Day 1 Workshop Session 2
4:00pm

Clinical Evaluation of Advanced Therapeutics

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Outline

- Pathway and Clinical Data Package
- Case of TEMCELL®
- Case of HeartSheet®
- Points to be Considered in Clinical Trial

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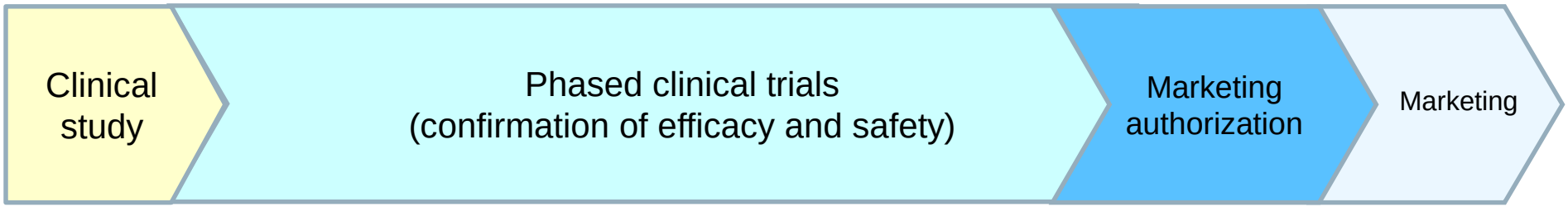
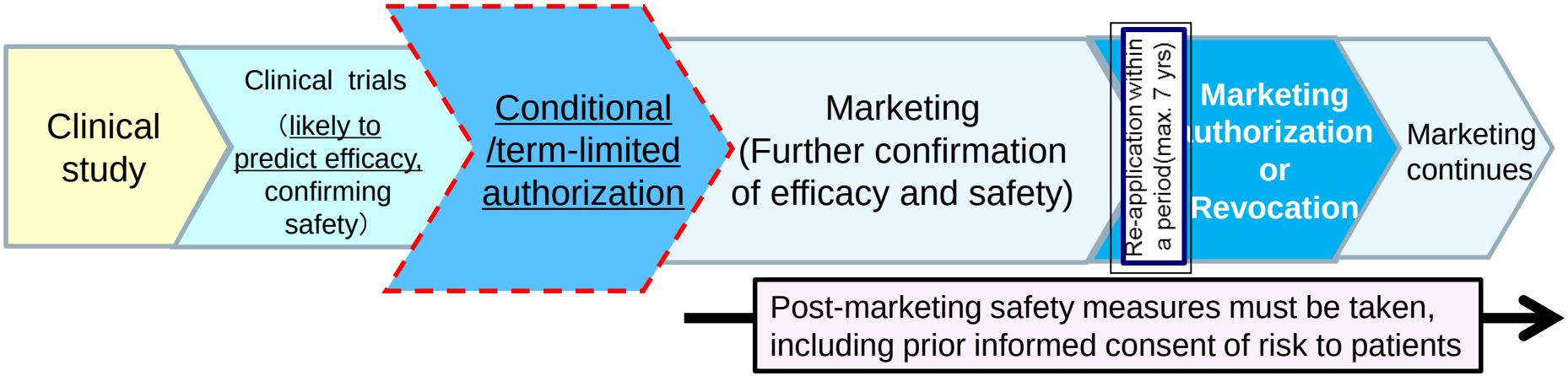
Expedited Approval System under PMD Act

< Drawback of traditional PAL approval system >
Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, **such as non-uniform quality** reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]

