Post marketing safety requirements (Japan)

―Re-examination system of Regenerative Medicinal Products―

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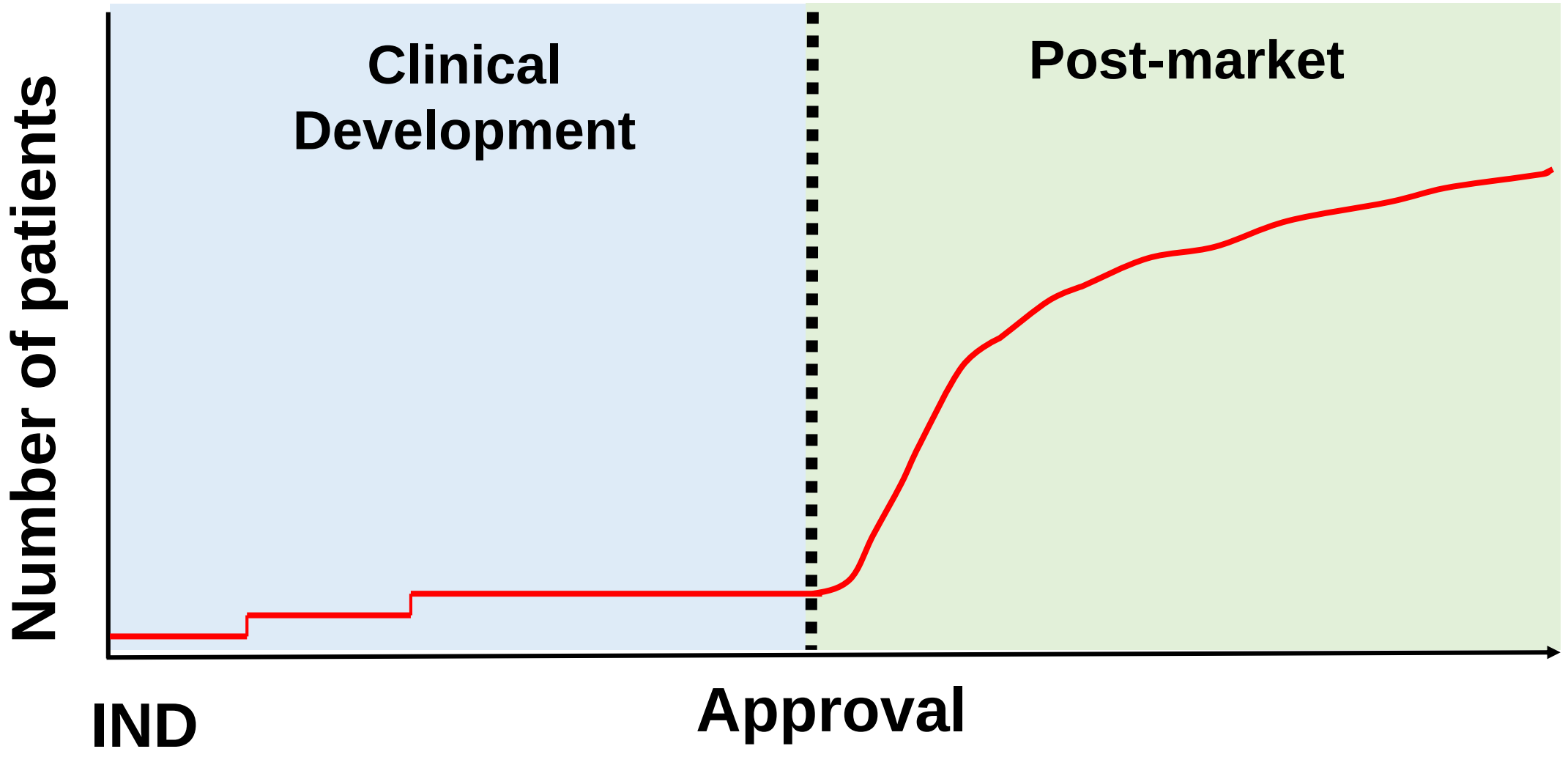
Limitations of Clinical Trials



Re-examination system

Objective:

- **To collect post-marketing information for a predetermined period**

- **To reconfirm the quality, efficacy and safety of products after approval by regulatory bodies (MHLW/PMDA)**

Period	Type of new product
10 years	Orphan products
8 years	Products with new constitutive cells /new transgenes
6 years	Products with new structure Products with new route of administration
4 years	Products with new indication/new dosage/methods of usage

Re-examination results

Regulatory bodies (PMDA/MHLW) judge whether the marketing authorization should be maintained, varied, suspended or withdrawn according to the following three categories:

Category	Result	Decision on marketing authorization
Category 1	Quality, efficacy and safety of drug is conformed	Maintain
Category 2	Quality, efficacy and safety of drug is conformed by a partial change in approval	Vary
Category 3	Quality, efficacy and safety of drug is not confirmed	Withdraw

Post-Marketing Study

Post marketing observational study with primary data collection (Use-results survey)

- Information in routine clinical practice is obtained directly from medical institutions.

