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Nonclinical Vehicle Use in Studies by Multiple Routes in Multiple Species

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The laboratory toxicologist is frequently faced with the challenge of selecting appropriate vehicles or developing utilitarian formulations for use in in vivo nonclinical safety assessment studies. Although there are many vehicles available that may meet physical and chemical requirements for chemical or pharmaceutical formulation, there are wide differences in species and route of administration specific to tolerances to these vehicles. In current practice, these differences are largely approached on a basis of individual experience as there is only scattered literature on individual vehicles and no comprehensive treatment or information source. This approach leads to excessive animal use and unplanned delays in testing and development. To address this need, a consulting firm and three contract research organizations conducted a rigorous data mining operation of control (vehicle) data from studies dating from 1991 to present. The results identified 65 single component vehicles used in 368 studies across multiple species (dog, primate, rat, mouse, rabbit, guinea pig, minipig, chick embryo, and cat) by multiple routes. Reported here are the results of this effort, including maximum tolerated use levels by species, route, and duration of study, with accompanying dose limiting toxicity. Also included are basic chemical information and a review of available literature on each vehicle, as well as guidance on volume limits and pH by route and some basic guidance on nonclinical formulation development.

Keywords Animals, Nonclinical Studies, Routes, Safety, Species, Vehicles

Formulation, even at the rudimentary level employed for initial studies used to evaluate the safety of new drug candidates, is perhaps the weakest link in both pharmacology and toxicology for drugs and industrial and agricultural chemicals.

In the preclinical safety assessment of potential new drugs, it is required that the material of interest must be suitably formulated in a manner that allows adequate administration of the test substance, with little or no effects in test animals that is attributable to the vehicles used in producing such a formulation. The formulation must be suitable for the intended route of administration, maintain the stability of the active ingredient, and preferably maximize the systemic bioavailability of the drug. Occasionally, the vehicle(s) or formulation is specified by the sponsor of a study, but more frequently is the informed choice of the laboratory conducting specified safety studies.

Because the process of vehicle selection has been mostly one of custom or personal choice, there are many vehicles which have seen use in preclinical formulation. However, results as to their suitability, utility, and limitations on their use are not generally reflected in the literature or taught in any formal manner. Certainly such information is not attainable in any readily available place. This paper is intended to at least begin to fill this gap.

General Preclinical Formulation Principles

Dosing formulations for preclinical studies should be selected with consideration of a number of desirable characteristics as summarized in Table 1 (Gad 1994; Gad and Chengelis 1997).

Animal use and care guidance provides limits to volumes that may most commonly be administered by each of the common routes. These limits are presented in Table 2 (Gad 1994; Gad and Chengelis 1997).

To provide information to all those who in the future must select suitable vehicles for formulation for nonclinical dosing of animals, a data mining operation was undertaken.

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TABLE 1
Desirable characteristics of a dosing formulation and its preparation

Preparation of the formulation should not involve heating of the test material to a point anywhere near altering its chemical or physical characteristics, or so as to harm test animals receiving the formulation.
If the material is a solid and is to be assessed for dermal effects, its shape and particle size should be preserved. If intended for use in man, topical studies should be conducted with the closest possible formulation to that to be used on humans.
Multicomponent test materials (mixtures) should be formulated so that the administered form accurately represents the original mixture (i.e., components should not be selectively suspended or taken into solution).
Formulation should preserve the chemical stability and identity of the test material.
The formulation should be such as to minimize total administered test volumes. Use just enough solvent or vehicle unless there is reason to dilute the active ingredient.
The formulation should be as easy as possible to accurately administer. Highly viscous solutions or suspensions should be avoided.
The pH of dosing formulations should be between 5 and 9, if possible.
Acids or bases should not be used to dilute or solubilize (for both humane reasons and to avoid pH partitioning or stability issues in either the gut or the renal tubule) the test material.
If a parenteral route is to be employed, final solutions should be as nearly isotonic as possible. Do not assume a solution will remain such upon injection into the blood stream. It is usually a good idea to verify that the drug stays in solution upon injection by placing some drops into plasma.
Formulations for use by parenteral routes should be as endotoxin free as possible. Particularly if the test material (or formulation component) is biologically derived or produced, they should be evaluated for acceptable endotoxin content before actual formulation preparation to preclude problems.
Particularly if use is to be more than a single injection, steps (such as filtration) should be taken to ensure suitable sterility.

Gad 1994; Gad and Chengelis 1997.

