Global Drug Development
Technical R&D / Regulatory CMC

Points to consider and challenges in CMC for regenerative medical products

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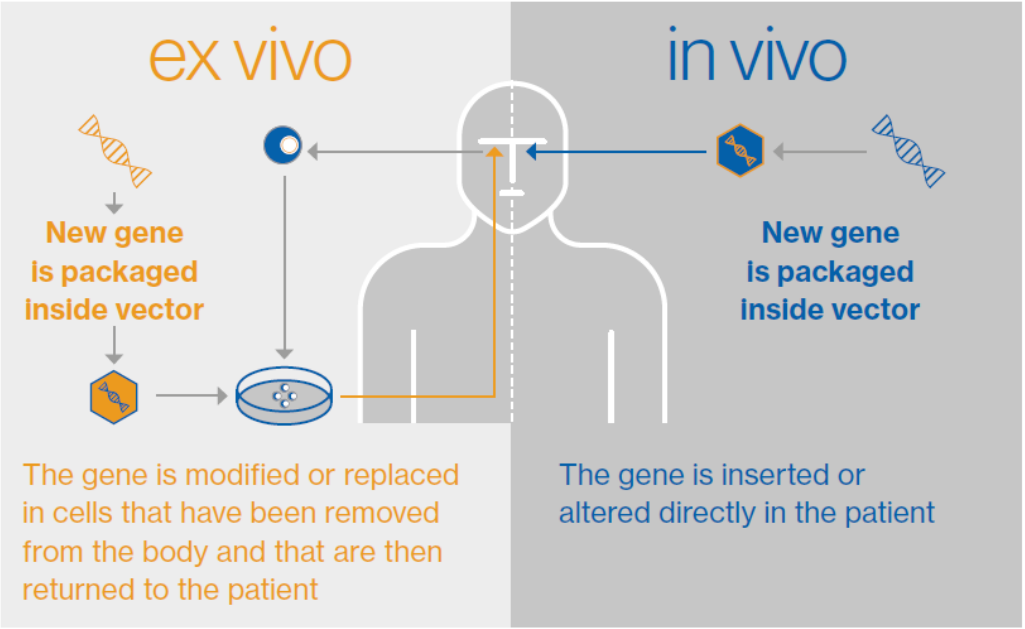
Agenda

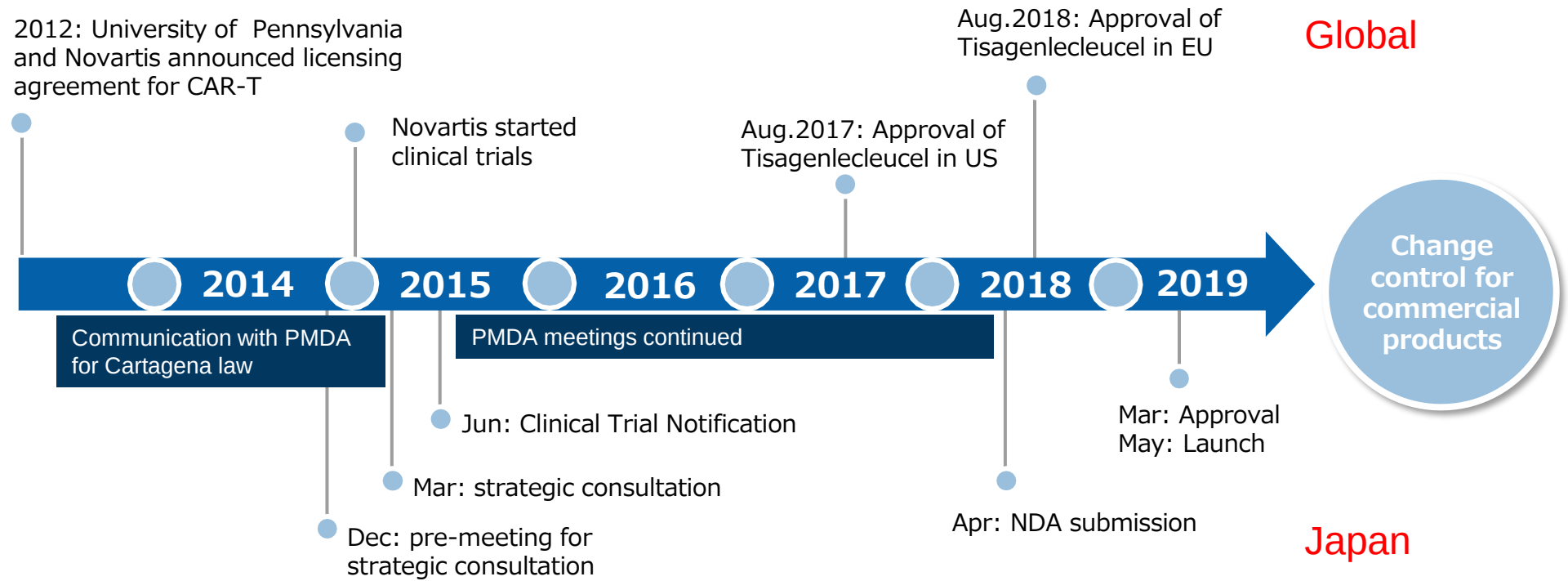
1. Regenerative medical products in Novartis
   - Tisagenlecleucel
   - Onasemnogene abeparvovec
2. Points to consider and challenges
   - Regulation for Living Modified Organisms (LMO)
   - In-country Testing
   - Change control of commercial products

