GaBI Educational Workshops

30 April 2019, Hilton Bogotá, Colombia

3rd Colombian Educational Workshop on
REGULATORY ASSESSMENT OF BIOSIMILARS

Yolanda Elias Gramajo, MD, Canada

- Senior Clinical Evaluator, Clinical Trials Division, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, Biologics and Genetic Therapies Directorate, Health Products & Food Branch, Health Canada

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International

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Head-to-head clinical studies and biosimilarity studies to assess biosimilar medicinal products

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Head-to-head Clinical Studies and Biosimilarity Studies to Assess Biosimilar Medicinal Products

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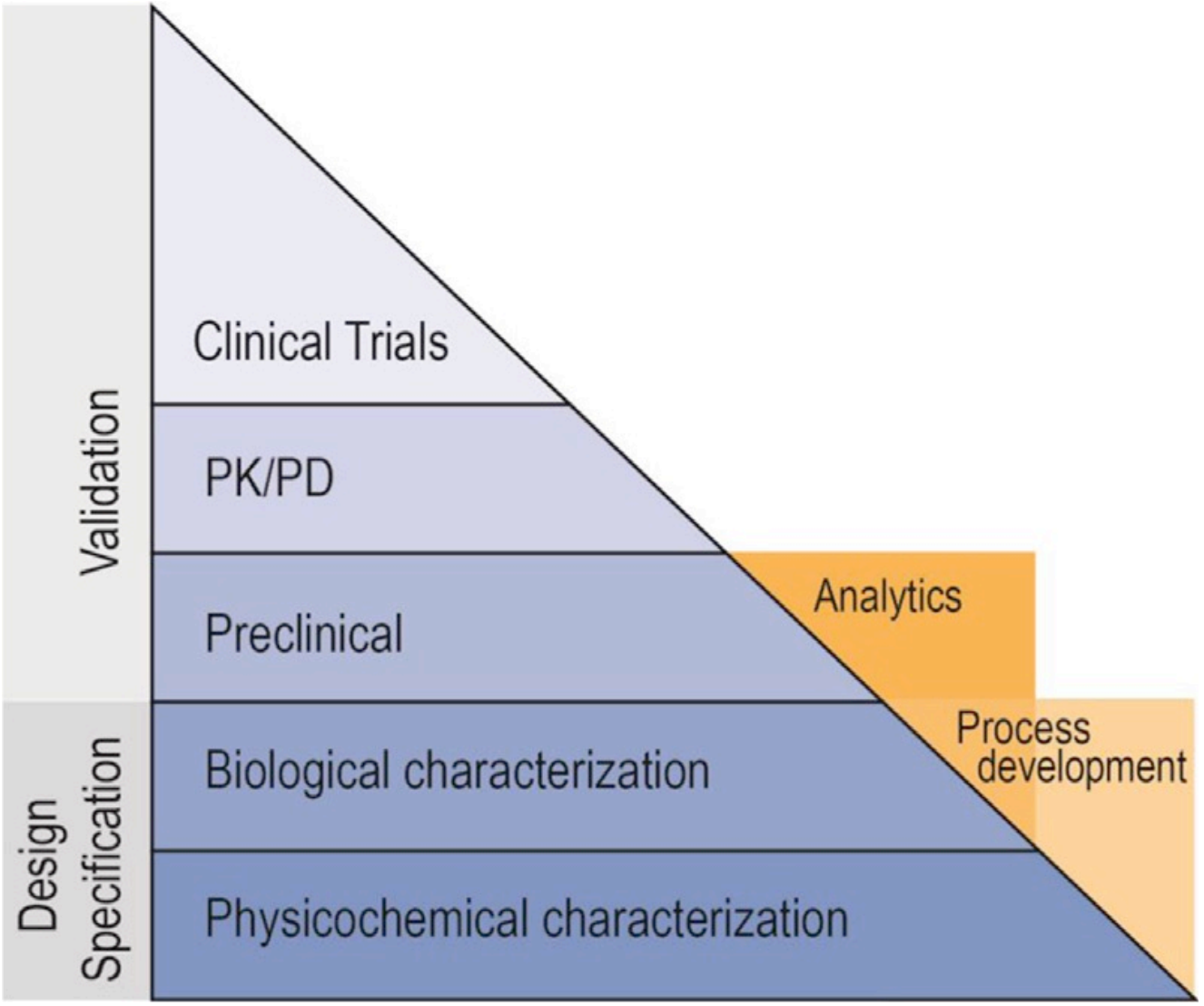
YOUR HEALTH AND SAFETY... OUR PRIORITY.

