

Composition of the application material on quality for the MAA of regenerative medical products

Atsushi Nishikawa

Office of Cellular and Tissue-based Products

PMDA, Japan

The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

- Introduction
 - Study council on issues related to regenerative medical products (再生医療等製品の諸課題に関する検討会議)
- Composition of the application material on quality for the MAA
 - Related notices
 - Cellular and tissue-based products
 - *In vivo* gene therapy products
 - *Ex vivo* gene therapy products
- Pre-consultations prior to the MAA (審査予定事前面談)
 - Schedule for reviewing
 - GCTP inspections
 - GLP/GCP inspections
 - Application materials and others

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Study council on issues related to regenerative medical products

(再生医療等製品の諸課題に関する検討会議)

- Discuss solutions to issues in the development of regenerative medical products.

E.g.

- Composition of the application material
- Pre-consultations prior to the MAA
- Examples of minor changes

Industry

- JPMA
- FIRM
- MT JAPAN

Government

- MHLW
- PMDA

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“Points to be considered for marketing approval application of regenerative medical products”
(再生医療等製品の製造販売承認申請に際し留意すべき事項について)

PFSB/MDRMPE Notification No. 0812-5
August 12, 2014

- It describes what contents should be included in the application material.
- There is no fixed format, as long as the contents listed in this notice are included.

✓ The following slides show the structure of the CMC application materials in CTD format, but this is just an example.

Section

S.1 General Information

S.2 Manufacture

S.3 Characterisation

S.4 Control of Drug Substance

S.5 Reference Standards or Materials

S.6 Container Closure System

S.7 Stability

P.1 Description and Composition of the Drug Product

P.2 Pharmaceutical Development

P.3 Manufacture

P.4 Control of Excipients

P.5 Control of Drug Product

P.6 Reference Standards or Materials

P.7 Container Closure System

P.8 Stability

A.1 Facilities and Equipment

A.2 Adventitious Agents Safety Evaluation

A.3 Excipients

R Regional Information

- ✓ ICH M4Q provide guidelines for the preparation of CMC documentation.
- ✓ This format can be used for regenerative medical products.
- ✓ On the other hand, there are some points that differ from those for pharmaceutical products, and this section focuses on these points.

■ What to write in which section?

- For cellular/tissue-based products, there may be no distinction between the drug substance and the drug product in the manufacturing process.
- There is some overlap between S and P.
 - In that case, it is acceptable
 - ✓ to state "See 2.3.P.5" in 2.3.S.4, for example.
 - ✓ to omit the overlapping sections.

Examples of sections that can be omitted and that are referenced by each section

Sections which can be omitted	Sections referenced from each section
S.4 Control of Drug Substance	P.5 Control of Drug Product
S.5 Reference Standards or Materials	-
S.6 Container Closure System	P.7 Container Closure System
S.7 Stability	P.8 Stability
P.2.2.3 Physicochemical and Biological Properties	S.1.2 Structure/S.1.3 General Properties S.3.1 Elucidation of Structure and other Characteristics
P.2.3 Manufacturing Process Development	S.2.6 Manufacturing Process Development
P.3.1 Manufacturer(s)	S.2.1 Manufacturer(s)
P.3.3 Description of Manufacturing Process and Process Controls	S.2.2 Description of Manufacturing Process and Process Controls
P.3.4 Controls of Critical Steps and Intermediates	S.2.4 Controls of Critical Steps and Intermediates
P.3.5 Process Validation and/or Evaluation	S.2.5 Process Validation and/or Evaluation
P.5.5 Characterisation of Impurities	S.3.2 Impurities
P.6 Reference Standards or Materials	-

✓ These are just examples, and a certain section can be divided into S and P.

S.2.2 Description of Manufacturing Process and Process Controls

- Where does the manufacturing process originate?

- ① Products that do not create cell banks
(autologous/allogeneic somatic cells, etc)
- ② Products that create cell banks and are expected to renew cell banks
(somatic stem cells, etc)
 - The manufacturing process starts from the acceptance of source cells.