Approaches for gene therapy

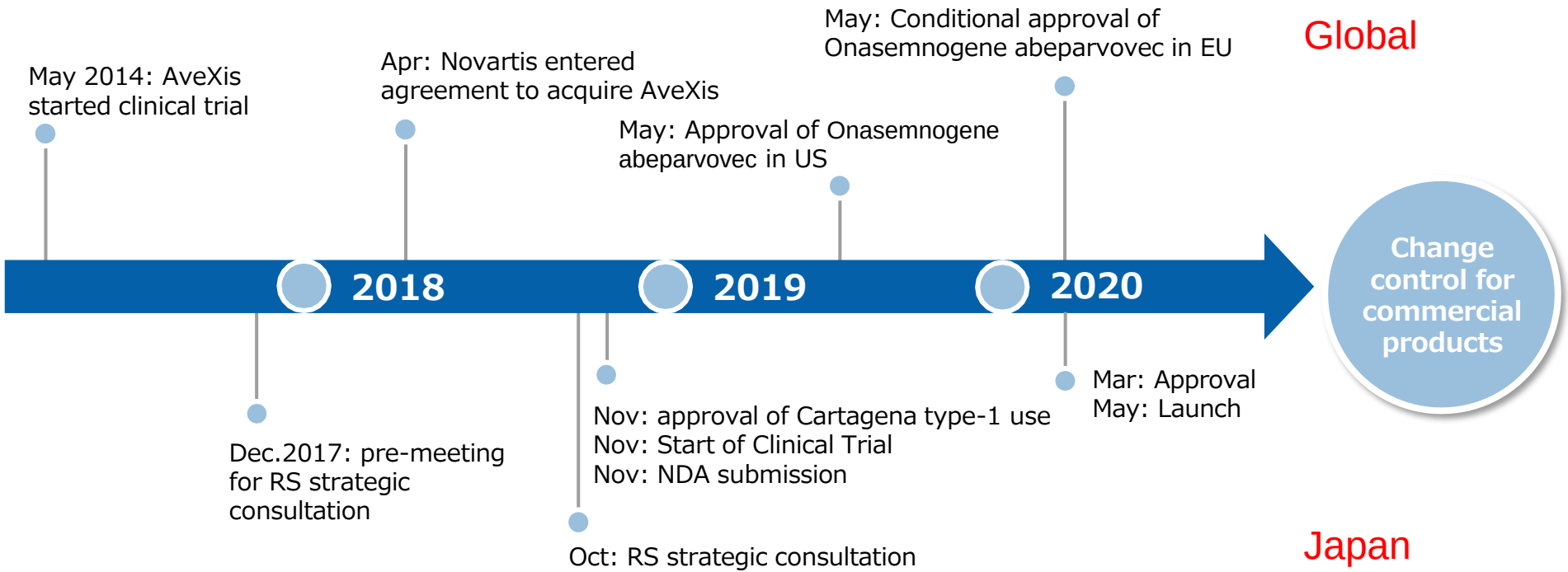


5. High KA. The Jeremiah Metzger Lecture: Gene Therapy for Inherited Disorders: From Christmas Disease to Leber's Amaurosis. Transactions of the American Clinical and Climatological Association. 2009; 120: 331-359.