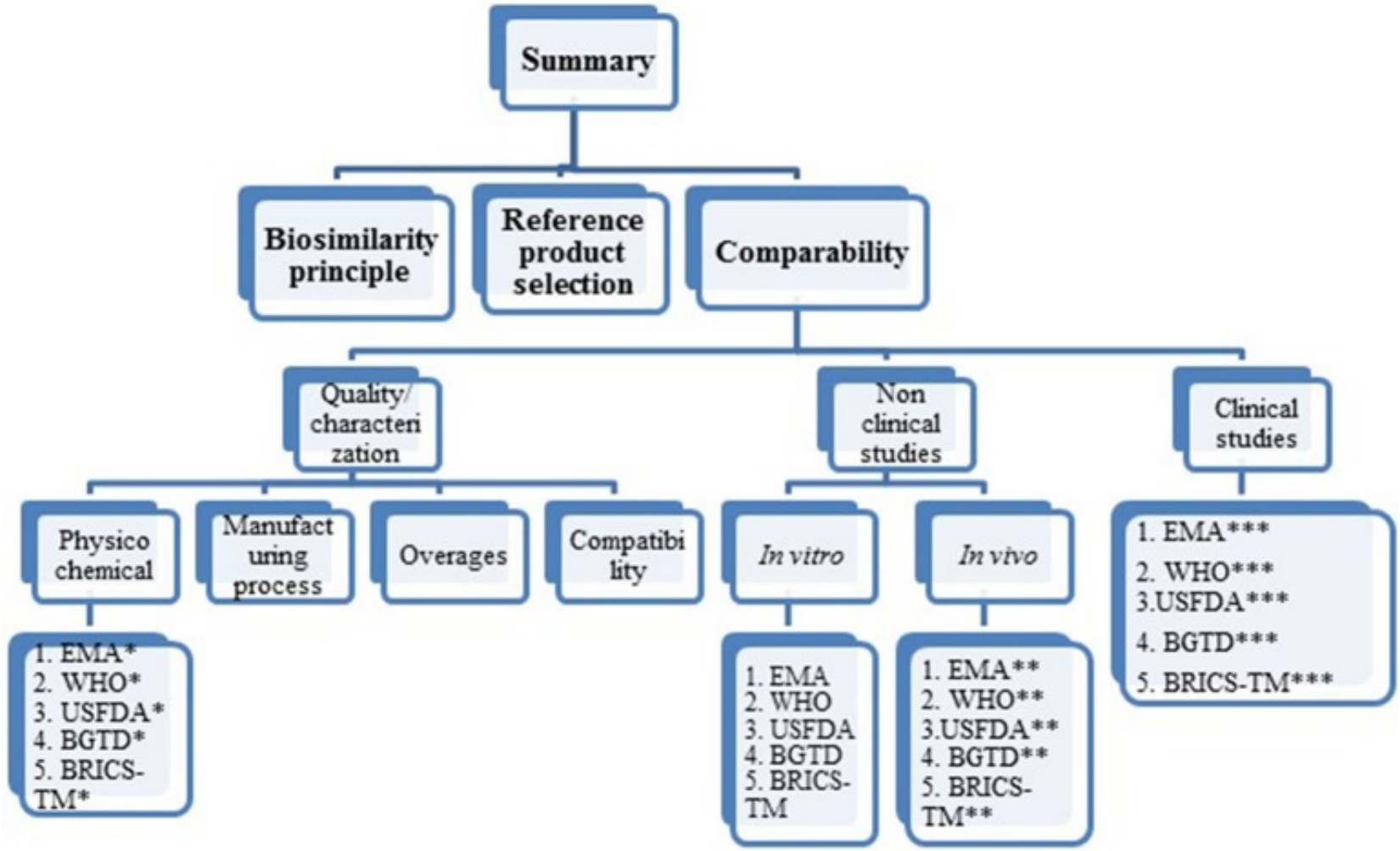
BIOSIMILAR DEVELOPMENT/APPROVAL

- **The pathway for biosimilar development is to demonstrate similarity to the reference product with respect to quality, safety and efficacy using a stepwise approach that includes analytical, nonclinical, and clinical studies.**

