occurring regardless of whether there is acceptance or rejection of a change or whether that change is large or small in terms of the degree of impact. Assessment is an evaluation of the degree of magnitude of changes of this type. It should be kept in mind that assessing existence or non-existence of risk is not the objective of Risk Assessment

For the details of Risk Management and Risk Assessment, refer to "Guidelines for Quality Risk Management", Ministerial Notification No.0901004 by Director, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MLHW, dated September 1, 2006,.

6．1 Risk Assessment

For Change Control, appropriate Risk Assessment should be implemented in consideration of technology documents related to design quality, understanding of processes and actual results of manufacturing quality, and the latest manufacturing science, during the early stage of drafting and policy approval etc. of individual changes. At that time, it is possible to use actual performance results and experience obtained in implementing past changes on the same or similar products.

In the Risk Assessment implemented prior to a change, the degree of potential impact of the change on quality should be evaluated.

For example, when implementing a change that is intended to improve the manufacturing process for, for example, process stabilization or to improve items related to quality control from the aspect of preventing deviation, consider doing a Risk Assessment at the poly-decision stage for deciding whether "a change that can be a preventive measure should be implemented immediately", or "it should be implemented after observation of the time course of corrective actions for a certain period", by taking the content of corrective actions into consideration. Then, at the stage of creating a concrete plan after the policy for implementing the change is decided, another Risk Assessment becomes necessary at an aspect different from the policy-panning stage. At the stage of consideration of this concrete plan, when multiple technical methods are presented, it is possible to decide by using selection methods such as FMEA (Failure Mode and Effect Analysis) etc. Before making a judgment, evaluations from the aspects of"whether a change is effective to reduce risk" and "whether it is possible to consider results of a change to lead to secondary problems" will also required.

Where knowledge etc. based on past data and similar products is not considered to be adequate for implementing Risk Assessment, the impacts on quality of the said change should be assessed in advance by test manufacturing, etc. It is possible to choose from newly-established experimental methods of appropriate scale, test evaluation in actual manufacturing equipment or others, depending on the contents of the change, taking product characteristics and development progress into consideration.

After creating a concrete plan and completing a change plan document, the next step is review of the change implementation plan, and it is required that the document for

the change plan contains information which will be used to decide the severity of the verification on the impacts on quality which will occur when the change is actually implemented, and whether or not validation is necessary, depending on the magnitude of risk related to the change. Therefore, the Risk Assessment result needs to contain methods for monitoring and for verification, etc. for risk occurrence during the change implementation in addition to the identification of risks and evaluation of impacts on quality.

In addition, when the impact of a change on quality is assessed as possibly extending to the following as a result of Risk Assessment, it is not possible to draw a conclusion based on a single evaluation done within a GMP organization, and evaluations/studies of a higher level, involving efficacy, safety, for the implementation of the change, from the aspects of product quality assurance, are required.

- When the impact of the change on product quality cannot be evaluated by established testing/analytical methods, standards, etc.
- When efficacy and safety evaluations, such as additional clinical studies, are needed because something different from already approved matters is revealed.
- When toxicity studies, etc. for the confirmation of the safety of new impurities, are needed in order to evaluate the impact of a change.
- When additional clinical studies etc., for the evaluation of impacts due to a significant change in the drug formulation, are needed.

As noted above, there are opportunities for implementing Risk Assessment differently at various stages of quality evaluation beginning from policy making, drafting of changes in plans, with all thought given to evaluation of the quality of the change. However, risk is so specific to respective products and manufacturing lines that individual risks need to be assessed multi-dimensionally through multiple views, considering the risk variation according to life-cycle when evaluating the impact on quality.

Since an evaluation needs to be done from multidimensional aspects, it should not be limited to the quality and manufacturing units but also to examining equipment/facility control, engineering, raw materials procurement, production planning, research and development, pharmaceutical affairs regulations, and delivery(marketing) etc., where appropriate depending on the content of the change. Persons responsible for these sections or functions should perform Risk Assessment from their own viewpoint and at their own responsibility, according to the contents of the change.

One probable example would be in Risk Assessment at the stage of deciding proposal/implementation policy, manufacturing, quality control, engineering, research and development and pharmaceutical affairs regulations; and at the stage of selecting a concrete change plan, responsible persons working in the sections related to the

assessment or who perform certain functions in the assessment are appointed to be involved in Risk Assessment, depending on the intricacy of technological evaluation or follow-up tracking procedures considered necessary in the practical process of change. It does not necessarily mean participation as an organization, but individuals or multiple people in charge who can manage necessary functions are allowed. The important point is to make Risk Assessment effective by recruiting the necessary personnel resources, assigning responsibilities, and establishing procedures.