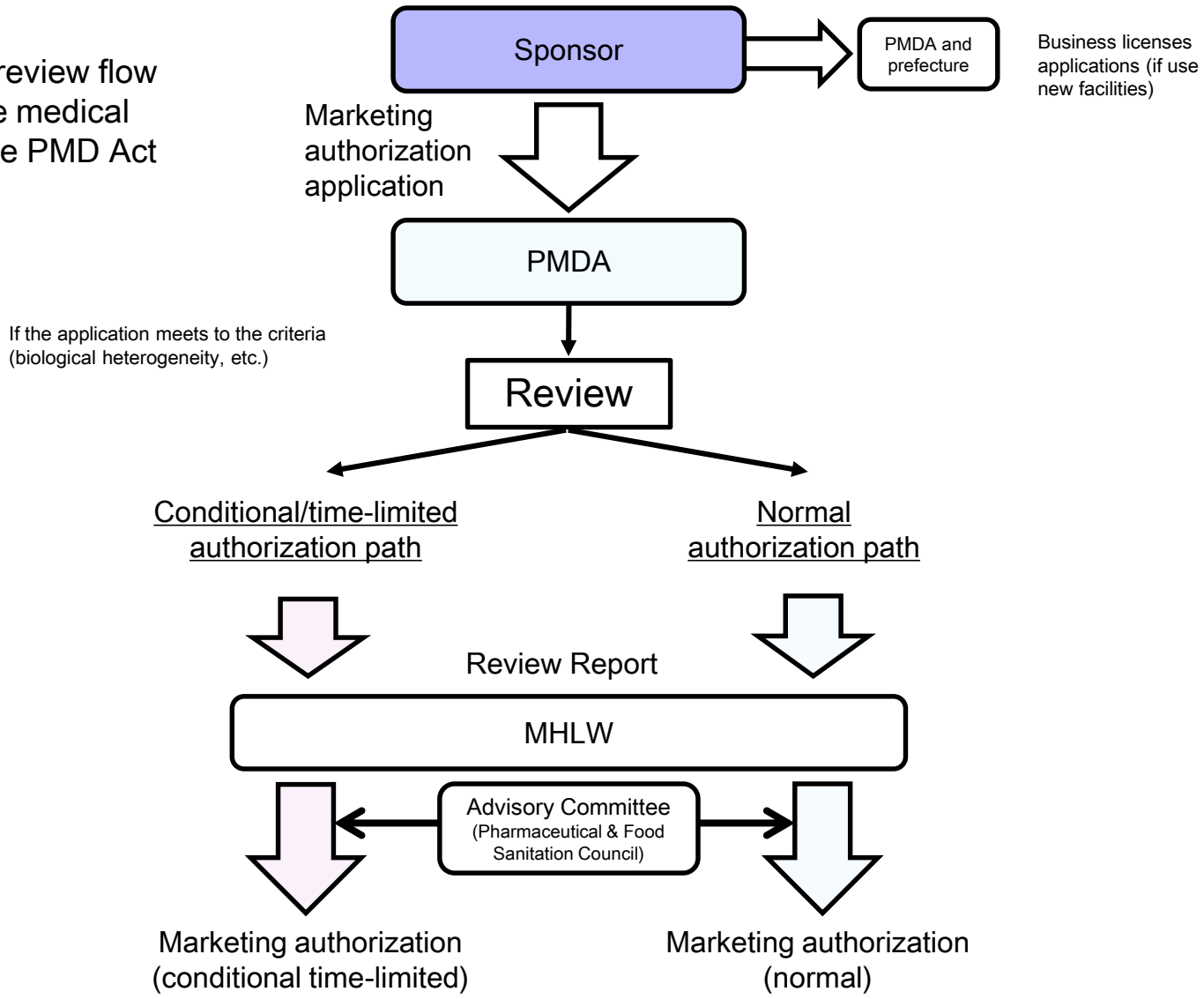


[New scheme for regenerative medical products]