Development history of Tisagenlecleucel



Development history of Onasemnogene abeparvovec



Regulation for LMO (Cartagena Act)

Regulation for LMO (Cartagena Act)

Cartagena Type-1 use (Usage in non containment area)

- Applicability is judged by presence of infectious vector in final product
  - in vivo gene therapy: Cartagena type-1 use
  - ex-vivo gene therapy: need to be confirmed with PMDA if final product contains infectious vector (Concept of residual non-replicating recombinant viruses used in the production of gene modified cell; December 10, 2020)
- Stipulate handling in clinical site, etc.

Cartagena Type-2 use (Usage in containment area)

- Applied to domestic manufacturing site, testing site etc.

Points to consider

Applicability of Cartagena Type-1 use for ex-vivo gene therapy

- Applicability can be confirmed at Cartagena Act related matter consultation

Lead time to start Cartagena Type-1/2 use

- Approval of Type-1 use is needed before starting clinical trial
- PMDA review for Type-2 use is necessary before clinical manufacturing

Information in environmental risk assessment

- e.g. Presence of Open Reading Frame, Homology search

Points to consider

Challenge in acquisition of vector information from third party

- Referring to Drug Master File (DMF) or Regulatory Support File (RSF) in Cartagena type-1/2 review is not allowed

Confidentiality of vector information

- Environmental risk assessment for Type-1 use will be publicly disclosed on the Web, but masking of confidential information is negotiable with MHLW

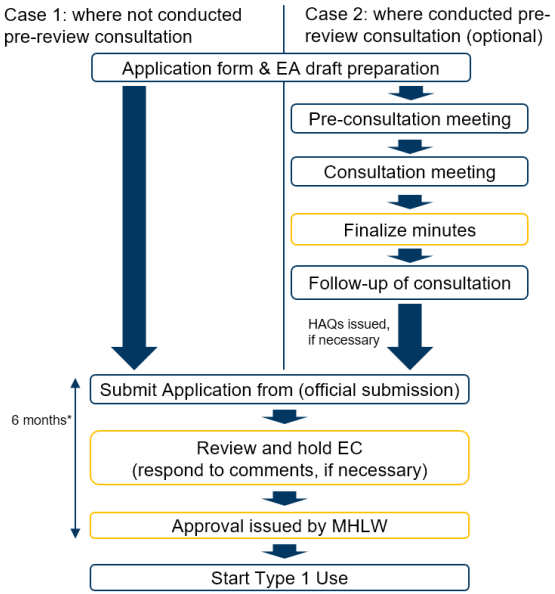
Points to consider

Steps in Applicant or PMDA is shown as following:

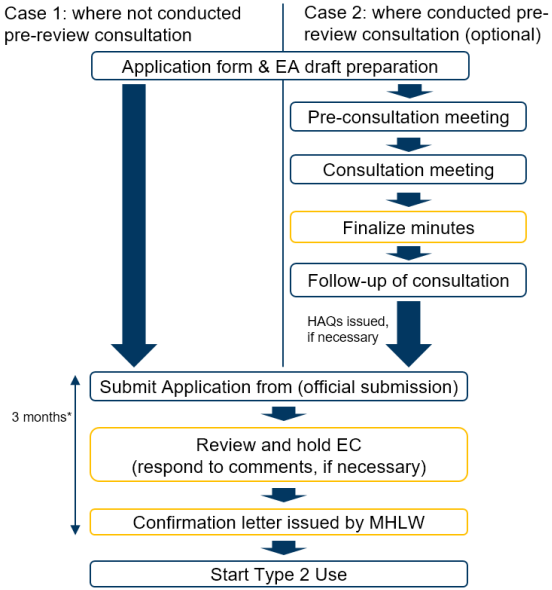
Applicant

PMDA

Application process for Type-1 use



Application process for Type-2 use



*time for process in PMDA not including time for the applicant to deal with HAQ
EA; environmental assessment, EC; expert committee, HAQs; health authority questions, NMT; not more than

第一種使用等に係る承認申請の手続きについて | 独立行政法人 医薬品医療機器総合機構 (pmda.go.jp)

第二種使用等に係る確認申請の手続きについて | 独立行政法人 医薬品医療機器総合機構 (pmda.go.jp)

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In-country testing

In-country Testing

Current status of requirement for local release testing

- In-country test is required for regenerative medical products manufactured outside Japan in accordance with GCTP* Ordinance
- Waiver of in-country testing based on MRA/MOU is not applicable for regenerative medical products
- Test items for in-country testing to be conducted are judged on case-by-case basis considering availability of samples etc.

