ICH
harmonisation for better health

Module 7
Selection of comparators

ICH E17: General principles for planning and design of Multi-Regional Clinical Trials

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

- This presentation is protected by copyright and may, with the exception of the ICH logo, be used, reproduced, incorporated into other works, adapted, modified, translated or distributed under a public license provided that ICH's copyright in the presentation is acknowledged at all times. In case of any adaption, modification or translation of the presentation, reasonable steps must be taken to clearly label, demarcate or otherwise identify that changes were made to or based on the original presentation. Any impression that the adaption, modification or translation of the original presentation is endorsed or sponsored by the ICH must be avoided.
- The presentation is provided "as is" without warranty of any kind. In no event shall the ICH or the authors of the original presentation be liable for any claim, damages or other liability arising from the use of the presentation.
- The above-mentioned permissions do not apply to content supplied by third parties. Therefore, for documents where the copyright vests in a third party, permission for reproduction must be obtained from this copyright holder.

Outline

- Introduction
- How to select a comparator
- Using comparators not approved in some regions
- Concluding remarks

Introduction

- **Comparators in an MRCT should be considered in the context of available standard therapies.**
- **In principle, the same approved comparators (e.g., same indication, dose, dosage form and route of administration) should be used in participating regions to enable interpretation of trial results.**
- **In some cases, the selected comparator is not approved in some regions. This module will provide considerations for such situations.**

How to select a comparator

Global

- Research international, leading professional societies' recommended treatment, i.e., global standard therapies, treatment algorithms, doses and dosage forms

Local

- Research current treatment in each region, i.e., all relevant examples of local standard care, treatment algorithms, doses and dosage forms

MRCT

- Select the most appropriate comparator for use in the MRCT

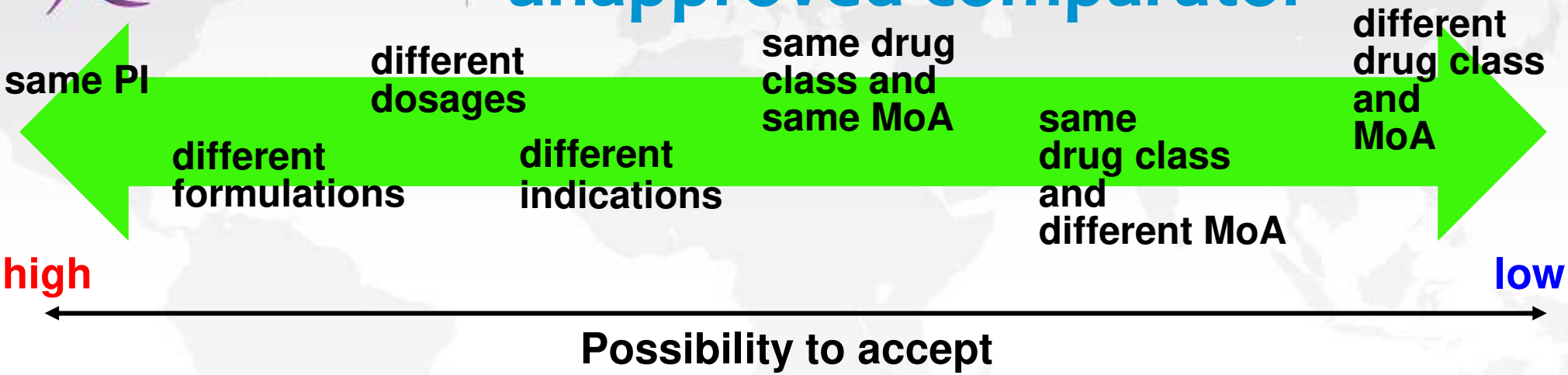
Situations where an unapproved comparator may be considered

- There is no established standard treatment for the target disease
- The comparator is in late stage of development (e.g., ongoing confirmatory study) in the region in question
- There is documented clinical experience of the comparator in one or more ICH regions included in the trial
- The comparator has been recognised as a standard therapy in an international clinical treatment guideline
- There are no concerns related to safety or lack of efficacy of the comparator in existing clinical study data and/or in the post-marketing data
- The comparator is unlikely to be sensitive to intrinsic and/or extrinsic factors relevant for the regions in question

Considerations for use of unapproved comparators

- Justification for the use of an unapproved comparator should be based on scientific information (e.g., from comparisons against treatments which are approved in the region in question). A risk assessment of the unapproved comparator is also needed.
- If a non-inferiority trial is planned:
  - Is sufficient information available to select an appropriate non-inferiority margin?
  - Is sufficient information available to establish product similarity with approved therapies in the region in question? (see next slide)

Justifications for using an unapproved comparator



The following external information may support the use of an unapproved comparator.

- product information (PI) from sourcing regions
- publications, regulatory authorities' reports
- medical and scientific literature
- meta-analyses
- comparative PK and/or PD and/or extrapolations
- supporting regional study
- interventional clinical study

MoA: Mechanism of Action
PK: pharmacokinetics
PD: pharmacodynamics

Additional considerations

- **In order to ensure consistent quality of the active comparators, it is recommended to use comparators from the same manufacturing source in all participating regions.**
- **Quality and sourcing of the comparator is particularly important for biologicals.**
- **The most comprehensive product information used in a participating region should be used consistently in all participating regions.**

Concluding remarks

- Comparators in MRCTs should ideally be approved in all participating regions.
- However, there could be situations where the most appropriate comparator:
  - is not approved in a particular region, or
  - is approved but has different indications, dose strengths or formulations
- If a comparator not approved in some regions is selected, scientific justifications should be provided for use of the unapproved product in those regions.
- The selection of comparators should be discussed and agreed with relevant regulatory authorities.