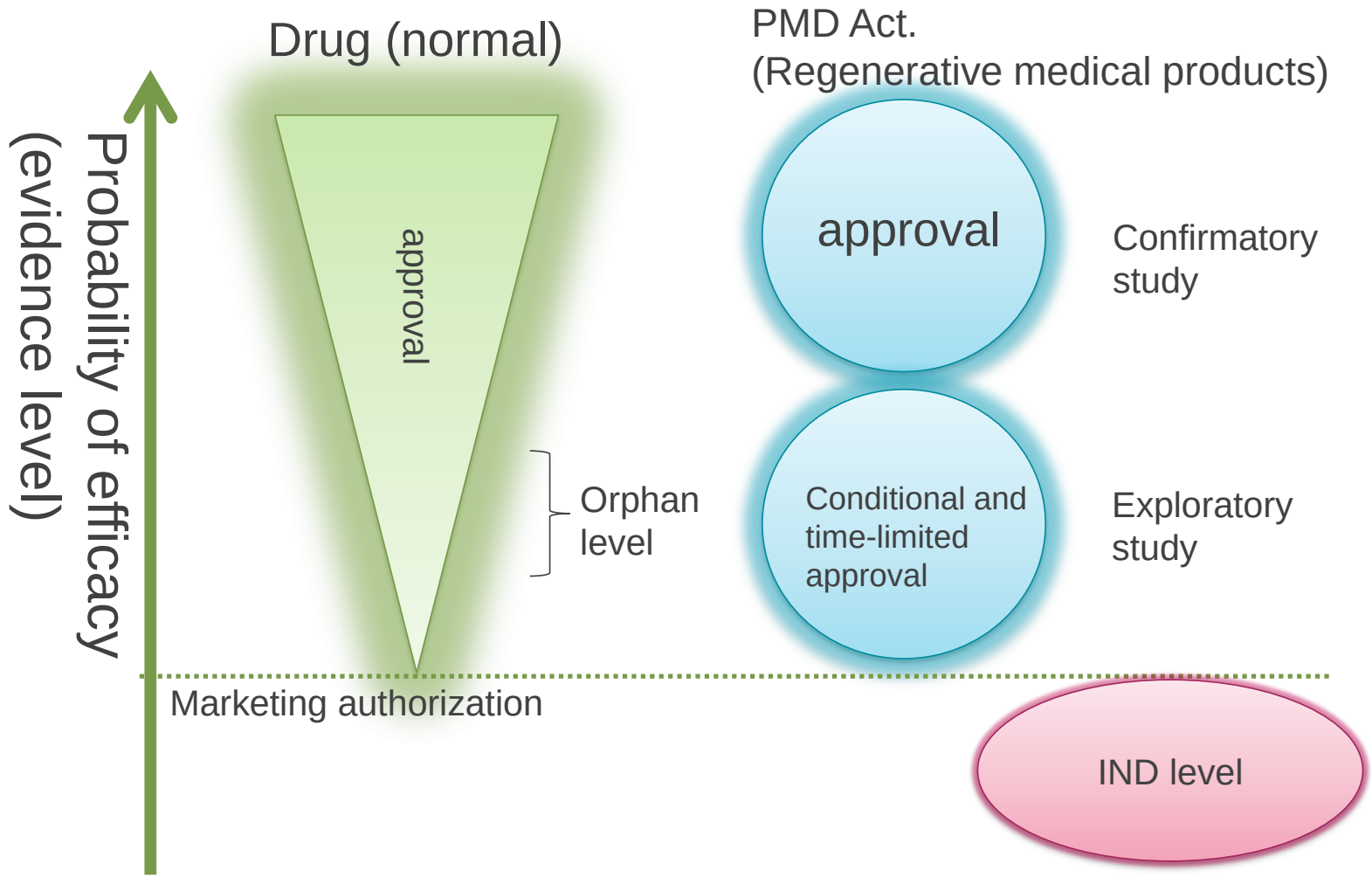


Review Pathway of Regenerative Medical Products

Application and review flow of regenerative medical product under the PMD Act



Evidence Level of Efficacy: Drug (normal) vs. HCT/P



Two New Products will Approved under New Regulatory Framework

- In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.
- Positive opinions were made for approval by Regenerative Medical Product and Biologics Committee, PFSC on September 2015.

1. Bone marrow mesenchymal stem cells (MSCs) for graft versus host disease (GVHD) **(normal approval)**
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease **(conditional and time-limited approval)**

*PFSC: Pharmaceutical Affairs and Food Sanitation Council

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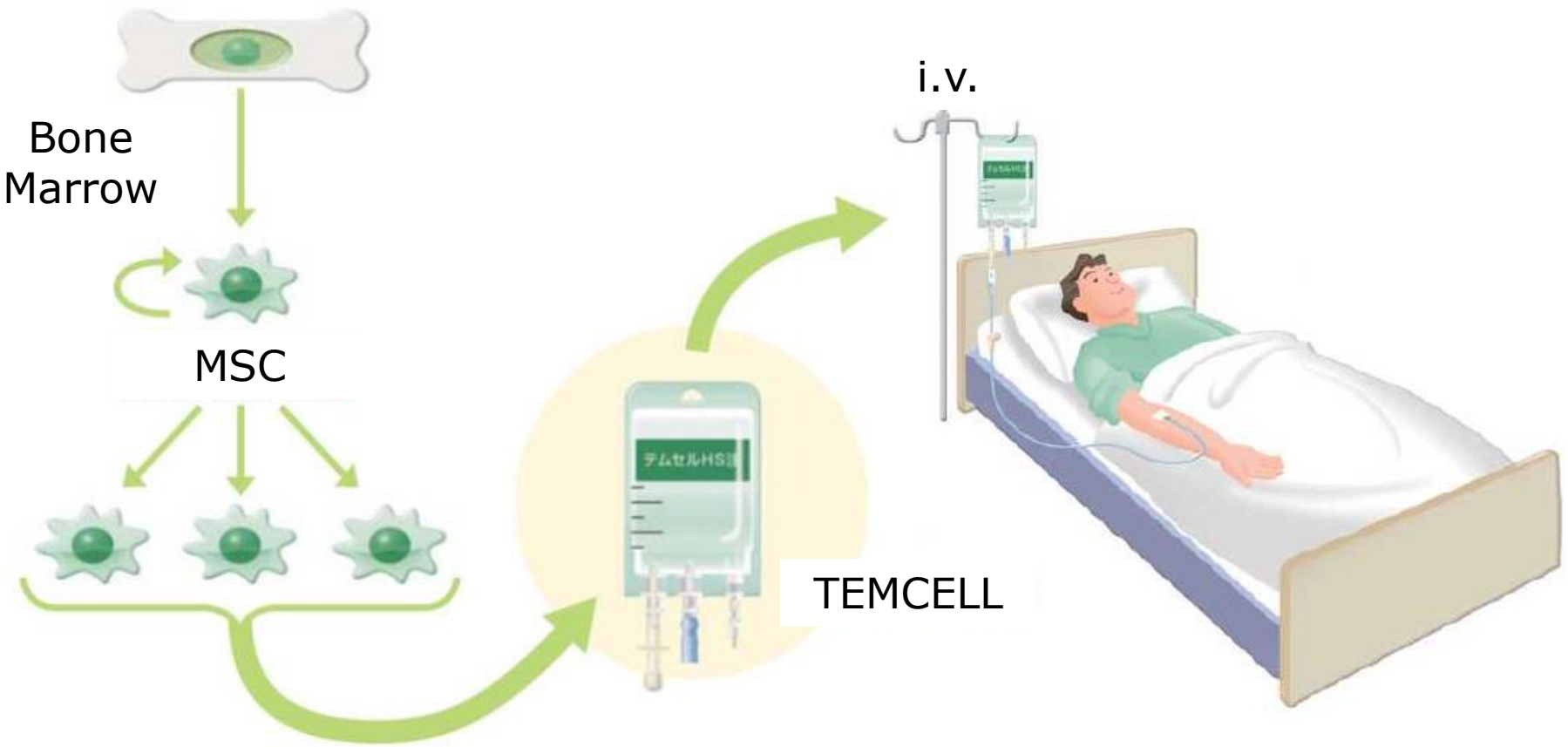
TEMCELL