*: Good Gene, Cellular, and Tissue-based Products Manufacturing Practice

Challenges in in-country testing

ex-vivo gene therapy

- Since most of ex-vivo gene therapies are derived from autologous cells, only limited sample is available for release test
- In-country testing may delay patient access to products although many of patients in target population of product need early treatment

in-vivo gene therapy

- Since target of gene therapy is specific gene and patient number is limited in general, manufacturing scale is much smaller than biologics such as antibodies. In-country testing may consume significant part of a batch and impact on costs considerably

Common

- Some of biological tests are complex and difficult to transfer to in-country testing site
- Huge cost and effort for in-country testing may make products unprofitable
- Since necessary in-country testing is judged on case-by-case basis, lack of clear requirements causes unpredictability

Points to consider and proposals

Preparation for in-country testing

- Early discussion with manufacturer and PMDA is recommended
- Justification should be explained why in-country testing is difficult to conduct

Proposal to Japanese health authorities

- Waiver of in-country testing for regenerative medical products manufactured at GCTP certified site based on CoA issued by the site
- Sharing examples in approved products after accumulating cases to improve predictability (e.g. issue notification or Q&A)

European Federation of Pharmaceutical Industries and Associations

Change control for Cell Therapy product: Utilization of PACMP and future perspective






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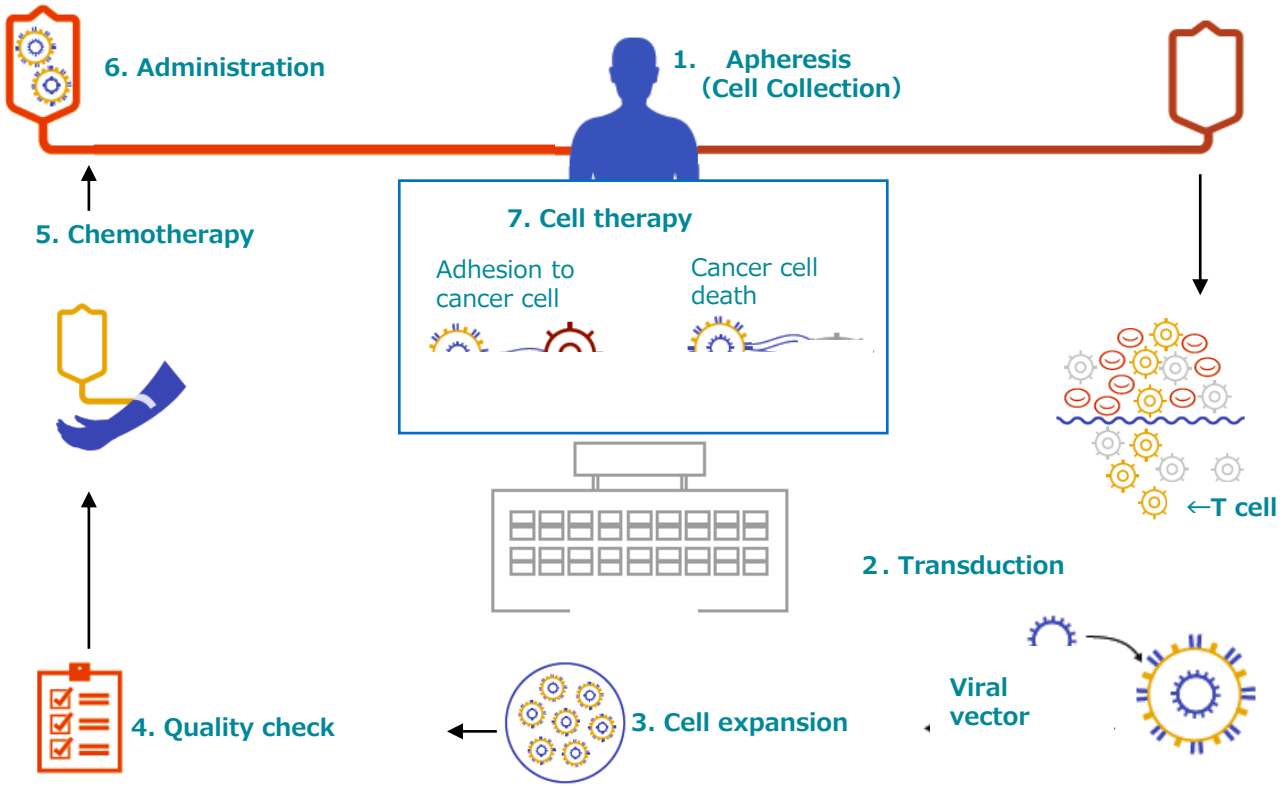
- This presentation contains current and future expectations. Therefore, the contents and future results may differ from the current forecast due to uncertain factors, unforeseeable risks, etc.
- This presentation may contain the views and opinions of the presenter.