✓ For difficult-to-judge cases, it is recommended to consult PMDA on a case-by-case manner.

S.2.2 Description of Manufacturing Process and Process Controls

- Where does the manufacturing process originate?
 - ③ Products that create cell banks and do not renew cell banks on a semi-permanent basis (cell lines, etc)
 - The manufacturing process starts from the thawing of the cell bank.
 - The history of the construction of the cell bank (procedures, raw materials, etc) should be described in S.2.3.

✓ For difficult-to-judge cases, it is recommended to consult PMDA on a case-by-case manner.

S.2.3 Control of Materials

- What should be included as source cell information?
 - Medical interviews and test items at donor screening
 - Collection procedure of source cells, composition of preservation solution and container
 - Shipping information
 - Shipping procedure to the manufacturing facility
 - Conditions (temperature and duration)
 - Summary and results of shipping validation
 - Acceptance criteria of source cells (or S.2.2, S.2.4)
 - Test items and acceptance criteria of the cell bank (for products that create cell banks)
 - The history of the construction of the cell bank (for products that do not renew cell banks on a semi-permanent basis).

S.2.5 Process Validation and/or Evaluation

- For cellular/tissue-based products, there may be cases in which it's necessary to implement continued process verification at post-marketing.
 - A description of the verification plan should be included in S.2.5.
 - ✓ Verification items
 - ✓ The rationale for their selection
 - Verification master plan should be created, but that plan will be checked in GCTP inspection and is not necessarily required in the review.

Critical intermediates controlled by setting specifications like drug substances

- There are cases in which samples in the middle of the process are frozen and stored for a long period of time as critical intermediates.
- A description of the control of the critical intermediate can be included in S.2.4 or S.4, S.6 and S.7.
 - ✓ Control of the critical intermediate in S.2.4 or S.4
 - ✓ Container Closure System in S.2.4 or S.6
 - ✓ Stability of the critical intermediate in S.2.4 or S.7

A.2 Adventitious Agents Safety Evaluation

- A number of biological raw materials derived from animals/humans are usually used.
- Information assessing the risk of infectious agents should be provided.
 - About the source cells and other biological materials
 - Explanation of response to each requirement of the “the Standard for Biological Ingredients” (MHLW Ministerial Announcement No. 210 of 2003)
 - About the source cells
 - Questionnaire and test items at donor screening
 - Testings for infectious agents (viruses, endotoxin, sterility, mycoplasma) at appropriate stages of production (source cells, cell banks, harvest, etc)

A.3 Excipients

- All excipients should be listed in A.3.
- Safety evaluation of all excipients should be performed based on the following procedure.
 - ① Taking account of the content of excipients in the product at the proposed clinical dose
 - ② Evaluating the safety of each excipient based on the following points
 - results of the toxicity studies
 - clinical use experience
 - literature information
 - physiologically active concentration

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A.1 Facilities and Equipment

A.2 Adventitious Agents Safety Evaluation

A.3 Excipients

R Regional Information

- ✓ Quality control of *in vivo* gene therapy products (viral vectors, etc) are similar to biological products (monoclonal antibodies, etc).
- ✓ CTD format can be used without modifying the structure.
- ✓ A.2 and A.3 should be prepared in the same manner as for cellular/tissue-based products.

S.2.3 Control of Materials

- Starting materials are cell substrates and plasmids.
 - ① Information about the cell substrate (HEK293 cells, etc)
 - History of the construction of the cell bank (procedures, raw materials, etc)
 - Test items and acceptance criteria
 - ② Information about the plasmids
 - History of the construction of the plasmids (structures, procedures, etc)
 - Procedures for manufacturing plasmids
 - Test items and acceptance criteria of the plasmids and plasmid cell banks
 - ✓ No need to prepare independent module S

Products that component cells are transduced with recombinant viral vector

- Viral vector is a critical intermediate controlled by setting specifications like drug substances.
 - Quality control of the viral vector should be detailed in an independent module S.
- Quality control of the component cells (and the product) should be detailed in the same manner as for cellular/tissue-based products described before.

