# 分担研究報告書　C

## 参考文献

## 生物医薬品に関する試験法及び各条規格の改正と国際調和に関する研究

***Resolution***

How to solve this? The first possibility would be to liaise with the Q7 group and work on certain definitions for 'critical' terms, such as starting/raw materials, critical steps and intermediates.

Another possibility is through the Maintenance Group, by gaining experience with the first applications submitted using the CTD 'format'. It could be easier to identify those points for which the CTD-Q has to be clarified.

The third possibility would be to revise some of the existing ICH guidelines but in this case we have first to identify which guidelines and set priorities.

The last possibility would be to develop a new guideline but I would propose that we first develop a guideline on the manufacturing process. It is indeed in this Section, where there is no ICH guideline reference, that we have experienced the difficulties in preparing the CTD and we have been obliged to provide more detail compared to other Sections.

**Conclusion**

In conclusion I would like to stress that, with the CTD-Q, TOC, and Quality Overall Summary we have reached a first 'step' in the process of developing a common application dossier.

However, this is only a format and does not include content. One knows that an application is evaluated on its *content*, not on its format, which is why I consider that there is now a need to go ahead and develop a common content – a full Common Technical Document.

## BIOTECH PROCESS EVALUATION

Dr Takao Hayakawa

In this presentation, I would like to describe some aspects of process evaluation regarding biotechnology products.

**What is 'Process Evaluation' and how does it Differ from so-called 'Process Validation'?**

When discussing this topic, a key question is what is 'process evaluation' and how does it differ from so-called 'process validation'? We can find both terms 'process evaluation' and 'process validation' in the CTD-Q document as well as in existing ICH guidelines. Therefore, of course, there should be some clear differences in these two terms and each term should represent their own respective meaning and unique concept.

According to the American Heritage Dictionary of English Language, it is evident that the linguistic meanings of the two words are apparently distinguishable.as shown in Table 1. The verb 'evaluate' means, for example, to examine and judge carefully. A typical synonym is 'estimate'. Of the verbs which mean to form a judgment of worth or significance, 'evaluate' implies considered judgment in ascertaining value.

The verb 'validate' means, for example, to establish the soundness of something. A typical synonym is 'confirm'. Of the verbs which mean to affirm the truth, accuracy or genuineness of something, 'validate' usually implies formal action taken to give legal force to something but can also refer to establishing the validity of something, such as a theory, claim or judgment.

*Table 1: Linguistic Meanings of 'Evaluation' and 'Validation' (from The American Heritage Dictionary of English*

| **evaluate (verb), evaluation (noun)** |
|---|
| 1. To ascertain or fix the value or worth of. |
| 2. To examine and judge carefully; appraise. See synonyms at estimate. |
| 3. Mathematics. To calculate the numerical value of; express numerically. |
| **validate (verb), validation (noun )** |
| 1. To declare or make legally valid. |
| 2. To mark with an indication of official sanction. |
| 3. To establish the soundness of; corroborate. See synonyms at confirm. |

However, since 'process evaluation' and 'process validation' are not clearly defined as a glossary in any ICH guidelines, certain different interpretations for these terms may exist among the users of the ICH guidelines.

According to FDA guidance[1], 'Process validation is establishing documented evidence which provided a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics'.

## Two Categories of 'Process Evaluation Study'

There may be two categories of 'Process Evaluation Study' as shown in Table 2.

*Table 2: Two Categories of 'Process Evaluation Study'*

| | |
|---|---|
| Process Evaluation Study | to identify critical operating/performance parameters and criteria and to lead to the Commercial Scale Validation Study. |
| Biotech Process Evaluation Study (Clearance Study) | in which it is impractical to perform validation studies at a commercial scale or due to GMP constraints. |

The first one may represent the wording that is used in a general sense and implies an important component of 'Process Validation'. This 'Process Evaluation Study' is performed with appropriate laboratory models in order to identify critical operating/performance parameters and criteria as a part of process development and evaluation.

