Assessing the Value of Nonclinical Combination Toxicity Studies for Supporting Development of Combination Products

First survey of its kind to evaluate current practices and rationale for nonclinical combination toxicity across a broad range of therapeutic areas

THE CHALLENGE

Interest in developing combination products to overcome drug resistance and treat complex diseases is growing. However, ambiguity remains around the value of combination toxicity studies to support combination products. A better understanding of current industry practices and rationale for nonclinical combination toxicity studies is needed. The IQ Nonclinical Safety Assessments to Support Development of Combination Products Working Group developed a survey to acquire this understanding. As the pharmaceutical industry's experience with combination products grows, these data will be critical for determining how relevant the nonclinical combination toxicity studies are for informing clinical development of combination products.

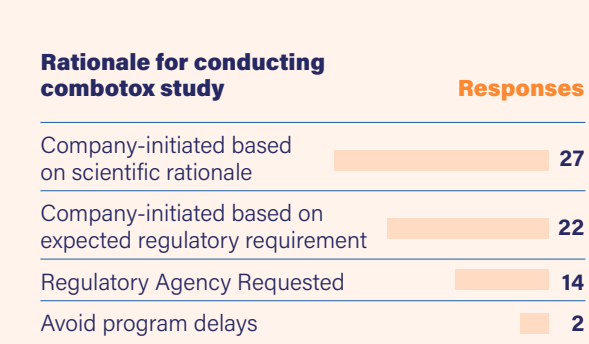
OBJECTIVES & APPROACH

This WG conducted a survey to evaluate industry experience with combination strategies, study designs and impact on clinical development. A survey was developed and distributed to all IQ member companies to evaluate industry experience with combination toxicity strategies, study designs, and their impact on clinical development. Companies were requested to provide information on development programs between 2010 and 2016 where two or more small and/or large molecules were being developed in combination. Drug/device combinations were not in scope.

RESULTS

Twenty companies responded, representing 79 combination programs. A nonclinical combination toxicity study was conducted to support 72% (57 of 79) of the programs. Combination toxicity studies were performed based on scientific rationale (47%; 27 of 57), regulatory agency request (25%; 14 of 57), and/or expected regulatory requirement (39%; 22 of 57). Combination toxicity study designs were varied (e.g., group numbers, dose selection rationale and endpoints assessed) with no evidence that any one study design was superior. Studies were perceived as adding value when they fulfilled a regulatory requirement; avoided potential development delays; or when new or exaggerated toxicity or pharmacokinetic interactions were identified. However, the survey results suggested that the value perceived was very dependent on the perspective of the respondent.

Nonclinical combination toxicology studies should be designed to address safety data gaps such that adequate guidance can be provided to the clinical program and with consideration to the principles of 3Rs. However, results from a relatively small number of the combination toxicity studies (12%; 7 of 57 programs) had an impact on clinical trial design (i.e., modification of clinical dose or dosing regimen, additional monitoring, or addition of a safety biomarker). Results also suggested some respondents conducted such studies to avoid program delays based on the expectation that regulatory agencies would require the study; whereas, proactive dialog with regulatory agencies may have resulted in these studies not being required.



IMPACT

This is the first survey of its kind to interrogate and collate how combination products are being developed from a nonclinical perspective across IQ member companies, and to evaluate the impact of these studies on clinical development across a broad range of therapeutic areas.

While combination toxicity studies can add value, more often than not these studies do not alter clinical development study design. The design of the nonclinical combination toxicity studies, and whether to conduct them, should be based on sound scientific judgement and proactive engagement with regulatory agencies. This may require the pharmaceutical industry and regulatory agencies to develop alternative approaches for more rapid, informal interactions.

To encourage scientists to engage proactively with regulators and more carefully consider when and how combination toxicology studies should be conducted, the Working Group has published the findings, presented at multiple scientific meetings, and held discussions with FDA reviewers, DruSafe, BioSafe, and EFPIA. Results were presented at the 2017 American College of Toxicology annual meeting poster session, published in the Regulatory Toxicology and Pharmacology Journal (*Regul Toxicol Pharmacol* 2019, 102, 40-46), and presented at multiple international scientific associations.

These outcomes provide a framework for determining when a nonclinical combination toxicity study should be conducted, and advocate designing studies to address identified data gaps and/or specific safety concerns associated with the combination. It is anticipated that this research, and the increased interaction with regulatory agencies it supports, will lead to a significant reduction in the number of immaterial studies being conducted that have no relevant impact on clinical development.

The IQ Consortium is a not-for-profit organization of pharmaceutical and biotechnology companies with the mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader R&D community.

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Nonclinical Safety Assessments to Support Development of Combination Products Working Group

This WG conducted a survey to evaluate industry experience with combination strategies, study designs and impact on clinical development. This remains an area of interest as industry and regulatory authorities grapple with determining the design of and need for these studies.

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