6．2 Risk Assessment and Classification of Change

Classification of Change depending on the degree of risk is useful for Risk Management because differences occasionally occur, depending on the magnitude of extracted risks, in advance communication to a market approval holder, in verification items, which are established prior to implementation in the process where the change is implemented, and in procedures and methods for monitoring control of the process. The classification should be done in a manner that makes it possible to share an understanding of evaluation results: "it has an impact on quality" from the aspects of scientific technology. For example, it is possible to define it thus: "it has an impact on quality" means that a change in quality characteristics becomes apparent, while "it has no impact on quality" means that a change in quality characteristics is very small, or it does not contribute to the change in quality characteristics. Companies are considered to possess/accumulate data and information on factors in the process and equipment that affect quality characteristics and the degrees of occurrence of change in characteristics of quality such as a knowledge of design and manufacturing quality; and based upon such knowledge, it will become possible to estimate what changes are brought about by changes in processes or equipment. The quality change produced by a change is not zero. Thus, based on recognition that a change is equivocal, it is possible to consider that, in the GMP, the classification is an index for the particularity and rigidity of quality evaluation and the effectiveness confirmation done before versus after change.

From these aspects, the classification could be a tool for estimation of requisite resources at the time of an acceptance/rejection judgment of a change or implementing the change in consideration of the magnitude of impacts on quality based on the results of assessment. Furthermore, for marketing approval holders, it is useful for judging the impact on the market and the necessity of legal procedures for the descriptions in their approval letters, and is also useful as a tool facilitating negotiations with manufacturers. Meanwhile, care must be taken because there is a potential for a risk to be overlooked by a single-meaning, mechanical classification of risks.

Ranks once decided in the process of implementing a change by classification may change over the time until accomplishment of the change, making a reminder necessary

that class will vary at the time of re-assessment done at implementation stages where appropriate, or at the time of review of the results obtained at change implementation.

The following are classification examples:

（１）"Change where impacts on quality become apparent" means a change that is likely to have a significant impact on product quality and to become apparent in its impact, i.e. there is a risk of exerting an impact on design quality of the said product, and therefore, special attention should be given to safety and efficacy.

For example, the change in basic principles and methods of manufacturing procedures and quality control procedures corresponds to this case. Furthermore, changes in settings of parameters such as properties of raw materials, performance qualifications of equipment, and operational conditions etc., if they are assumed not to have been evaluated adequately in the past, in as far as past knowledge has been used, also correspond to this case.

In these evaluations, it is assumed that a change in quality characteristics may become apparent, making it necessary to evaluate/study sufficiently in advance, and also to implement evaluation and validation based on the rationale of suitability of specifications, etc. during the implementation process of the change. In addition, if there is a combination of multiple changes of conditions in equipment/processes, special attention should be paid to the validity of advanced prediction. Furthermore, if there is a selection from multiple technical elements, additional application of a Risk Assessment may become necessary as a means of implementation.

This change is considered to possibly conflict directly with or to potentially interfere with approved matters. Therefore, it may be required to request confirmation by marketing approval holders in advance and, additionally, to take requisite legal procedures for the "application for partial change in manufacturing approval", etc.

（２）"Change which impacts quality may potentially become apparent" means a change of which the impact on product quality cannot be denied. One example corresponding to this would be a change in which a change in the properties of product quality occurs, but stability within the scope of actual measurement results obtained in the past is expected when applying the data used for establishment of settings in parameters, such as properties of raw materials, performance qualification of equipment, and operational conditions etc, is considered. On the other hand, if it is a change for which the degree of changes is not clear or the impact is not predictable, a Risk Assessment must be done with special care during the evaluation of the change plan. It needs to be kept in mind that during the time course of implementation of a change, additional Risk Assessment may become necessary, and as a result, the class may shift to either "Change where impacts on quality become apparent" or "Change where there is no impact on quality".

（３）"Change where there is no impact on quality" means a change from which impacts on product quality is considered to be minimal. One example corresponding to this

would be a change in which, in association with the change, a change in properties of product quality is assumed to be slight or no change occurs, in consideration of the data used for establishment of settings for parameters such as properties of raw materials, performance qualifications of equipment, and operational conditions etc. Normally, this change can be implemented within daily control based on the GMP, with the prerequisite condition that the plant has appropriate procedures. Some renewal etc. of the operational equipment and instruments, written operational procedures, changes of written procedures for common unit operations in manufacturing, which are specified in the GMP, may fall under this category. If it is a facility etc. where facilities and equipment are shared with and used for the manufacture of multiple types of products, it is necessary to evaluate the impact of the change on each individual product manufactured. If it is a change that requires a re-validation of equipment especially , the classification will also change because of increased risk.

In this manner, the classification based on Risk Assessment is useful as a communication tool for sharing recognition, within a GMP organization and interrelationships with marketing approval holders, about the necessity of additional assessments and the rigidity of evaluation related to risk occurrence during change implementation. It is desirable to judge the acceptance of the risk of a change utilizing the results of assessment appropriately according to the magnitude of risk, and only after fixing the control content used during the implementation process, to implement the change.