Module	2.3(3.2).S.VIRAL VECTOR
	2.3(3.2).S.COMPONENT CELLS
	2.3(3.2).P.PRODUCT
	2.3(3.2).A

Storage solution for tissue shipping and Diluent for product administration

- Quality control of these can be detailed in an independent module P.
- In case there is a distinction between the drug substance and the drug product, the material can be divided into S and P.

Dosing devices

- Devices that also serve as containers (syringe, auto injector, etc) can be detailed in P.7.
- Special devices, such as those used as medical devices, can be detailed in Module R.

Materials also relevant for non-clinical safety assessment

- These information can be included in 2.6.6 or 2.3.
- Safety evaluation of process-related impurities (S.2)
- Safety evaluation of excipients (A.3)
- Gene insertion site analysis of viral vector for *Ex vivo* gene therapy products (S.3)

Operation in medical institutions

- Operations at the time of administration such as thawing, washing, etc. can be described in P.2.6.
- The compatibility of the drug product with dosage devices can be described in P.2.6.
- A summary and results of in-use stability testing can be described in P.2.6 or P.8.

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Pre-consultations prior to the MAA

(審査予定事前面談)

- As for regenerative medical products, Pre-consultations prior to the MAA are not essential.
- When implemented, it is within the framework of the normal pre-consultations process.
- Following information are provided.
 - Schedule for reviewing
 - GCTP compliance inspections
 - GLP/GCP inspections
 - Application materials and others

Typical event timing from an application to approval

Events	Priority review products	Standard review products
Initial meeting (初回面談)	1.5-2 months	2.5-3 months
Inquiries on important issues (重要事項照会)	2-2.5 months	3-3.5 months
Expert discussion (専門協議)	6-6.5 months	8-10 months
Reviews by the Committee on Regenerative Medicine Products and Biotechnology(部会)	8 months	10-11 months
Marketing approval(承認)	9 months	12 months

Note: "Inquiries on important issues" means inquiries made by PMDA after the initial meeting.

✓ This timeline is applicable when there are no particular concerns in the course of review.

“Explanation of the Schedule for GMP Compliance Inspection in the review for approval of New Drugs”
(新医薬品の承認審査時におけるGMP適合性調査のスケジュールに関する説明)

Notification, April 5, 2019
Office of Manufacturing Quality for Drugs
Pharmaceuticals and Medical Devices Agency

- Following information are provided.
 - Timing of GMP compliance inspection application
 - Determination of type of inspection (on-site or desk-top)
 - Procedure of GMP compliance inspection
 - Timing of process validation

✓ We would appreciate it if you would cooperate in the smooth implementation of the inspection.

“Comments from the Office of Non-clinical and Clinical Compliance in the Pre-consultations prior to the MAA”
(審査予定事前面談における信頼性保証部からの伝達事項について)

Notification, November 15, 2022
Office of Non-clinical and Clinical Compliance
Pharmaceuticals and Medical Devices Agency

- Following information are provided.
 - Timing of GLP/GCP inspections
 - How trials and sites to be inspected are determined
 - Determination of type of inspection (on-site or remote)

✓ We would appreciate it if you would cooperate in the smooth implementation of the inspection.

Submission of review materials

- Following materials are necessary to be submitted at the time of application for approval.
 - The application material in electronic media (paper materials are not required)
 - List of committee members involved in the preparation of application materials(申請資料作成関与委員リスト)
 - List of competing items and competing companies (競合品目・競合企業リスト)
 - List of committee members involved in competing items (競合品目に係る関与委員リスト)
- Materials required for the expert discussion will be communicated after the application is submitted.
- Materials for healthcare professionals and patients are necessary to be submitted with the response to inquiries on important issues.

Composition of the application material on quality for the MAA

- There is no fixed format, as long as the contents listed in the notice are included.

Pre-consultations prior to the MAA (審査予定事前面談)

- As for regenerative medical products, Pre-consultations prior to the MAA are not essential.
- When implemented, following information are provided.
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Thank you for your attention!



<http://www.pmda.go.jp/> (Japanese)

<http://www.pmda.go.jp/english/index.html> (English)