- Target: Steroid refractory acute GVHD
  - Fatal and Rare disease (approx. 1000-2000/y)
- Product: Allogeneic MSC
- Manufacturer JCR Pharmaceuticals Co., Ltd
- Resources and technology imported from Mesoblast, Ltd. (Osiris Therapeutics, Inc.)
  - Prochymal® (Brand Name)
    - Conditional approval in Canada and New Zealand

http://www.jcrpharm.co.jp/news/20151126_3991

TEMCELL Route of Administration



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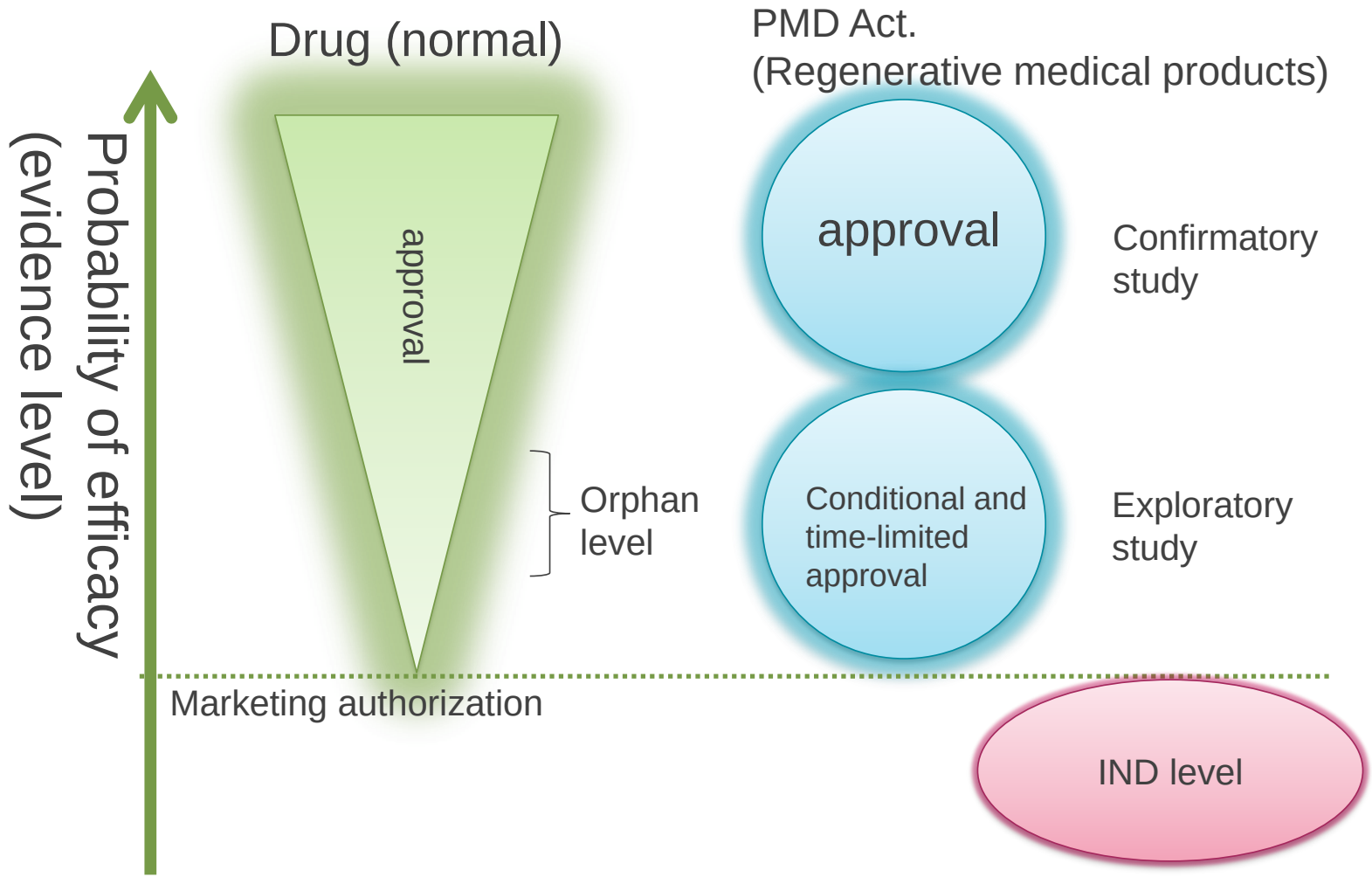