６．３ Consequence Analysis of Impact of Change on Quality(Verification)

As to the results of implementation of a change, it is necessary to verify that there is no serious influence on targeted use or the method of use of products, and it must be confirmed that quality is unaffected in terms of product release. For this objective, evaluation must be done to verify that the quality of the product after the change is within the scope of quality that is suited for the targeted use, and that the objective of the change was accomplished as planned. At this evaluation, the impact on quality before versus after the change should be evaluated following a protocol specified in the analysis and testing methods and validation plan, etc. Additionally, it is important to confirm the validity of Risk Assessments done in advance. In the above Consequence Analysis, it is required to at least verify the following specification compliance, and according to the content of the change and characteristics of the products, additional tests should be considered. It is necessary to evaluate the quality before versus after the change, with recognition that the possibility of an impact on quality not detectable by the current specifications and testing methods cannot be denied.

（１）Confirmation of Specification Compliance

At evaluation of the impact on quality by the change related to said product, it is necessary to confirm that the qualities of intermediates of drug substances, drug substances, intermediate products and/or drug formulations, which are affected by the change, meet the predetermined specifications.

Herein, specification means not only approved specifications but also includes self-specifications and standards such as in-process tests, etc, and it should be tested and analyzed with approved specifications and testing methods and with standardized process analysis methods. Furthermore, occasionally, modification of specifications and testing methods may become necessary at the time that a change is implemented.

Product quality after the change is evaluated from the aspects of specification compliance, and a variation before versus after the change, in specification items that are targets of trend analysis. Those in main characteristic values, that are in-process controlled, are also comparatively evaluated.

In evaluating the effectiveness of a change, product tests should be conducted not just for a single batch or a single lot, and trend analysis in quality, which is one of the effective tools in GMP control, should also applied.

（２）Additional Tests

At evaluation of the impact of a change on design quality, it is necessary to consider implementing evaluations of properties related to design quality of the product such as safety, efficacy and stability etc. which include chemical, physical, microbiological, biological properties, bioavailability, stability profiles etc. As evaluation at the time of change, it is necessary to not limit testing to that of products after the change, but to also to study whether or not it is necessary to implement additional tests including tests for intermediates, intermediate products, raw materials, reagents, materials for manufacturing, containers/plugging systems, etc. In addition, it is necessary to confirm that results of in-process tests show a similar trend before versus after the change.

Requisite additional tests vary depending on the content of the change in manufacturing, drug substances, characteristics of drug products, and the influence of the said product on quality. For example:

- At evaluation of changes in the impurity profile or degradation product profiles, profiling is done first using appropriate chromatographic techniques and then new impurities and degradation products are evaluated based on the observed changes in impurity profiles. In order to evaluate higher levels of impurities in products than before the change, toxicity studies may be implemented based on: "Guidelines for Impurities in New Drug Substances" , Ministerial Notification No.877 of September 25, 1995 by ELD, PAB, MLHW (Q3A); "Guidelines for Impurities in New Drug Substances (Revised)", Ministerial Notification No.1216001 of December 16, 2002 by ELD, PFSB, MLHW(Q3AR); "Guidelines for Impurities in New Drug Products （Revised） ",

Ministerial Notification No.1204001 of December 4, 2006 by ELD, PFSB, MLHW(Q3AR2); "Guidelines for Impurities in New Drug Products", Ministerial Notification No.539 of June 23, 1997 by ELD, PAB, MLHW (Q3B); "Guidelines for Impurities in New Drug Products (Revised)",Ministerial Notification No.0624001 of June 24, 2003 by ELD, PAB, MLHW (Q3BR) ; "Guidelines for Impurities in New Drug Products (Revised)", Ministerial Notification No.0703004 of July 3, 2006 by ELD, PFSB, MLHW (Q3BR2).

- At evaluation of the impact on bioequivalence of the change in dissolution profile of solid dosage forms, it is necessary, for example, to perform dissolution tests that use several solutions of different pH, using several sampling time points other than the points specified in the specifications and testing methods. Furthermore, if necessary, *in vivo* bioequivalence tests should also be considered.

It is important to cautiously judge whether or not there a significant change in the repeatability of specification compliance and in design quality, using a multi-faceted evaluation, if necessary, for main characteristics of the product. In order to confirm quality consistency, it is necessary to consider making a plan for selecting additional test items to be confirmed by periodic review, deciding the requisite number of consecutive lots to be evaluated starting immediately after the initiation of change implementation, or making a plan to skip tests, according to the magnitude of the risk of a change.

7. Procedures for Change Control in GMP

For a Change Control in GMP, it is required to confirm, by implementing the assessment of the impact of change on product quality, that quality is maintained as an important property throughout, before versus after the change. In addition, for this object, it is required that a control system in which approval by the quality unit is an essential element, and procedures for the control be established.

The following are procedures for Change Control of GMP, and points to be given attention. These items are also shown in chapter 12 "Change Control" of "GMP Guidelines for Drugs/Quasi-drugs (Products)".

12.10 Changes attributable to stipulations in laws, etc, in addition to changes attributable to complaints and recalls etc should be subjected to Change Control.

