

Pre-clinical requirements for combination studies

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WORLD Political Map



1260Km 0 1260 2520 3780 5040Km

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Clinical Trial Approval Process

- New Zealand
 - Standing Committee on Therapeutic Trials (SCOTT)
 - Ethics approval
- Australia
 - CTX: Regulatory review + Ethics approval
 - CTN: Ethics approval only

New Zealand

- SCOTT
 - Advisory to Ministry of Health
 - Adheres mainly to ICH Guidelines

Regulatory Requirements for Combination Studies

	2 marketed drugs	≥ 1 marketed drug + 1 new entity	2 new entities
FDA	Pre-clinical combination study may not be required	Bridging study up to 90 days in one species	90 day bridging study required for combination in most appropriate species
EMA	Pre-clinical combination study not usually required.	Pre-clinical combination studies not required for small scale studies (up to 1 month)	Combination study equivalent to clinical trial duration; Up to 90 days single species
ICH	Not required if adequate clinical co-administration data; Not required for small scale studies (up to 3 months)	Pre-clinical combination studies not required for small scale studies (up to 1 month)	Combination study equivalent to clinical trial duration; Up to 90 days single species

Personal View

Two new entities

Provided there is adequate individual toxicology data

- No overlapping toxicity
- Different mode of action
- No PK interaction

Short term (< 3 months) combination studies can be approved.

Combination studies appropriate safe-guards.

Bridging the Data Gap: From Discovery to Approval HCV Drug Development Overview



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Animal Data to Support Combination Use

- Nonclinical combination studies may not be useful for safety assessment of combination clinical trials
 - Review of nonclinical combination studies did not yield new data when compared to data from single agent studies
 - Nonclinical Safety Evaluation of Drug or Biologic Combinations Guidance suggests dosing animals with agents at a comparable human AUC exposure (basically a PK study, not a toxicity study)

Animal Data to Support Combination Use

- Long term nonclinical studies with each individual agent are preferred over nonclinical combination studies
 - A minimum of 3 months of nonclinical data on each individual agent is needed to support combination dosing up to 90 days in humans depending on toxicology profile
 - Longer term data on individual agents (6 month rodent, 9 month nonrodent) could support longer duration combination clinical trials, depending on the toxicity profile
- Nonclinical combination studies to support clinical trials of any duration with SOC + new direct acting agent not necessary