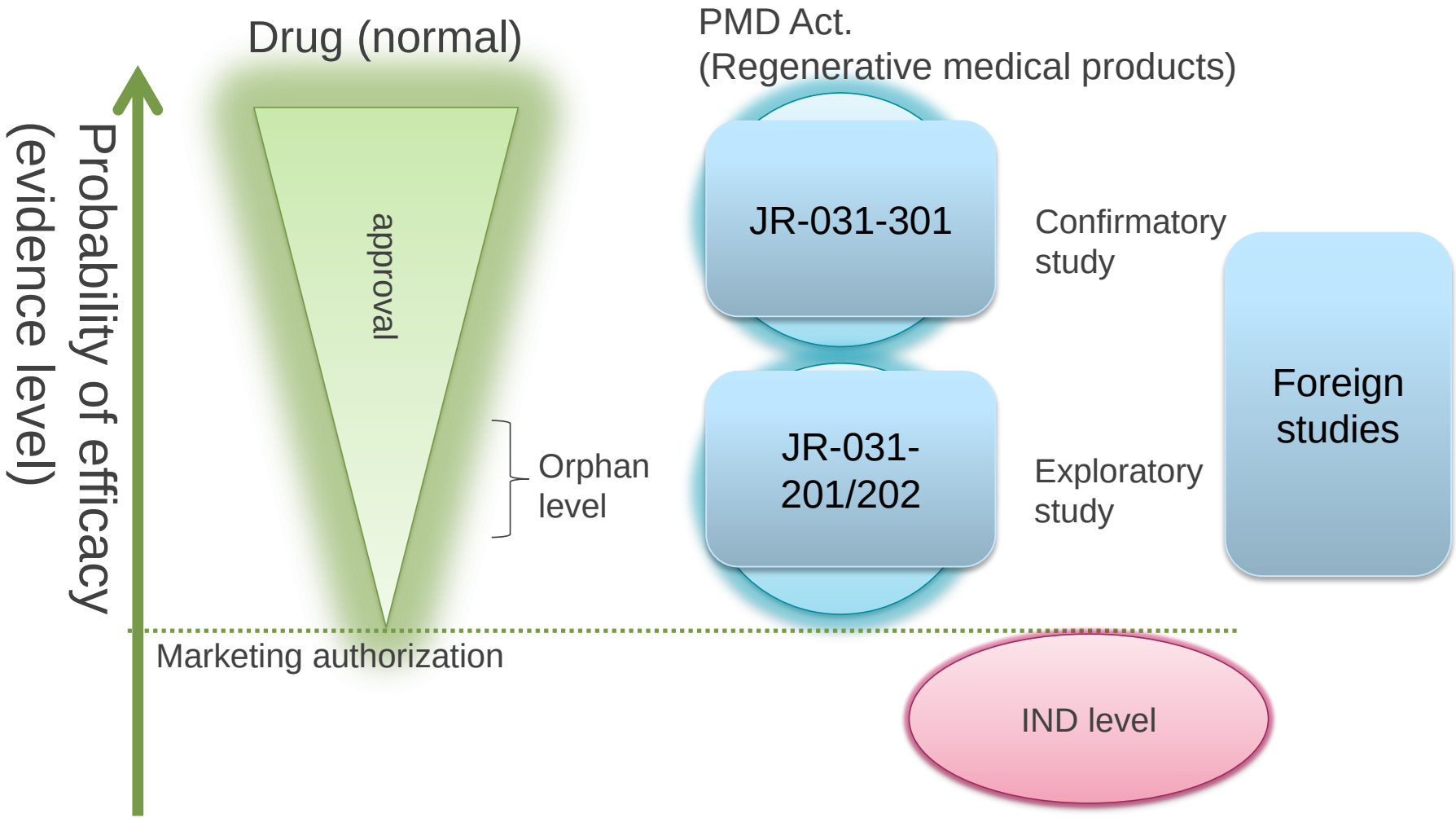
TEMCELL Clinical Studies

- Japan
  - JR-031-201/202 study(Phase I/II)
    Single arm clinical trial, 14 subjects. Grade II-IV.
  - JR-031-301 study (Phase II/III)
    Single arm clinical trial, 25 subjects. Grade III-IV.
- Foreign (Prochymal ®)
  - 280 study
    Placebo-controlled RCT, 216 adults and 28 pediatric subjects. Grade B-D.
  - 275 study
    Single arm clinical trial, 75 pediatric subjects.