12.11 As changes involving "the documents related to change control procedures prepared pursuant to stipulation in Article 8, Paragraph 4 of GMP Ordinance for Drugs/Quasi-drugs" (hereinafter referred to as "Change Control Procedures"), changes related to the system for management/control of quality, raw materials

and materials (including changes in suppliers), specifications, manufacturing methods, analysis and testing methods, and building and facilities (including relevant software) should be included.

12.12 Change should be drafted and reviewed by the appropriate unit or units, and approved by the quality unit.

12.13 Change Control Procedures should include the following:

1) Evaluation of the necessity of re-validation, the necessity of additional test analysis and testing required for the validity of a change, and the necessity of application for partial change in manufacturing approval, as one of the evaluations in Article 14, item 1 of GMP Ordinance for Drugs/Quasi-drugs,
2) To establish evaluation methods for product quality after the change (including accelerated stability tests and stability monitoring measurement programs etc) and acceptance criteria, prior to the change.
3) To establish procedures for the revision of documents related to a change and for the training of personnel, prior to the change, to definitively implement the revisions of the document and the training.
4) To decide whether or not it is necessary to revise specifications and testing methods, shelf-life/expiration-date, and labeling, prior to the change, as one of the other necessary measures in Article 14, item 2 of GMP Ordinance for Drugs/Quasi-drugs,

12.14 To initially evaluate several lots of the product manufactured and to analyze them in the changed state after the implementation of a change.

Procedures of Change Control should be defined and documented under the GMP organization and system of manufacturers. Procedures should be defined according to each organization, and the primary items in procedures of Change Control are that 1) the validity of each change should be approved by the quality unit and 2) documented.

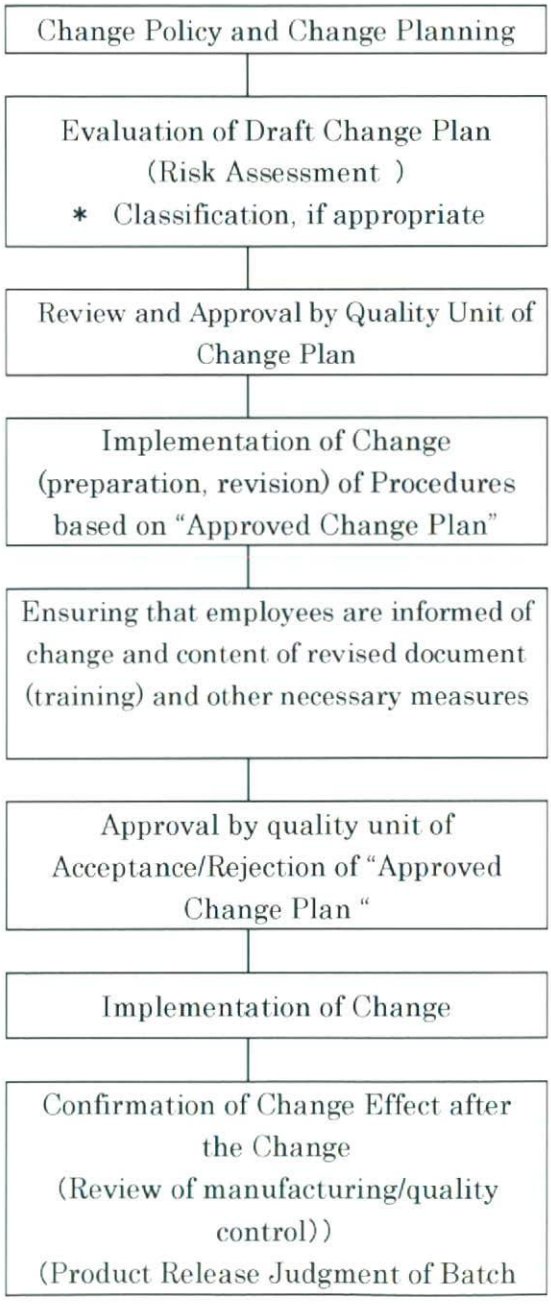
The quality unit should be given the authority to approve Change Control, and Change Control manager and persons in charge of Change Control should be assigned in advance.

An appropriate unit in the organization prepares a draft of a change, and the draft is evaluated for its necessity, validity, impacts on product quality, etc. The change after this evaluation is prepared for implementation only after approval by the quality unit. Revision/alteration of procedures, etc. should be done appropriately, followed by training of personnel and other necessary measures should be taken, and then, operation after the change should be implemented. A series of these measures should be

documented, and preserved. An example of basic procedures is shown below.

Meanwhile, it is allowed, in consideration of inclusion of multi-faceted viewpoints as a form of Risk Management, to operate Change Control in a organization such as a "Change Control administrative office" or a "Change Control committee" consisting of a manager and several of staff members in charge.

Example of Change Control Procedures in GMP



after Change)
(Planning and Follow-up of Periodic Review)

8. General Requirements in Control of Documents related to Change

At implementation of a change, it is essential that the documents pertaining to said change are revised in accordance with predetermined procedures for change, and approved by the authorized person, because documented items usually become a target of the change.