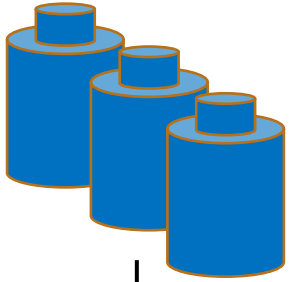
Manufacturing process of Cell Therapy product



Characteristics of Cell Therapy product

Bio-product

Drug substance



Drug product

Cell Therapy product

Viral vector

Product

Characteristics

・Shelf-life extension requires Partial Change Application (PCA).
・Technically developing in both manufacturing process and testing procedure.
  ・ Vendor's kit is used for specification test.
  ・ There is a test method with no experience in bio-product.

・Product is manufactured individually.
  ・ Unable to accumulate inventory.
  ・ Multiple sites may be used due to the large number of manufacturing lots.

Issues in change control of Cell Therapy product

Case	Issues
Shelf-life extension	Partial Change Application (PCA) is required.
PCA, e.g., addition of manufacturing site and process changes	Review period for PCA is long (standard: 12 months). There is a possibility that Japan may become a bottleneck compared to EU and US.
Change (Relaxation) of specification criteria	There is a possibility that criteria may be reconsidered due to limited manufacturing experience. If criteria are not met, remanufacture is difficult. It is required to find appropriate criteria and make changes in a timely manner.
Change of analytical procedure	If vender's kit is updated and the test method is changed, time is required for the change. There is an expiry date for the original kit, which limits when testing can continue.

Change control should be carried out in a timely manner.

Standard review period in Japan

	Chemical product	Bio-product	Regenerative medicine
Notification of Minor Change (NMC) (Do&Tell)	No review	No review	No review
PCA	6M	12M	12M
Accelerated PCA (General)	3～5M (For addition of manufacturing site)	Not Applicable	Not Applicable
Accelerated PCA (Request to MHLW)	No regulatory system	No regulatory system	No regulatory system
PACMP	6M	12M	Not specified

Assessed whether the existing system could solve the issues to smoothly carry out change control (PACMP usability assessment).

PACMP usability assessment

- **Scoring according to:**
  - Period from protocol preparation to study:
    - If the period is short, PACMP is not useful.
  - Potential protocol changes:
    - If the frequency of changes is high, the regulatory procedure will be complicated.
  - Potential deviation from the acceptance criteria:
    - If the acceptance criteria are not met, it takes time to explain the validity.

Items	Scoring (Example)		
Period	≦1 Month : 1	≦1 Year : 2	≧1 Year : 3
Protocol changes	≧2 times : 1	1 time : 2	No : 3
Deviation	≧10% : 1	≦10% : 2	No : 3

- **Multiply each item by the score and assess usability for each change.**
  - ≦9: Not useful
  - ≧10: Useful