Evidence Level of Efficacy: Drug (normal) vs. HCT/P



Evidence Level of Efficacy: TEMCELL



Summary for Review

- JR-031-301 study (Phase II/III)
- Primary Endpoint; Durable Complete Response (≥ 28 days)
- Results; Response rate 48.0% (12/25, 95%CI 27.8-68.7)

✓ Response rate of the JR-031-301 study was better than 21.6% (11/51), durable complete response of the grade-matched subgroup from 280 study placebo arm.

- Previous reports

✓ Anti-Thymocyte Globulin: 20.3% (16/79)

✓ Mycophenolate Mofetil: 15.4% (2/13)

>> Approval

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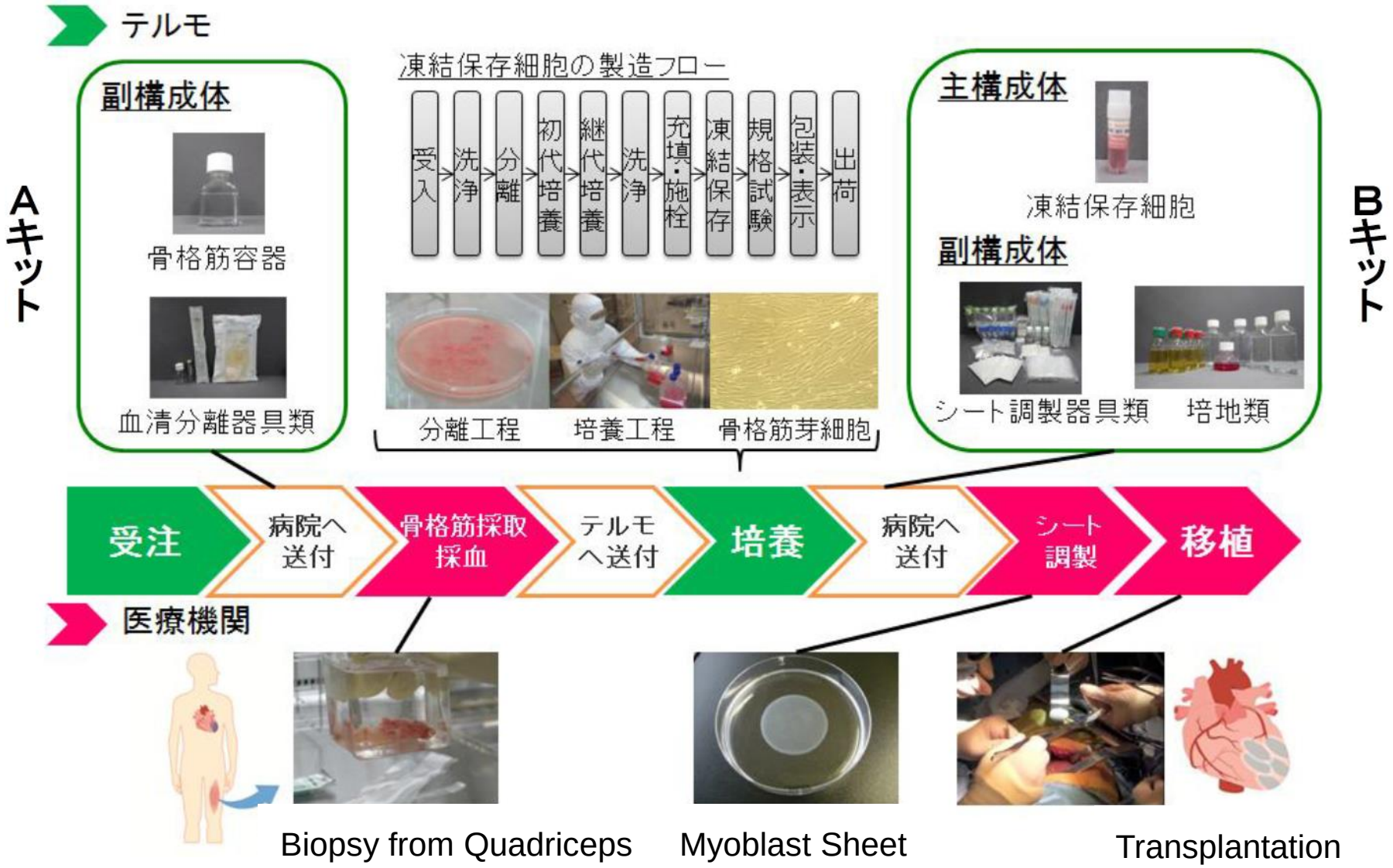
HeartSheet

- Target: Serious heart failure due to IHD
  - Chronic and Poor prognosis
- Product: Autologous skeletal myoblast
- Manufacturer: Terumo Corporation
- Manufacturing
  - Biopsy from Quadriceps
  - Final product is manufactured at CPC in hospital