All contents of a change should be documented and controlled. As to a document for Risk Assessment, it is useful to show the validity of a change, thus making it is desirable to preserve it in files related to procedures for Change Control.

It is desirable to establish procedures in which all results of Change Control implemented based on the GMP are listed together with results of handling applications for partial change in manufacturing approval etc., and printed in annual reports. This is an effective method of showing how appropriately Change Control procedures are carried out.

9. Collaboration of Manufacturers and Marketing Approval Holders

The one who implements a change is the manufacturer, but an appropriate collaboration between manufacturers and marketing approval holders is indispensable for maintaining the consistent quality of drug products. This chapter deals with the collaboration between manufacturers and marketing approval holders which becomes necessary at the time of a change.

9. 1 Handling of Change Control

As a result of revision of the Pharmaceutical Affairs Law of 2005, Change Control is now a requirement of the GMP. In "Ministerial Ordinance on Standards for Quality Control for Drugs, Quasi-Drugs, Cosmetics and Medical Devices" (GQP Ordinance), the marketing approval holder is required to supervise manufacturers and Change Control of manufacturing is defined as one of the items to be supervised (in Article 7, item 5, and Article 10, Paragraph 3; and therefore the marketing approval holder and the manufacturers should address Change Control jointly and appropriately).

9. 2 Change Communication

It is likely that technology information (research and development information, etc.)

disclosed by the marketing approval holder to the manufacture is limited Therefore, it is very dangerous for the manufacturer to make a judgment alone about acceptance or rejection of a change .It is a principle that the manufacturer notifies the marketing approval holder about any change, if it has a possible impact on quality, regardless of the size of that probability. However, the targets subjected to Change Control, which are handled by the manufacturer, are vast, ranging from "something directly related" to manufacturing/marketing products to "something absolutely not related", such that it may be not rational that the marketing approval holder decides acceptance or rejection for every item after judging impacts on product quality for every change in manufacturing plants. For this reason, the marketing approval holder needs to explain sufficiently to the manufacturer the idea of what changes notification should be given for. Providing the manufacturer with tools such as the classification of Change Control communication and communication methods, together with examples thereof, is useful for Change Control communication.

9．3 Collaboration about Information

Generally speaking, the situation is that the marketing approval holder has the technological information on research and development of a drug product, but does not sufficiently grasp the technological information obtained in actual manufacturing fields. The manufacturer, on the other hand, can obtain only limited information on research and development, but can accumulate the technical information obtained in actual manufacturing fields. In consideration of these circumstances, the marketing approval holder should provide information on research and development thereby supporting the manufacturer in the planning of a change such that the manufacturer can implement the evaluation appropriately without omitting the impact of the change on product quality, according to necessity. Furthermore, the manufacturer should provide various forms of appropriate technical information and experience related to the actual production, as the one well informed about manufacturing sites (actual production).

In order to appropriately carry out "6.2 Risk Assessment and Classification of Change" and "6.3 Consequence Analysis of Impact of Change on Quality (Verification)", both the marketing approval holder and the manufacturer should clearly realize that appropriate mutual disclosure of information to each other and collaboration between the two parties are indispensable.

9．4 Collaboration with Other Manufacturers

In cases where multiple manufacturers are involved in the manufacture of a drug product, there is a possibility that a change in a process by one manufacturer will exert an influence on a processes etc. of the manufacturer of the next step (hereinafter referred to as "the next step manufacturer"). Therefore, the marketing approval holder should provide information on the content and timing etc. of a change not only to the

manufacturer who executes the change but also to the next step manufacturers in advance. Naturally, if a change is one which requires quality evaluation or equipment investment, collaboration with the next step manufacturers should be initiated appropriately from the planning stage.

全般
1.　We appreciate the MHLW's efforts to simultaneously distribute an English translation for review during the public comment period.　This approach inviting the wider global comments is very welcome. 意見募集にレビュー用英訳文を同時に添付いただきまして、貴省のご対応について感謝いたします。このように広く海外から意見を求めようと取り組んでいただき、大変喜ばしく存じます。
全般
2.　It is very important that the overall objectives for this draft guideline, including how it will be utilized, be clearly described in the introduction to the document. Historically, the outcome of MHLW Grant Study Group sometimes became the foundation of the following formal PMDA or MHLW main office's guidelines (legal enforcement as Notification) and became simple guidance for industry/regulator (no legal enforcement) in other cases.　The clear positioning of this guideline will help to further understand the Study Group's intention. 本ガイドライン案につきましては、その取扱いを含んだ全般的な方針を序文に明確に記載することが非常に重要であると考えます。 過去において、貴省科学研究班における研究報告は、しばしばPMDAまたは貴省が後に発行する正式なガイドライン(通知など法的強制力のあるもの)の基礎となったり、あるいは業界/監督機関に対する簡易指導(法的強制力のないもの)となったケースもございました。本ガイドラインの趣旨を明確に位置付けることにより、貴研究班の意図に対する理解は一層深まることになると考えます。
全般
3. This is complex draft guideline to read and comprehend well.　The guidance, however, encourages continuous improvement and stable product supply by introducing two new sub-category of quality as "design quality" and "manufacturing quality (please see below specific comments on this new definition)", and encourages post approval changes that will improve the latter without adversely affecting the former which is a logical base that matches the spirit of quality by design. 本ガイドライン案は、読み十分に理解するには少々複雑ですが、品質について新たな２つの分類区分、「設計品質」と「製造品質」を設けることで、継続的改善および製品の安定供給を奨励するものであると考えます(この新たな定義についての詳細コメントは下記をご参照願います)。また、本案は、「設計品質」の精神にかなった論理上の基盤を損なうことなく「製造品質」を改善する承認後変更を奨励するものと考