Relative data requirements for novel biologics and biosimilars



OVERVIEW OF REGULATORY REQUIREMENTS



BIOSIMILAR DEVELOPMENT PROGRAMME

- **Full chemistry and manufacturing package with extensive structural and functional characterization:**
- (e.g., amino acid sequences), higher order structures, enzymatic post-translational modifications (e.g., glycosylation patterns), other variants (e.g., deamidation or charge variants), and any other intentional modifications (e.g., addition of PEGylation)
- **<u>Using</u>: Highly accurate, sensitive and specific physiochemical and biologic analyses**
- **Establishing similarity at the analytical/functional level forms the basis for a reduced clinical package**

CLINICAL PROGRAMME

➢**The purpose of the clinical comparability exercise is to show similar <u>efficacy, safety and/or immunogenicity to the reference product</u>**

The Comparative exercise includes:

- **COMPARATIVE PK/PD**
- **CLINICAL STUDIES:**

EFFICACY AND SAFETY

IMMUNOGENICITY

Comparative PK and PD Studies

- PK should be comparative and able to detect differences between the biosimilar and the reference product
- Can be done in healthy volunteers
- Single/multiple dose; cross-over or parallel design
- Use same route of administration and same therapeutic dose range as reference
- Should captured: absorption/bioavailability, and elimination characteristics
- Early and ongoing consultation with regulators is encouraged

Comparative PK and PD Studies

- Traditional equivalence range: 80-125 %
- 90% CI for the main parameter

PD Studies:

- Performed in combination with PK studies
- Parameters should be clinically relevant
- Applies principles relevant to equivalence trials

CLINICAL TRIALS

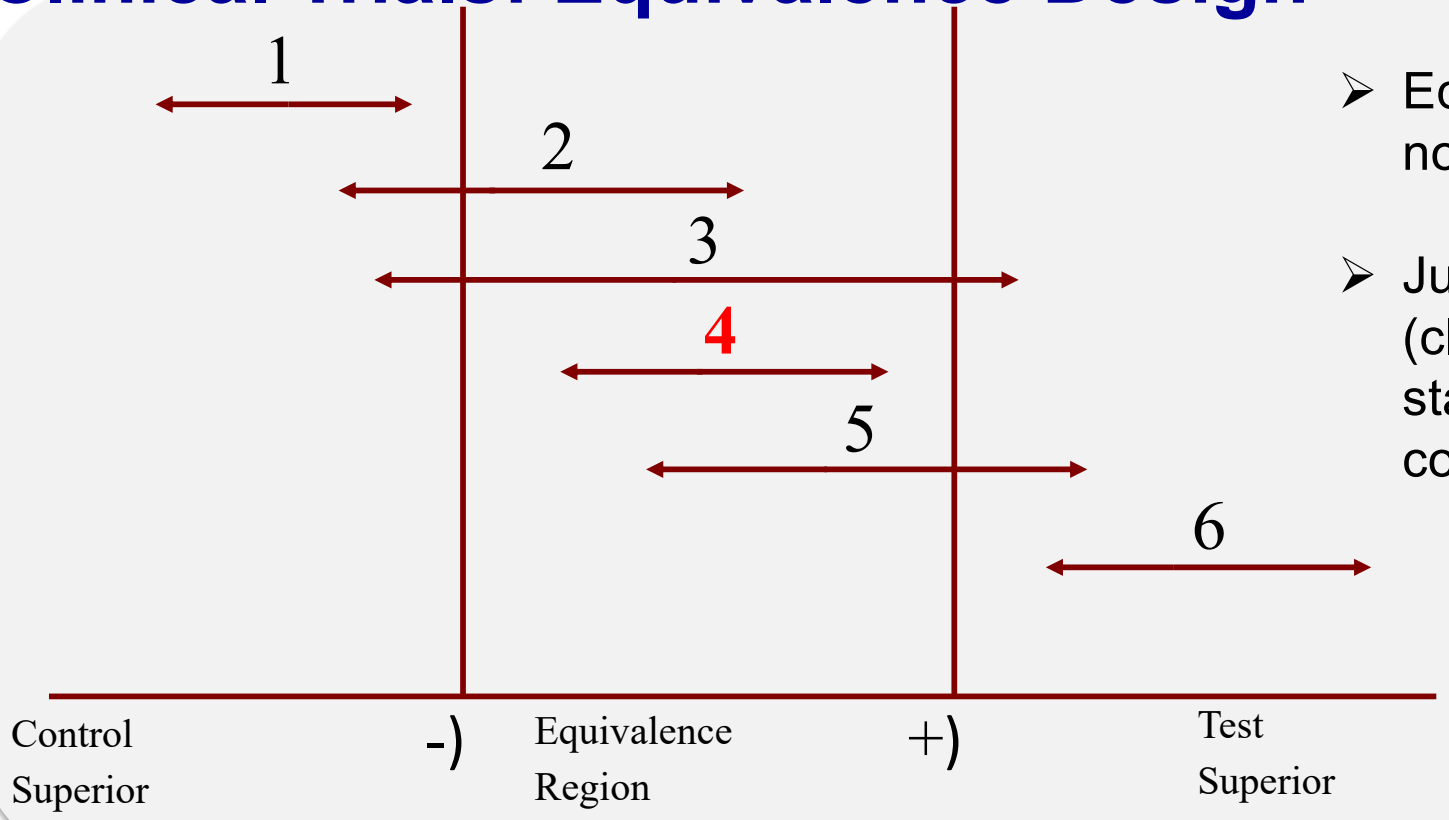
- Usually required to demonstrate similar efficacy, safety and immunogenicity between the biosimilar and the reference
- Phase III for at least one indication
- Confirmatory comparative PK/PD may suffice if :
    - PK/PD of reference are well characterised
    - PD marker is linked to efficacy (one)
    - Relationship of Dose/exposure, relevant PD marker, and response/efficacy of reference is well established.