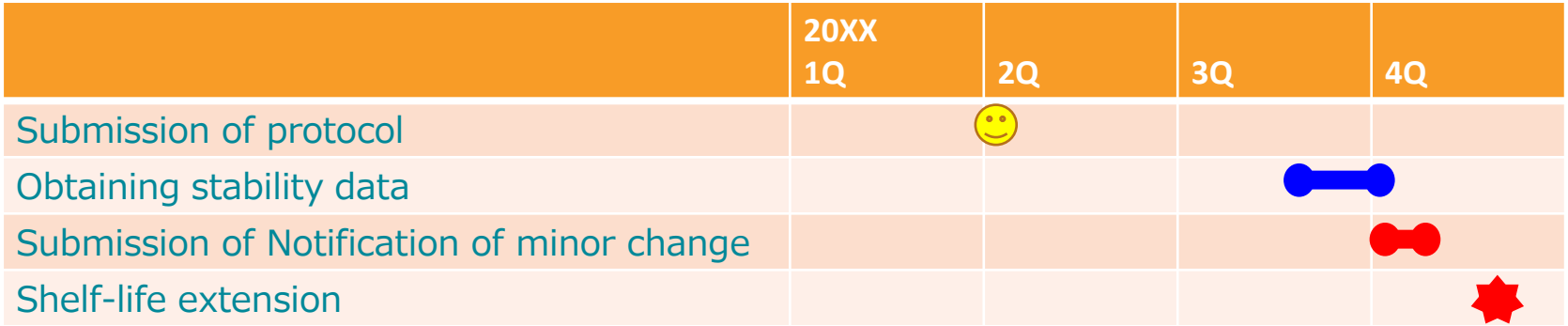
PACMP usability assessment

Change items		Period	Protocol changes	Deviation	Total Score	Usability
Addition of manufacturing site	Before PPQ (including comparability evaluation)	3	2	2	**12**	**Useful**
	After PPQ protocol preparation	2	3	3	**18**	**Useful**
Process changes	Before PPQ (including comparability evaluation)	3	1	1	3	Not useful
	After PPQ protocol preparation	2	3	3	**18**	**Useful**
Analytical procedure changes		1	3	3	9	Not useful
Release Specification changes		1	3	3	9	Not useful
Shelf-life extension		3	3	3	**27**	**Useful**
Shelf-life specification change (EU and US)		3	3	3	**27**	**Useful**

PACMP would be useful in:
addition of manufacturing sites, process changes, shelf-life extension, and shelf-life specification change.

Case study of PACMP

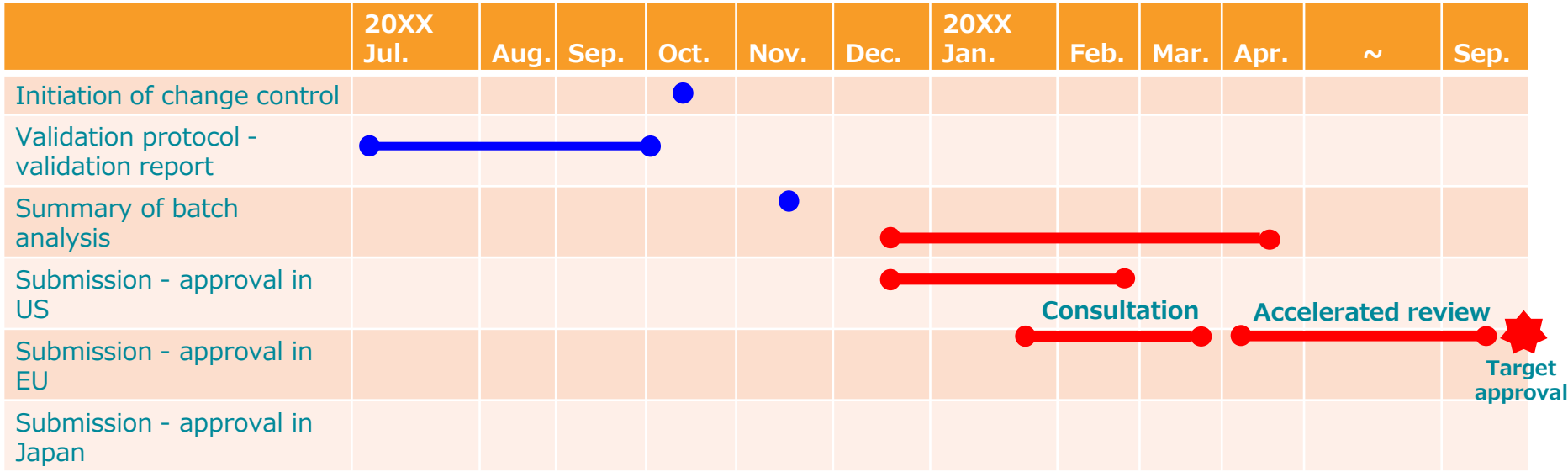
- **Shelf-life extension of viral vector**



- **The review period was shorter than standard review period of PCA.**
- **Shelf-life extension was achieved earlier than PCA.**

How can we leverage PACMP?