えます。
全般
4.　The quality risk management has been greatly emphasized in this guideline that encourages risk assessment be used to determine the impact of post approval changes and leaves assessment of impact to manufacturers or license holders by allowing flexibility based on product knowledge and understanding 本ガイドライン案は、品質リスクマネジメントを非常に強調しており、承認後変更がもたらす影響を評価するリスクアセスメントを行うことを奨励し、また、製造業者あるいは製造販売業者に、製品に対する知識および理解に基づいた評価を行わせるという柔軟な対応を考慮したものと考えます。
全般
5.　It seems to be trying to supplement Q9 Quality Risk Management to clarify change management requirements but does not do this in a sufficiently clear way to be readily and consistently implemented. It should either strive for further clarity or specificity or carefully reconsider the depth of the detail it provides to prevent misinterpretation. When the change is out with the need to communicate to the Agency e.g. as a PAC, then these aspects of change management would better be left for the company to define and enact within its quality system. 品質リスクマネジメント(Q9)における変更管理の要件を明らかにし、Q9 を補おうとするものと見受けられますが、速やか、かつ一貫して施行するにあたっては十分に明確な方法ではないと考えられます。誤った解釈を招かないよう、さらなる明瞭性、あるいは具体性に努めるか、またはその詳細の度合いについて慎重に再考する必要があると考えます。 当局への通知を要する変更が発生した場合(承認後変更など)、このような変更の管理については企業に一任し、企業内の品質システムにおいて定義および確立したほうがよいと思われます。
全般
6.　It was no mention of the responsibilities of the quality responsible person in this draft guideline 本ガイドライン案では、品質管理責任者の責務について言及がないように見受けられます。
全般
6. It is commendable that the guidance recognizes upfront different levels of control during development to the post marketing ガイドラインが開発から承認後まで異なった管理レベルを認めているのはすばらし

い
全般
7. The guidance does not address how QbD/design space/control strategy and change control are linked ガイダンスはどのように QbD/設計スペース/管理戦略、変更管理がリンクしているのか明確にしていない
全般
変更管理の記載は特定の品目に関する設備・手順を対象としているように読める。品目不特定の基準書・手順書等が当変更管理ガイドラインの対象となるか否か、より明確に分かるように記載して欲しい。

全般
設計品質および製造品質の定義は JIS Z8101-1981 品質管理用語に収載されていたが、1999 年に廃止となり、現在の JIS 規格からは削除されている。引用を適切にするようにお願いいたします。

全般
当該ガイドラインは、日本国内に適応するガドラインであり、海外サイトには適応しないと考えて宜しいでしょうか。

全般
当該ガイドラインは、GMP に関わる事項のみ対象としているが、日本への薬事制度へも関与させる必要があると考えます。

全般
当該ガイドラインは、バイオ医薬品へも適応すると考えて宜しいでしょうか。

3.2 Changes and Change Control in this guideline, page 2 -last paragraph 3.2 本ガイドラインにおける変更と変更管理 (P. 2)－最終段落
This paragraph mentions that the guideline doesn't address PAC and Minor Change Notifications and say that these are controlled by the PAL "depending upon the existence or non-existence of the description on Drug Approval Lette or Drug Approval Documents". However, the revised J-PAL manufacturing method descriptions defines two change categories (Major vs. Minor) and use of different bracket types (target set/values and “”) for process/process parameters. This simple matrix has already contained the change control system in itself (at least the strategy of change control system). It seems that this draft guideline significantly addresses the matters related J-PAL Application Form change control and it is contradict against the above statement. Additionally, it also contradict to the following statement; Section 6.2, Risk Assessment and Classification of Change, (1) “Changes where impacts on quality become apparent,” last paragraph, states, “it may be required to request confirmation by marketing approval holders in advance and, additionally, to take requisite legal procedures for the “application for partial change in manufacturing approval”, etc.”. As stated in the general comments #2, it is necessary to provide the clear positioning as well as intention of draft guideline vs. J-PAL AF related change control; system. この段落の記述によれば、「一部変更承認申請および軽微変更届については、このガイドラインでは言及しない」としています。また、これら変更届は「承認書あるいは承認申請資料における記載の有無に関連して派生する薬事法に係る」ものである、とされています。しかしながら、改正薬事法における製造方法の記載においては、工程/工程パラメータについて、変更を二つに分類し(Major と Minor)、異なる種類の括弧(目標値/設定値および“”)を使い分けると定義しています。この単純マトリクスにおいて、既に変更管理のシステム(少なくとも、変更管理システムの戦略)を内包していることから、本ガイドライン案は、日本薬事法の申請書の変更管理に係る事項を有意に取り扱うと見受けられ、これは前記の内容と矛盾します。なお、これは 6.2 リスクアセスメントと変更のクラス分類 (1) 「品質への影響が顕在化する変更」の最終段落の記述にある「事前に製造販売業者に確認を求めるほか、承認事項の一変申請等の法的な手続きが必要となることも想定される」にも相反するものと考えます。 概要 2 で述べたように、日本薬事法の申請書関連の変更管理システムに対比して、本ガイドライン案の意図を明らかにするとともに、明確に位置づける必要があると考えます。