PD/PD parameters should be pre-defined and justified

Comparative (95% CI)

BIOSIMILARS: CLINICAL DEVELOPMENT PROGRAMME

Clinical Trials: Equivalence Design



- Equivalence over non-inferiority
- Justified margins (clinical and statistical considerations)

ICH E9: A trial with the primary objective of showing that the response to two or more treatments differs by an amount which is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.

CLINICAL TRIALS

- Equivalence margins (two-sided-test) should be pre-specified and based on clinical relevance
- Based on historical data and small enough to detect any difference
- Justified clinical and statistical
- equivalence margin is the largest difference that can be judged as clinically acceptable for the SEB and should be smaller than differences observed in superiority trials of the reference
- General guidance: ICH E9, ICH E10, E6
- Health Canada https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/comparative-bioavailability-standards-formulations-used-systemic-effects.html.

Comparative Clinical Studies Key Considerations

- Equivalence design preferred
- In general, 95%-CI, acceptable equivalence margin
- Randomised, double blind/adequately powered
- Power and sample size sufficient to detect difference
- Dose and route consistent with reference
- Population endpoints and duration are sensitive to detect efficacy and safety differences
- Efficacy must be within the pre-specified margin of equivalence
- Safety: are the incidence and types of ADRs comparable?

Sensitive Clinical Study Population

The comparative clinical study should be conducted in a sufficiently sensitive population that is representative of the authorized indications to detect differences between the biosimilar and the reference.

- A homogeneous population would give a better chance to detect potential differences between a biosimilar and its reference
- Observed clinical effects are the direct action by the biosimilar or the reference without interference of other drugs
- A large body of historical data is available for validation of study outcomes
- Mechanism of action is well-understood and representative
- Large effect size

Sensitive Clinical Study Endpoint

A sensitive study endpoint should be considered to improve the detection of potential differences between the biosimilar and the reference within the sensitive population.

- A study endpoint different from the innovator's original study endpoint(s) may be used, e.g., ORR or PFS as primary endpoint instead of OS in oncology trials for biosimilars.
- A new surrogate or a more sensitive clinical endpoint identified in clinical practice may be acceptable, e.g., assess clinical response before the plateau phase for better sensitivity (time-dependent sensitivity).