Post-marketing Database study

- Information is acquired from the medical information database.

Post-marketing clinical trial

- Trials conducted according to approved indications and usage to collect information not available in routine clinical practice.

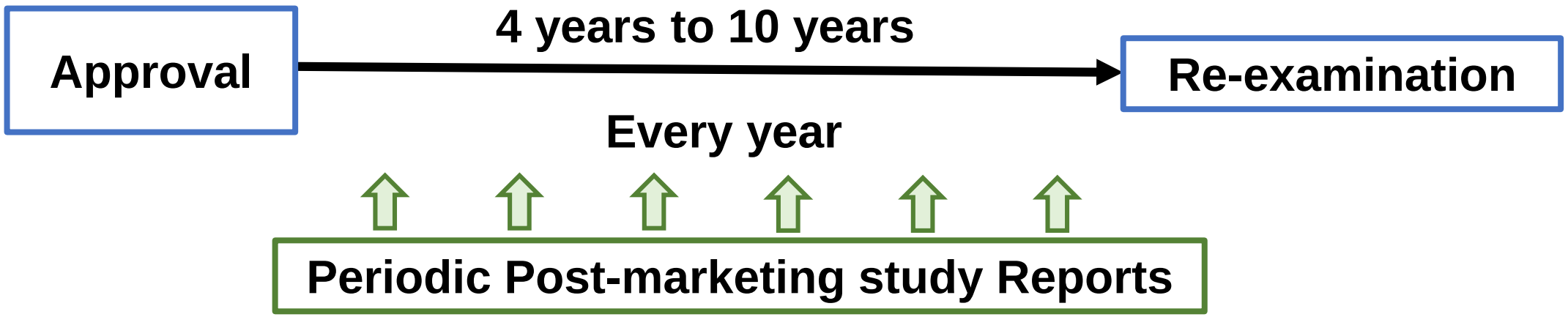
Post-Marketing Study covering all patients

- **Currently, all approved regenerative medical products are required to perform Post-Marketing Study covering all patients treated with the product in the post-marketing setting.**

- **The objective of this system are:**
  - ✓ **To collect post-marketing information promptly and without bias.**
  - ✓ **To collect information necessary for proper use promptly .**

- **All patients who use the product are needed to be registered by HCPs before the start of the use of the product.**

Process From Approval to Re-examination



Contents of Periodic Post-marketing study Reports and Re-examination documentation:

- Results of Post-marketing studies
- Reports of AR and infection during the period…etc.

Re-examination : JACE

Approved on 2007

Autologous Culture Epidermis
JACE

＜Indication＞
serious burns treatment (limited to the burns of more than 30% of the body surface area)

Clinical trial： J-TEC003 (2 patients)

Epithelialization rate at 4 week		
Patient #1	Age 34	50%
Patient #2	Age 35	100%

Re-examined on 2017

Post-marketing study covering all patients

<Safety>

	Number of patients (%) N=359
All AEs after product transplantation	181 (50.4%)
AEs (casual relationship to product could not be ruled out)	25 (7.0%)

<Efficacy>

Epithelialization rate at 4 week			
Total		51.0±37.00%	N=334
Pediatric	Age ≤ 10	58.7±33.30%	N=20
Geriatric	Age ≥ 65	44.4±39.13%	N=111

Summary

- **Because only a limited number of patients participated in the clinical studies of the new product, MAH is required to conduct post-marketing study in order to collect safety and efficacy data in the post-market setting, and thereby to apply for re-examination.**

- **4 years to 10 years after approval, Regulatory bodies (PMDA/MHLW) reconfirm the quality, efficacy and safety of products in re-examination.**

- **All regenerative medical products are required to perform Post-Marketing Study covering all patients treated with the product in the post-marketing setting in order to collect post-marketing information promptly and without bias, etc.**