回答：

3.3 Change Control during Development Stages, page 3 - First paragraph 3.3 開発段階における変更管理(P. 3)－第一段落:
It is not clear what the guideline intends regarding change management in the development stage. The guideline says it is not intended to be directly applied to change control in the development phase (this is supported) but also changes in this phase should be "controlled appropriately". It would be better to omit this remark re: the development stage as it is unclear what "appropriate control" would be based on the rest of the guideline. 開発段階における変更管理について、ガイドラインの意図が不明確です。ガイドラインでは、「開発段階での変更管理に直接適用することを意図していないが、この段階における変更についても"適切に管理する"ことが必要となる」としています。"適切な管理"とは何を指すのかに対し、ガイドラインのその後の記述においても明確にされていませんので、開発段階についてのこの記述は削除したほうがよいと考えます。

回答：

5. Product Quality and Change, page 6 Flow Chart 5. 製品品質と変更 (P.6) の図
Some terms used in this document are new or different compared to those in the ICH guidelines or the U.S. regulations. Examples include "Design Quality" and "Manufacturing Quality" in the flowchart and in the text immediately thereafter 本文書で使用されている用語の中には、ICH のガイドライン、または米国の規定では使用されていないものがあります。例としては、5. 製品品質と変更の項の図、およびその直後の文章に見られる"設計品質 (Design Quality)"、"製造品質 (Manufacturing Quality)"などがあります。

6. Risk Management, page 7 second last line 6. リスクマネジメント (P.7) 最後から２行目
Risk is stated to be "a deviation from the established or expected results". This definition should be considered against other definitions of risk (e.g. in ICH Q9) and considered for replacement herein with "the potential for a deviation from the required quality". リスクについて、「設定あるいは想定した結果からの乖離」であると述べられていますが、これはリスクに関する他の定義(ICH Q9 などでの)に反すると考えられます。「要求する品質から乖離する可能性」に置換するべきであると思われます。

6.2 Risk assessment and Classification of Change, page 10 6.2 リスクアセスメントと変更のクラス分類 (P.10)
This section seems overly prescriptive. Is such detail needed to support Q9 guidance on risk assessment? Also, the difference between classes "change where impact on quality become apparent" and "change which impacts quality may potentially become apparent" are not clear as before the assessment of the change it could be that potential impact is being assessed ion both cases. So this section of the guideline may be overly complex or lacking in clarity to allow for consistent interpretation. Perhaps some further clarity could be given, e.g. by reflecting changes and change management needs against critical / non-critical aspects of the process. Furthermore the regulatory action at the end of managing a change classed as "may impact potentially" is not clear from the guideline (The chapter "may impact potentially" states the PCA). 6.2 については、過度に詳細な記述であるように思われます。Q9 のガイドラインの補足として、これだけの詳細さが必要でしょうか? また、クラス分類においては、「品質への影響が顕在化する変更」と「品質への影響が顕在化する可能性のある変更」の違いがよくわかりません。つまり、どちらのクラスにおいても、変更を評価する以前に、予測される影響は評価されているだろうからです。ゆえに、本案 6.2 の記述は非常に複雑に受け取られる可能性があり、あるいは不明確さにより一貫性のある解釈を損なう場合があります。例えば、重要工程/非重要工程に対する変更および変更管理の必要性などを引証して説明すると、おそらくもう少し明確になると思われます。さらに、ガイドラインでは「品質への影響が顕在化する可能性のある変更」の法的な取り扱い方について明確にされていないと思います(「品質への影響が顕在化する変更」の項の最後では一変申請について触れています)。

Page 11, example 2
Liked the use of examples of definitions although example 2 could be clearer - quite difficult to understand. More clarity is required when giving examples クラス分類の２は若干わかりづらいがクリアーですが、定義の例をリンクすればよい。