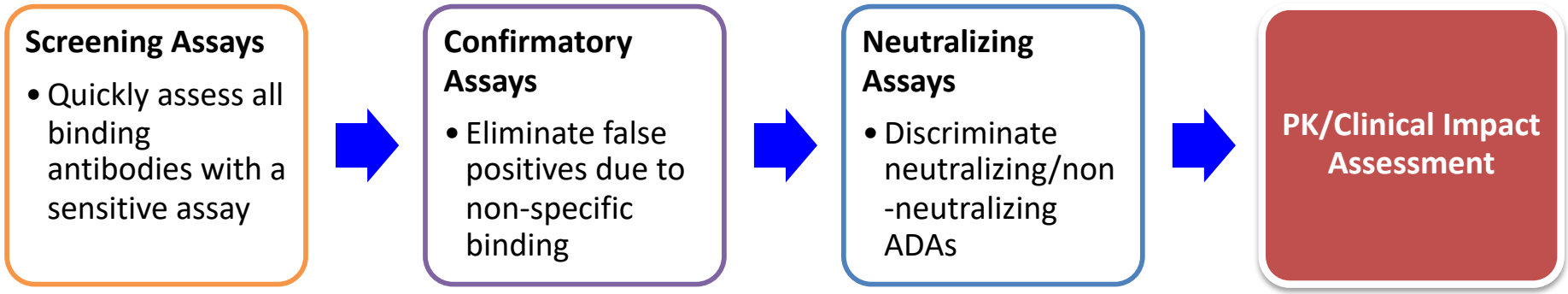
- Pre-specify different endpoints/statistical power in same study for various regulatory requirements.

SAFETY

- Immunogenicity is the most important aspect
- Evaluated in at least one study(more sensitive population)
- Sufficient sample size (>100) and acceptable period of time (at least one year)
- Needs to demonstrate that immunogenicity is not increased compared to innovator
- No change in terms of : concentration , titre, and type
- Use state-of-the- art validated assays (two)
- Most concerning : neutralizing and cross-reactive antibodies
- Assessment on the impact of Abs on the Safety and efficacy

Anti-Drug Antibody (ADA) Formation Is a Key Concern

- Immunogenicity should be compared between the biosimilar and the reference in at least one clinical study that enrolled a sufficient number of patients for a sufficient period of time.
- Immunogenicity assessment strategy:



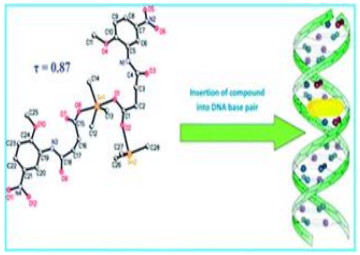
A biosimilar should not be more immunogenic than its reference in terms of ADA incidence or ADA concentration

SAFETY CONTINUED ……

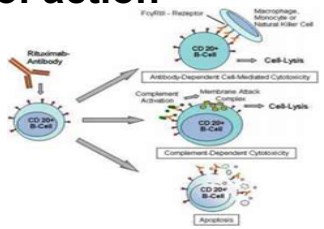
- Nature, severity and frequency of AEs
- Safety assessment taking into account the safety profile of the innovator
- Safety monitoring – post marketing – Risk management plan
- Periodic safety updates
- Serious adverse drug reactions report (15 days)

Consideration for Granting Therapeutic Indications

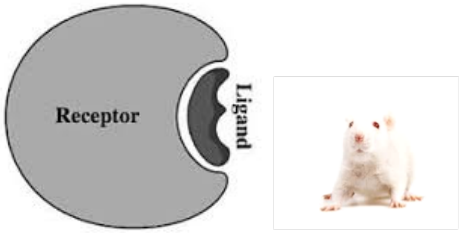
Physicochemical characterization



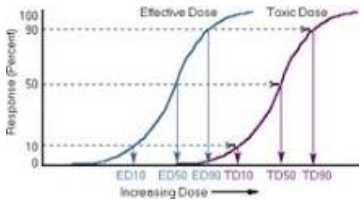
Biological activity/Mechanism of action



Non-clinical studies

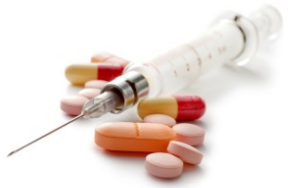


PK/PD Profile



Clinical Trial, Route of Admin & Dosage Range

Monotherapy & Combination Therapy



Biosimilars can receive all indications held by the reference based on the totality of evidence obtained from all comparative analyses.

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Health Canada Santé Canada

Canada

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- ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.
- Guidance Document: Conduct and Analysis of Comparative Bioavailability Studies and Comparative Bioavailability Standards: Formulations used for Systemic Effects
- Guidance Document - Submission of Risk Management Plans and Follow-up Commitments.