*Figure 1. Process evaluation study to identify critical operating/performance parameters and criteria and to lead to the commercial scale validation study*

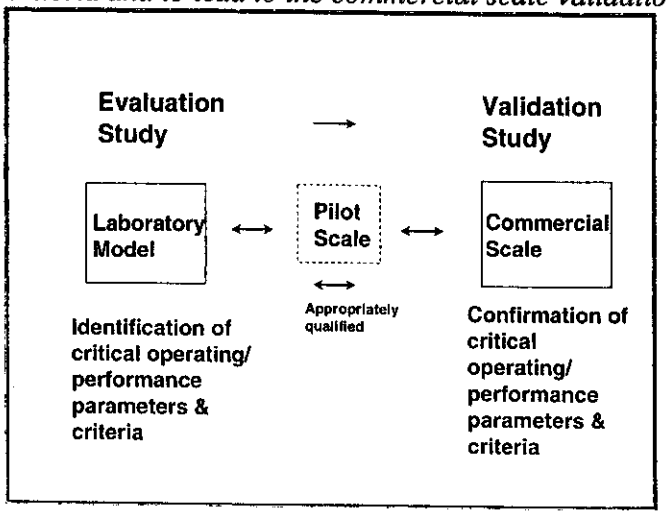


*Table 4. An Extract of the ICH Q6B (Specifications) Guideline*

'Clearance studies, which could include spiking experiments at the laboratory scale, to demonstrate the removal of cell substrate-derived impurities such as nucleic acid and host cell proteins may sometimes be used to eliminate the need for establishing acceptance criteria for these impurities.

For intentionally introduced, endogenous and adventitious viruses, the ability of the manufacturing process to remove and/or inactivate viruses should be demonstrated as described in the ICH Viral Safety Guideline.'

*Reference:ICH Q6B: Specifications for New Drug Substances and Products: Biotechnological Substances*

Table 4 shows an extract of the ICH Q6B, Specifications Guideline[2]. Here, one can see some key words that represent the concept of 'Biotech Process Evaluation'. They are

- 'spiking experiments at the laboratory scale';
- 'clearance studies to demonstrate the removal of cell substrate-derived impurities such as nucleic acid and host cell proteins';
- 'to eliminate the need for establishing acceptance criteria for these impurities; and
- 'intentionally introduced viruses'.

For process evaluation of virus clearance, more detailed information is described in the ICH Viral Safety guideline (Q5A)[3].

***Objective and Experimental Approach***

The objective and experimental approach of 'Biotech Process Evaluation Study' are typically indicated in the ICH Viral Safety guideline. The objective of viral clearance studies is to assess relevant process step(s) that can be considered to be effective in inactivating/removing viruses and to estimate quantitatively the overall level of virus reduction obtained by the process. This should be achieved by the deliberate addition ('spiking') of a virus to the crude material and/or to different fractions obtained during the various process steps and demonstrating its removal or inactivation during subsequent steps.

***Justification of Study***

Manufacturers should explain and justify the approach used in studies in evaluating virus clearance.

***Facility and Scale***

It is inappropriate to introduce any virus into a production facility because of GMP constraints. Therefore, viral clearance studies should be conducted in a separate laboratory equipped for virological work and performed by staff with virological expertise in conjunction with production personnel involved in designing and preparing a scaled-down version of the purification process.

***Validity of a Scaled-down Production System***

The validity of the scaling down should be demonstrated. The level of the scaled-down version should represent as closely as possible the production procedure.

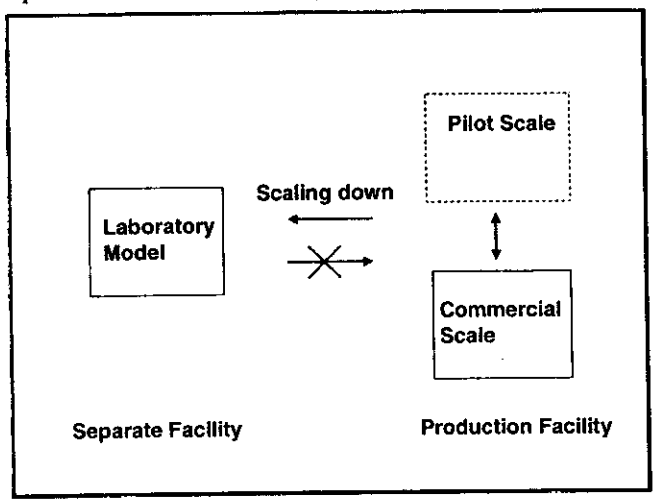
***Biotech Process Evaluation Study***

The second one is 'Biotech Process Evaluation Study' in which it is impractical to perform validation studies at a commercial scale or due to GMP constraints. This is very specific for biotechnology products. Hereafter, I will refer to this type of 'Process Evaluation' as 'Biotech Process Evaluation'. It should be noted that in the ICH guidelines sometimes the concept of this type of 'Process Evaluation Study' is represented as a 'Clearance Study'.