6.2 Risk assessment and Classification of Change, page 12 end first paragraph 6.2 リスクアセスメントと変更のクラス分類 (P.12) 最初の段落の最後
Guideline suggests change may have to be assessed across all products made in a facility. This is overly simplistic in its wording (In English at least) - and should be clarified to ensure that only products affected by the change need be assessed. ガイドラインでは、当該施設で製造している全品目について変更の評価をする必要もあり得ると示唆していますが、過度に単純化した表現と捕らえられます(少なくとも英語表現では)。変更の影響が及ぶ品目のみを評価の対象とするべきであることを確実に表現するように分かりやすく記述すべきだと考えます。

6.3 Consequence Analysis of Impact of Change on Quality (Verification), page 12 last paragraph 6.3 変更の品質への影響評価(検証) (P.12) 最終段落
It would be useful to add words to state that the need to evaluate methods to ensure detectability should be considered on a risk assessed basis and may not be required for certain classes of change. 「各リスクの評価に際して、試験法の検出能を評価するかどうかについて、必要性を考慮するべきであり、変更のクラスによっては試験法の評価を必要としない場合がある」という文章を追加すると有用であると思われます。

6.3 Consequence Analysis of Impact of Change on Quality (Verification) (1) Confirmation of Specification Compliance, page 13 first paragraph 6.3 変更の品質への影響評価(検証) (1)規格の確認 (P.13) 第一段落
The guideline seems to suggest that equivalence need be shown at all stages affected by the change. This is not necessary - one would not have to show equivalence at every one of these. For example it should not be necessary to show equivalence at intermediates if equivalence is shown at the API. And if equivalence is shown at the API it should not be necessary to show equivalence at the product. And if equivalence is shown at a key API intermediate it should not be necessary to show equivalence at either API or at the product. This lack of clarity here on this key point weakens the guideline and in the view of this reader leaves it lacking in significant value. ガイドラインでは、変更によって影響を受ける全ての製品段階において、同等性を示す必要性を示唆しているようですが、これは不要と考えられます。つまり、製品の段階ごとに同等性を示す必要はありません。例えば、原薬について同等性が証明されていれば、原薬の中間体について証明する必要はなく、製剤について同等性が証明されていれば、原薬について同等性を証明する必要はありません。また、原薬の要の中間体について同等性が証明されていれば、原薬、又は製剤の一方について同等性を証明する必要はありません。このような主要点において、明確さを欠いているためにガイドラインは脆弱化し、それにより、読み手はガイドラインに重要性を見出せなくなってしまうと考えます。

6.3 Consequence Analysis of Impact of Change on Quality (Verification), 4th paragraph 6.3 変更の品質への影響評価(検証) 第四段落
The guideline states that change evaluation should not be conducted for a single batch - this is a disappointingly position as dependent upon the significance of a change and its likely impact the number and scale of batches that would need to be assessed could be different and one may well suffice for some changes. Again this lack of specifics will mean that this

guidance will not be easily capable of consistent application by industry or by inspectors.
ガイドラインでは、変更の評価を単一のバッチに対して行うべきではないとしていますが、これは残念な見解です。変更の重要度、および予想される影響によって、評価の対象となるバッチ数/規模は異なり、数点の変更に対しては１バッチ/ロットで十分であろうと思われるからです。繰り返しになりますが、明確性が欠如しているということは、業界、あるいは査察官にとって、本ガイドラインを整合的に適用することが容易でなくなるいということを意味しています。

9.2 Change communication, page 18 first paragraph
9.2 変更連絡 (P. 18) 第一段落

The guideline states that the manufacturer notifies the marketing approval holder about any change if it has a possible impact on quality regardless of the size of that probability. If the change is inside a working space / design space known not to have any impact on quality then presumably no such notification would be required. This should be clarified.
ガイドラインでは、「製造業者は、品質に影響を及ぼす可能性のある変更に関しては、可能性の大きさに拘わらずすべての変更について当該品目の製造販売業者に連絡する」としています。品質に影響を及ぼさないことが明白な作業領域/設計領域の枠を超えない変更の場合、上記のような連絡は必要ないと考えますが、この点を明確にしておくべきだと思います。

May be translation related:
翻訳によると思われるもの
5. Product Quality and Change-Page 5 (line 7 from bottom to line 4 from bottom)
5. 製品品質と変更 (P.5) 下から７行目～下から４行目

Guideline states "Furthermore, these guidelines also emphasize necessity of reviewing the initially-approved specifications and test methods and judgment criteria at an appropriate time after starting actual production ... when appropriate experience and more data are obtained". This seems to suggest that all specification requirements might require review and perhaps change post-approval. However an initial acceptance criterion could have been established on the basis of safety or the assurance of a critical quality requirement without much reference to or reliance on batch data.
ガイドラインでは、「また、その原薬や製剤が実生産されるようになって、より多くの経験やデータが得られた時点で、当初に承認された試験方法と判定基準について....見直す必要性を強調する」と記載されておりますが、これは、全ての規格要件は見直し、また、おそらくは承認後の変更を行うことが必要になるということを示唆するものと見受けられます。しかしながら、最初に設定された受入基準は、ロットのデータをほとんど考慮せず、また、それらに依存することなく、安全性、あるいは重要品質要件の保証の基に設定され