positive influence, and because all of our companies are responsible, we understand the issue and we want to do good science. It is why we have to do it. We are responsible. This peer review must be a positive input to the study. We have to select, even for sponsor peer reviews, the pathologist who can positively influence this review. Positively means to bring more accuracy and more security to a difficult process in the toxicology studies.

Dr. Oishi: While it is my personal opinion, if we assume that any person is capable of wrongdoing, no regulation may be able to prevent such wrongdoing. And yet, if we were to take that stance and maintain the assumption that pathologists of the manufacturers have a tendency of working to induce profits for the manufacturers, I believe that the GLP institution authentication to facilities in the manufacturers is extremely paradoxical. Since the pathologists at the manufacturers actually take full charge when conducting in-house studies, I think that the discussion of the pressure from the sponsors (manufacturers) being a hindrance of peer reviews would lead to the question on the presence of a stronger bias for in-house studies conducted at the manufacturers.

When I first heard about the instructions of PDMA, personally I was greatly devastated and angry with the thinking that there was someone who would sell out his/her heart among us pathologists. I was very much in shock at the time when the authority said that pathologists of the sponsors have a possibility to lead a CRO to a guided conclusion beneficial to the sponsor. I still remember feeling really miserable about that. As we conduct debates among us
pathologists like this one, what we end up with is the need for discussions among us pathologists. Communication among the pathologists was extremely valuable and also essential for us to improve our skills which I mentioned in the last session this past year and wish to reiterate again here. I truly believe this is the case.

I would like to have engaged in a more heated debate despite the little time we had today, but the time is up for us soon. Therefore, I would like to start wrapping up. Basically the Japanese Society of Toxicologic Pathology has already stated its full support to the STP position paper. There are quite a number of points which challenge the instructions given by the Japanese authority at this point. While we have stated that we agree with the position paper as the Japanese Society of Toxicologic Pathology, I am very much interested in how everyone will actually engage in the topics we discussed today after you go home, especially what kind of stance those of you from the corporations will take. GLP inspection is scheduled two weeks later at our laboratory, but I am hoping that things will turn out better in this area and that everyone will work hard and take full responsibility over the items they are evaluating so that the integrity of the pathologists will not be brought to question.

As for the digital data discussed in the first half of this session, I worry that the definition of “raw data” will be extremely ambiguous if the Society of Toxicologic Pathology of each country will not take seriously the line drawn that basically image data that do not serve as the base of a data are not raw data. I believe that various publications on this topic will be released from the department in charge of regulatory matters at the IFSTP. As Dr. Manabe is in charge of the matter, if you have any opinions or suggestions, we would greatly appreciate it if you would contact Dr. Manabe or the Secretariat of the Japanese Society of Toxicologic Pathology. Although it was a compiled discussion today due in spite of tight schedule, thank you very much for your participation. That is all, thank you very much.