HeartSheet; Manufacturing and Final Products



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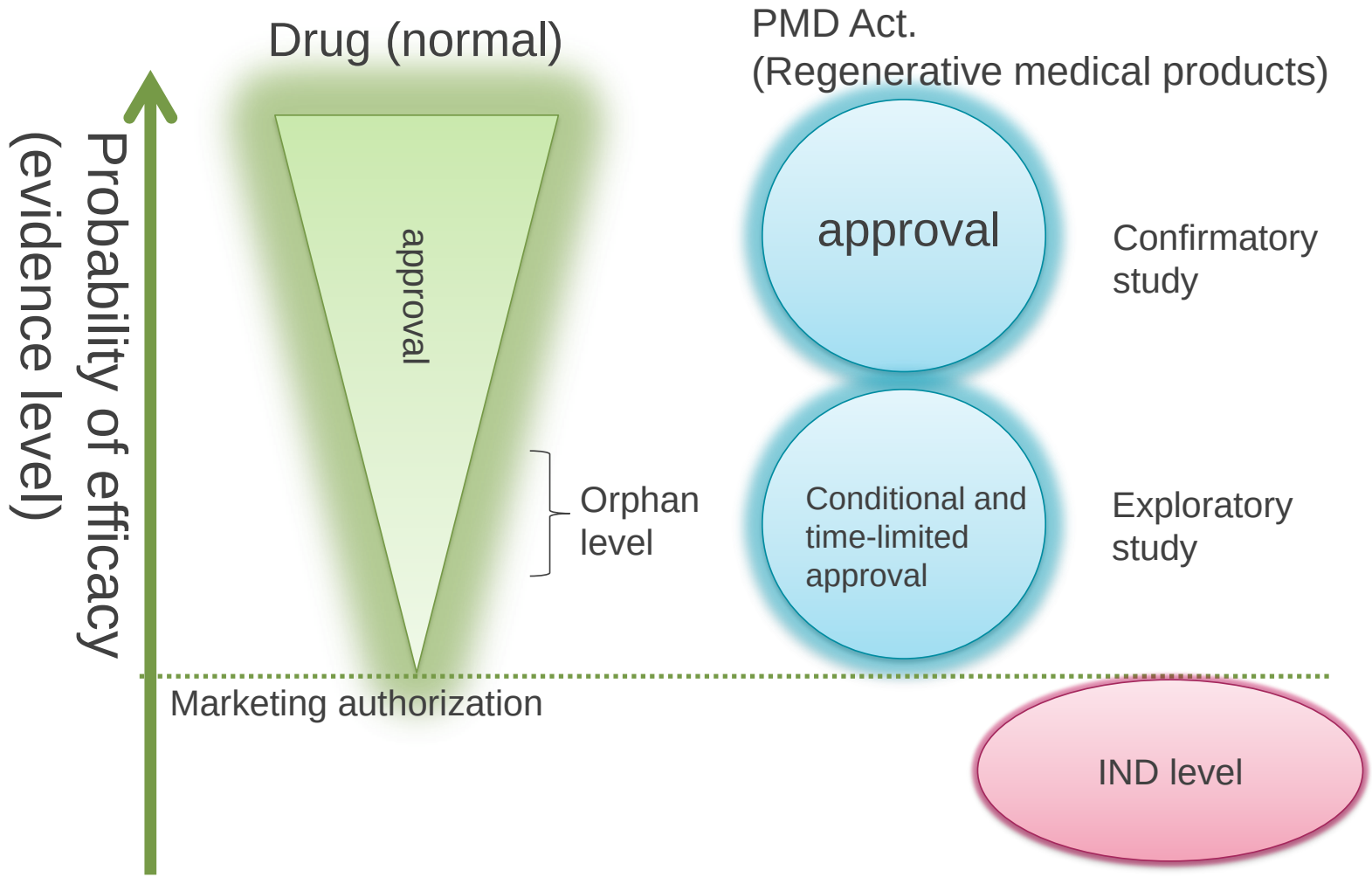
HeartSheet; Clinical Study