As shown in Fig. 2, 'Biotech Process Evaluation Study' is performed for the laboratory model as a scientific approximation of the proposed production process. In contrast to a general process evaluation study, this never leads to the 'Commercial Scale Validation Study.'

I would like to focus my talk on this topic.

*Figure 2. Biotech process evaluation study*




**Outline of Biotech Process Evaluation Study (Clearance Study)**

Table 3 highlights key points of 'Biotech Process Evaluation'. They are described in the ICH guidelines on the 'Specifications for biopharmaceuticals'[2] and 'Viral Safety'[3].

*Table 3: Key Points Concerning Biotech Process Evaluation*

- Objective: to assess process effectiveness
- Experimental approach: spiking experiment
- Facility: separate laboratory
- Scale: scaled-down model
- Validity and justification
- Judgement, interpretation and limitation
- Re-evaluation
- Impact
- Timing: product development stage
- One part of a total control strategy

### *Judgment, Interpretation and Limitation*

A combination of factors must be considered when judging the data supporting the effectiveness of virus inactivation/removal procedures. A number of factors in the design and execution of clearance studies may lead to an incorrect estimate of the ability of the process to remove virus infectivity or certain impurities.

### *Re-evaluation*

Whenever significant changes in the production or purification process are made, the effect of that change, both direct and indirect, on clearance should be considered and the system re-evaluated as needed.

### *Impact*

Relevant 'Biotech Process Evaluation Studies' impact on control strategy and assurance of consistent product quality and safety. For certain impurities, testing of either the drug substance or the drug product may not be necessary and may not need to be included in the specifications if efficient control or removal to acceptable levels is demonstrated by suitable studies.

Viral clearance studies are useful for contributing to the assurance that an acceptable level of safety in the final product is achieved, but do not by themselves establish safety.

### Summary

As far as we have learned, 'Biotech Process Evaluation Studies' are one of the indispensable approaches, which are mostly performed during biopharmaceuticals development, for demonstrating the ability of the proposed manufacturing process to clear viruses, cell substrate-derived impurities such as nucleic acid and host cell proteins.

'Biotech Process Evaluation Studies' should be performed for a validated scaled-down model manufacturing process and usually, in a laboratory that is separated from the real drug production facility. When designing and performing a study, as well as judging data, a number of factors that may affect the quality of the study and data should be taken into account.

Relevant 'Biotech Process Evaluation Studies' are one part of a total control strategy designed to ensure product quality, safety and consistency. The results impact on the control strategy and assurance of consistent product quality and safety.

*References*

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2. *Specifications for New Drug Substance and Products: Biotechnological Substances, ICH Q6B.*
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以降のページは雑誌/図書等に掲載された論文となりますので「参考文献」をご参照ください。下記「参考文献」後「分担研究報告書　参考文献F」が続きます。

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# 分担研究報告書　G

## 参考文献

## 溶出試験法の日米間の相違及びシステム適合性に関する研究

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# 分担研究報告書　H

## 参考文献

## 科学の進歩と国際調和に対応した医薬品の名称，化学名，構造式の改正に関する研究

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*Japanese Pharmacopoeia Fourteenth Edition (JP14) Database*

[Japanese | English]

データベース更新日：2001/08/17 [更新履歴]

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ア イ ウ エ オ　カ キ ク ケ コ　サ シ ス セ ソ　タ チ ツ テ ト　ナ ニ ヌ ネ ノ
ハ ヒ フ ヘ ホ　マ ミ ム メ モ　ヤ イ ユ エ ヨ　ラ リ ル レ ロ　ワ

[ 日本名または日本名別名検索 ] [ 消去 ]

| A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z |

[ 英名検索 ] [ 消去 ]

**第一部収載品リスト**

ア イ ウ エ オ　カ キ ク ケ コ　サ シ ス セ ソ　タ チ ツ テ ト　ナ ニ ヌ ネ ノ
ハ ヒ フ ヘ ホ　マ ミ ム メ モ　ヤ イ ユ エ ヨ　ラ リ ル レ ロ　ワ

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ハ ヒ フ ヘ ホ　マ ミ ム メ モ　ヤ イ ユ エ ヨ　ラ リ ル レ ロ　ワ

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