



INHALATION CASE STUDY 01

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Covance problem solving saved a client over \$5 million in test article during a chronic inhalation toxicity study in primates.

BACKGROUND

A primary objective of the Covance inhalation studies group is to conduct all studies using the most efficient test article delivery methods available in order to contain and minimize the cost of preclinical product testing to our customers. While aerosol production in the preclinical setting is typically more efficient than can be achieved in the clinic, animal exposure systems are at the same time highly wasteful of test article.

Large animal (dog, minipig or primate) facemask exposure systems highlight this contradiction in that the initially efficient test article generation is offset by combined losses within the delivery system, as a result most of the test article is not usually presented to the animals.

These losses are associated with high aerosol concentrations, airflows that must exceed the minute volume of the species used, dynamic (continuous) aerosol production throughout the respiratory cycle and losses within the delivery piping due to delivery system complexity.

This combination of factors means that a significant proportion of the test article generated does not reach the facemask position or is taken directly to the system exhaust filters. This compares unfavorably with the relatively high proportion of drug substance that is delivered to the respiratory tract by the demand systems that are commonly used by patients in clinical practice.

THE CHALLENGE

The client approached Covance for a chronic toxicity study in a large animal species with a biopharmaceutical that was to be presented clinically as a dry powder generated from capsules using a commercially available inhaler.

Test article consumption in this early work had been significantly greater than had been estimated pre-study, with much of the excess passing directly to exhaust filters.

As the projected cost of continuing the program using facemask methods for the preclinical work was threatening to become the rate limiting factor, the client approached Covance with the challenge of bringing product development back within the available budget.

THE SOLUTION

The Covance aerosol technology and inhalation engineering services groups designed and manufactured a unique, micro-processor controlled oro-pharyngeal delivery system employing powder ejection directly from the client's clinical capsules.

Initial trials confirmed the potential of the concept and subsequent aerosol sampling from the prototype device and mass balance work in vivo showed that upwards of 40% of the test article dispensed from each capsule was delivered. Although satisfactory in terms of the overall percentage delivery, the first prototype was labor intensive to operate, requiring two technicians to dose each animal.

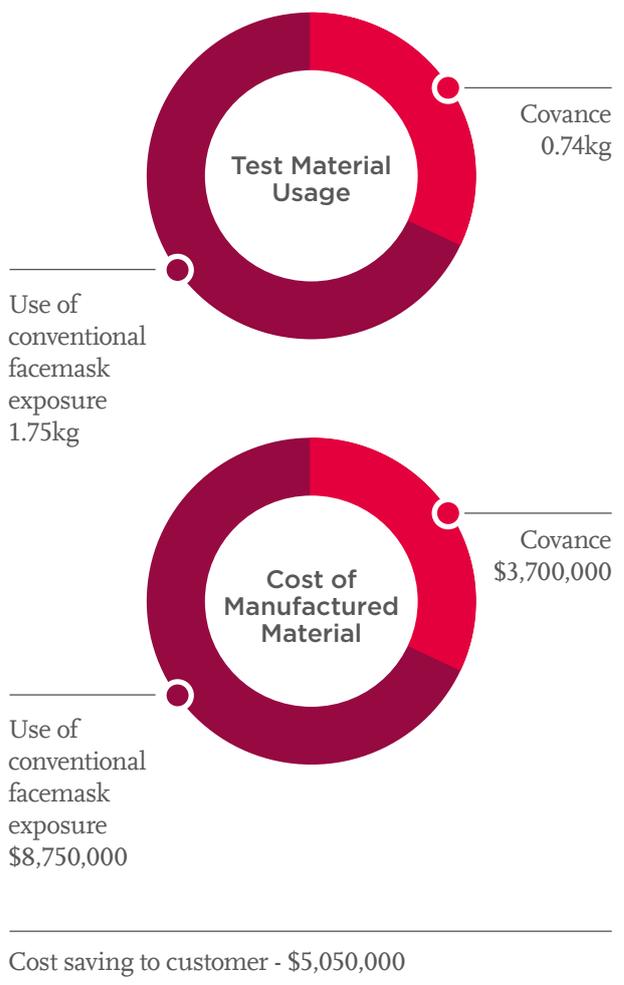
As a consequence the system was further refined and optimized to provide automated sequencing of capsules from a magazine such that the main study exposures could be performed by a single operator thus reducing the cost of the study.

Aerosol delivery efficiency with the final system was greater than 50% of the material dispensed and the preclinical delivery system employed methods that directly mimicked test article delivery in the clinic.

CUSTOMER BENEFITS

The predicted overall test article consumption for delivery using the conventional facemask exposure system was 1.75 kg for the study. Using the Covance designed and built methods the test material requirement was only 0.74 kg. The saving achieved by placing the chronic toxicity study with Covance was 1.01 kg of test article at a manufacturing cost of \$5000 per g.

By using Covance designed equipment and methods the client saved an estimated \$5,050,000 in test article for a single 12 month chronic toxicity study in primates – savings that were substantially greater than the price of the study!



To find out more about how our unique approaches can save you time, money and resources in your development program contact us today

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