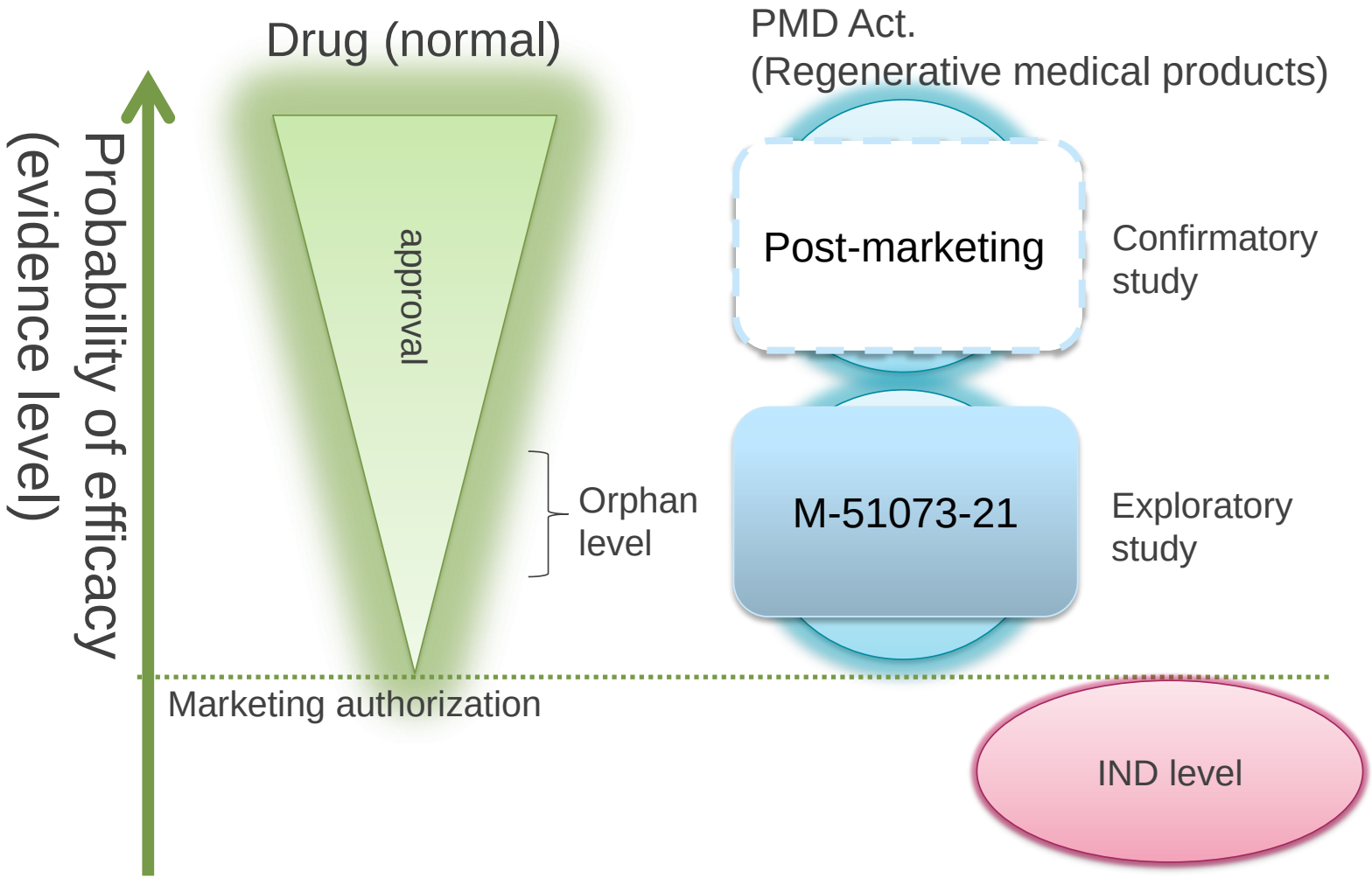
- Japan; M-51073-21 study
  Single arm clinical trial, 7 subjects.
- Foreign; None

- Endpoint
  - Prespecified
    - LVEF (RI, CT, Echo)
  - Post-hoc
    - Comprehensive clinical evaluation
    - Survival (External control comparison)

Evidence Level of Efficacy: Drug (normal) vs. HCT/P



Evidence Level of Efficacy: HeartSheet



Summary for Review

- Efficacy evaluation
  - LVEF (RI, CT, Echo)
  - Comprehensive clinical evaluation
    >>Improvement of clinical symptoms
  - Survival (External control comparison)

  >> Skeletal Myoblast Sheet: All subjects survived

>> Conditional and time-limited approval

- Post-marketing evaluation

➢Concurrent external control comparison
- Endpoint: Survival
- Skeletal Myoblast Sheet: 60 subjects
- Control: 120 subjects

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How to Expedite R&D and Review for Regenerative Medicine

- Designed for unmet needs under the present treatment: limited number of patients available for CT
- Difficult to conduct controlled study to demonstrate statistical significance in "true end point" of clinical benefit
- Heterogeneity of Quality affected by source materials

Would it take long time for CTs and review if regulator pursues the conventional drug pathway too much?

What Do You Derive from Trials?

Endpoints

True or surrogate

Apart from medical/academic interest, you should select the endpoints likely to demonstrate the difference between active drug group and control group, with statistical power and clinical significance

Justifiable control

Randomized placebo control study may be most appropriate. Otherwise, control arm will be selected from similar patients to those treated with the active drug.

for single arm study, threshold should be justified by comparison from the result of currently available treatments

Safety and Efficacy Evaluation of Limited Number of Subjects in the Trial for Conditional Approval

- Challenge on new designs and statistical methodologies for small population
- How to secure evidence level?
  - ✓Design : controlled / blinded, possibility.
  - ✓Clinical endpoint (efficacy) : clinical significance, objectiveness, surrogacy, etc.
- At least, Maximize the information from a single subject in terms of safety and efficacy.
- Post-marketing study?

Conclusion

How to evaluate efficacy & safety of Regenerative Medical Products?

- Evaluation from multiple points of view
- Maximize information from one subject
- Maximize information from one study

Well Designed Clinical Trial & Thorough Evaluation

Thank you for your attention!