INHALATION CASE STUDY 03

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BACKGROUND

A major component of the cost of conducting preclinical studies by the inhalation route can be the amount of test article required, this can be as much as ten fold greater when compared with that required for other routes of administration (such as oral gavage, intraveneous, dietary or dermal).

The high usage of compound in inhalation studies is a consequence of the combination of:

- Continuous delivery of aerosol to the animal breathing zone of delivery systems
- Deposition of material on the internal surfaces of exposure systems
- Low respirable aerosol generation efficiencies in some instances with a high proportion of test article aerosol passing directly through the exposure systems to collect on the exhaust filters

The industry average generation efficiency (the amount of test article delivered to the animals compared with the amount used) for a standard rodent inhalation exposure system is approximately 40%.

This means that 60% of the manufactured test article that is aerosolised is not delivered to the animals and is typically drawn directly to waste.

THE CHALLENGE

Our customer approached Covance with the specific challenge to reduce the amount of test article by >50% of what is traditionally required for a standard 28 day rodent inhalation toxicity study. In this instance test article costs were a key consideration in the overall project budget.

It is an industry standard practice to consider wastage in any test article usage calculation and also to ensure reserve powder compound containers are available in case of problems encountered during the study. Typically 8-10g of the contents of each powder generation system reservoir is unusable due to the design limitations of commercially available units.

If a standard three dose group study uses one powder reservoir per group and a further two containers are prepared as a contingency in case of problems, as much as 50g of unusable compound may be retained in the combined dead volume of the reservoirs.

THE SOLUTION

Minimisation of test article consumption in this customer's program was achieved by multiple initiatives. As a first step the 'unusable packed powder' issue was addressed by modification of the selected dust generator powder reservoirs.

After liaising with our in house Inhalation Engineering Services team a much shorter reservoir was designed and manufactured which reduced the unusable powder depth from 8mm to 1mm, whilst still maintaining reliable test article delivery. In parallel with reduction in dead space losses, the standard test article overage and operating airflows which are usually applied to inhalation studies were also substantially reduced.

The second element challenged the industry accepted notion of test article generation efficiency. Again we utilised the experience and expertise of Covance's inhalation engineering group.

Through a structured development process it was possible to increase the generation efficiency of a standard flow through inhalation exposure system to between 60% and as high as 90% for all groups.

This was accomplished by the design and manufacturing of an aerodynamically efficient sealed cylinder positioned inside the main body of the exposure chamber. This decreased the internal volume by over half and redirected the aerosol flow towards the breathing zone of the animals.

This innovation permitted a reduction in the delivered airflow by over half whilst both maintaining the necessary air supply to the animals and retaining the original system equilibration time.

CUSTOMER BENEFITS

Covance reduced the standard requirement of test article for a three dose group, 28 day rodent powder study to a third of the typical amount - saving the customer approximately £500,000 (approx. $750,000).

Covance's proactive approach in developing theoretical and practical solutions meant the customer's studies were successfully completed with no costly delays.

The reduction in test article requirement had a significant cost saving implication for the customer and, in conjunction with similar initiatives for the large animal studies in the program, prevented test article availability from becoming a rate limiting factor in the compound's development.

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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