This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

<table>
<thead>
<tr>
<th>ITEM</th>
<th>DESCRIPTION</th>
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</thead>
<tbody>
<tr>
<td>Building Block (BB) Title</td>
<td>Study Group on Unapproved and Off-label Drugs of High Medical Need</td>
</tr>
<tr>
<td>References</td>
<td>• MHLW’s website: Study Group on Unapproved and Off-label Drugs of High Medical Need (Japanese)</td>
</tr>
<tr>
<td></td>
<td>o <a href="https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701.html">https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701.html</a></td>
</tr>
<tr>
<td>Description</td>
<td>The objective of the Study Group is to evaluate medical need, investigate necessary studies for market approval, and request company to develop medicinal products to solve the problem of unapproved drug and off-label use with medical need. Public consultations are conducted to gather requests from public.</td>
</tr>
</tbody>
</table>

### Process Flow

- **Criteria in Study Group**
  - Unapproved drugs in Japan
  - Approved in three of five Western countries: US, UK, Germany, France, and Australia
  - Off-label use drugs in Japan
  - Approved in at least five of these six Western countries, including with a specific dosage that is widely used based on a certain evidence.
  - Accelerating scheme for practical use
  - Unapproved in all the 6 Western countries but satisfies a certain criteria

- **The drug has to satisfy both of (1) and (2), high medical need**
  - (1) Severity of the target disease is either below.
    - (a) Life threatening (latter)
    - (b) Irreversible progression and significantly affected daily life
    - (c) Other type of significantly affected daily life
  - (2) Medical usefulness is either below.
  - Unapproved drugs, off-label uses
  - (a) No existing therapy in Japan
  - (b) Efficacy/safety in clinical trials in these countries is clearly superior to the existing therapy
  - (c) Its treatment is regarded as a standard therapy in these countries, and its efficacy is highly expected in Japan despite differences of medical environment.

- **Accelerating scheme for practical use**
  - (a) No existing therapy in Japan
  - (b) Efficacy/safety in domestic or international clinical trials is clearly superior to the existing therapy

- **[Academia, patients group]**
  - Requests on unapproved/off-label use
  - Summary:
    - 1st consultation: 374 cases
    - 2nd consultation: 200 cases
    - 3rd consultation: 168 cases
    - 4th consultation: 56 cases

- **[Related academia, pharmaceutical industry]**
  - Submitting its opinion

- **[Pharmaceutical industry]**
  - Development for market application

- **[Governmental support for development]**
  - Designation of orphan medicinal products
  - Validation of public knowledge-based application
  - Validation of necessary test for market application

- **[Study Group on Unapproved and Off-label Drugs of High Medical Need]**
  - 7 Working Groups

- **Evaluating medical need**
  - Statistical by the end of May 2023
  - Required to industry
    - 1st consultation: 100
    - 2nd consultation: 110
    - 3rd consultation: 50
    - 4th consultation: 10

- **Recruitment for applicant**
  - 1st consultation: 20
  - 2nd consultation: 15
  - 3rd consultation: 5
  - 4th consultation: 2
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<th>ITEM</th>
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<tbody>
<tr>
<td>Category</td>
<td>Regulatory Building Block</td>
</tr>
<tr>
<td>Geographical scope</td>
<td>Japan</td>
</tr>
<tr>
<td>Availability</td>
<td>Applicants developing medicines for rare and non-rare diseases</td>
</tr>
<tr>
<td>Scope of use</td>
<td>The scope of this initiative is to evaluate medical need, investigate necessary studies, and promote drug developments for market approval to solve the problem of unapproved drug and off-label use with medical need.</td>
</tr>
</tbody>
</table>
| Stakeholders | • Patient Group  
• Academia (Academic Societies)  
• Individuals  
• Drugs developers  
• Study Group (Physicians, Pharmacists, and other medical professions) |
| Enablers/ Requirements | Applicable criteria  
• Unapproved drugs in Japan  
  o Approved in either of 6 countries (US, UK, Germany, France, Canada, and Australia (but not Japan))  
• Off-label use drugs in Japan (Approved for other indication in Japan)  
  o Approved in either of above 6 countries, or |
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<td>o widely used in either of above 6 countries with a specific dosage, based on a certain evidence</td>
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<tr>
<td></td>
<td>• Accelerating scheme for practical use</td>
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<tr>
<td></td>
<td>o Unapproved in all 6 countries but satisfies a certain criterion such as the existence of ongoing/completed investigator-initiated phase III trial in Japan or adequate evidence from clinical study.</td>
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<tr>
<td>Output</td>
<td>Request of drug development and various support to company</td>
</tr>
<tr>
<td>Best time to apply and time window</td>
<td>At the time of public consultation conducted</td>
</tr>
<tr>
<td>Expert tips</td>
<td>For more information, please refer to information in Japanese.</td>
</tr>
<tr>
<td>PROs:</td>
<td>Possible Incentives currently applicable to development on Unapproved Drugs or Off-label Drugs</td>
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<tr>
<td></td>
<td>• Priority Review</td>
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<td></td>
<td>• Orphan Drug Designation</td>
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<td>• Conditional Early Approval System for Drugs</td>
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