- **Retrospective evaluation of a request for accelerated review to MHLW**
  - Potency ELISA kit update (Analytical procedure change)

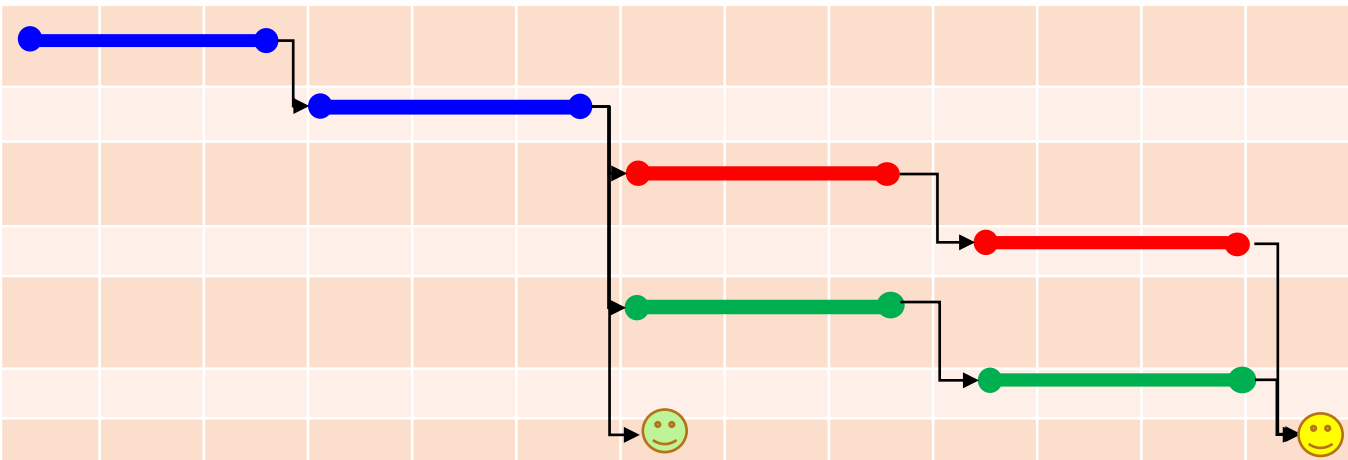


PACMP was not useful for this analytical procedure change.

How can we leverage PACMP?

- **Process change (Example of future change control)**

Manufac-turing site	Activity	Period
Site A	Comparability exercise	
	PPQ	
Alternative site B	Technical transfer	
	PPQ	
Alternative site C	Technical transfer	
	PPQ	
-	Submission	



- **PCA after completion of PPQ at each manufacturing site**
- **PACMP→Change can be implemented earlier than PCA.**

Issues in change control of Cell Therapy product.

Case	Issues	Resolution
Shelf-life extension	Partial Change Application (PCA) is required.	**Using PACMP**
PCA, e.g., addition of manufacturing site and process changes	Review period for PCA is long (standard: 12 months). There is a possibility that Japan may become a bottleneck compared to EU and US.	**Some resolution possible with PACMP**
Change (Relaxation) of specification criteria	There is a possibility that criteria may be reconsidered due to limited manufacturing experience.	**No resolution**
Change of analytical procedure	If vender's kit is updated and the test method is changed, time is required for the change.	**No resolution**

Shortening of PCA review period may be required in some case, especially in specification and analytical procedure changes.

Summary and future perspective

- Cell Therapy products have different characteristics from bio product, therefore change control should be carried out smoothly.
- PACMP would be a useful option to carry out change control smoothly.
- There is room for improvement in PCA review period in some case, especially in specification and analytical procedure changes that are difficult to use PACMP. There is also a gap in the review period with EU and US.

Further improvement is expected for CMC change control on Cell Therapy products

Thank you

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