METHODS

Four separate organizations undertook a review of their files to identify and collect data on control vehicles they had used in studies over the previous 15 years (1991 to present). Each in vivo study conducted during this period had its vehicle control group evaluated. If the vehicle was other than water, the highest no-observable-adverse-effect level (NOAEL) for the vehicle formulation used was determined and this was added to the database. Extracted in this manner by the participating organizations (Calvert, CIT, Gad Consulting Services [GCS], and MPI) were the maximum nontoxic volume identified in these reviewed studies by species, route, and duration. The nature of any dose limiting toxicity for a vehicle or vehicle combination was also identified. The number of single-vehicle formulations disclosed, as reflected in the body of this paper, was large, with more than 60 different formulations being reported here. There were also a number of combinations that are not included in this paper.

TABLE 2
General guidelines for maximum dose volumes by route

Route	Volume should not exceed	Notes
Oral	20 ml/kg	Fasted animals
Dermal	2 ml/kg	Limit in accuracy of dosing/available body surface
Intravenous	1 ml/kg	Over 5 min
Intramuscular	0.5 ml/kg	At any one site
Perocular	0.01 ml	Per eye
Rectal	0.5 ml/kg	
Vaginal	0.2 ml in rat; 1 ml in rabbit	
Inhalation	2 mg/L	
Nasal	0.1 ml/nostril in monkey or dog	

Gad 1994; Gad and Chengelis 1997.

GCS then assembled the provided data into the tables presented here, with materials listed in alphabetic order (but with these tables also indexed in Table 69). Table 69 also provides basic physical chemical data and general toxicity references on these vehicles.

The actual acceptable vehicle usage data is presented in Tables 3 to 68, with a single vehicle being presented per

TABLE 3
Acacia

	Route	Duration	Dose	Comments
Rat	Oral	30 days	500 mg/kg	Well tolerated
		90 days	10 ml/kg	As 20% of formulation; well tolerated
Primate	Oral	90 days	100 mg/kg	Well tolerated, but with some reduction in food intake

TABLE 4
Acetate Sodium

	Route	Duration	Dose	Comments
Rat	Intravenous	1 month	1 ml/kg	Well tolerated as 5 mM solution in saline

TABLE 5
Acetic Acid

	Route	Duration	Dose	Comments
Rat	Oral	90 days	5 ml/kg	Well tolerated (gavage) 3% solution
		1 month	10 ml/kg	Well tolerated, 20% solution
	Intravenous	1 month	as pH buffer	Well tolerated
Mouse	Oral	90 days	5 ml/kg	Well tolerated (gavage) 3% solution

TABLE 6
Acetone (2-Propanone)

	Route	Duration	Dose	Comments
Rat	Oral	2 weeks	5 ml/kg	Higher doses cause acidosis. Transitory neurobehavorial effects at this dose
	Dermal	30 days	5 ml/kg	Well tolerated
Mouse	Oral	2 weeks	3 ml/kg	Higher doses cause acidosis. Transitory neurobehavorial effects at this dose
	Dermal	2 years	0.5 ml	Well tolerated
Guinea pig	Dermal	1 month	1 ml	Well tolerated
Rabbit	Dermal	90 days	1 ml	Defatting of application site

TABLE 7
Alginic Acid

	Route	Duration	Dose	Comments
Rat	Intraperitoneal	1 month	100 mg/kg	Well tolerated

TABLE 8
Anecortave Acetate

	Route	Duration	Dose	Comments
Rat	Subcutaneous	4 doses	2 ml/kg	Well tolerated

TABLE 9
Benzoic Acid

	Route	Duration	Dose	Comments
Rat	Oral	N/A	100 mg	Well tolerated

table and arranged in alphabetical order according to common name.

Subsequent to the publication of this article, GCS will post this data to a website (www.gadconsulting.com), with a mechanism to submit additional vehicle data. GCS is committed

TABLE 11
Canola Oil

	Route	Duration	Dose	Comments
Dog	Oral	1 month	2 ml/kg	Well tolerated

TABLE 12
Capryol 90

	Route	Duration	Dose	Comments
Dog	Oral	28 days	1000 mg/kg	Well tolerated
		28 days	2500 mg/kg	Well tolerated
Rat	Oral	Acute		Well tolerated; $LD_{50} > 5$ g/kg
		28 days	500, 1500, 2500 mg/kg	NOAEL of 2500 mg/kg
		7 days	300, 1000, 2500 mg/kg	Well tolerated
Rabbit	Cutaneous	Acute	No dilution	Mildly irritant
	Ocular	Acute	No dilution	Moderately irritant

TABLE 10
Beta-cyclodextrin

	Route	Duration	Dose	Comments
Rat	Oral	12 months	500 g/kg	Hepatitis, nephrosis, acute tubular necrosis at dose levels above 20 g/kg
	Intravenous			Tubular hypertrophy at doses above 100 mg/kg/day at 3 months or longer
Primate	Oral	12 months		Tubular hypertrophy at doses above 100 mg/kg/day at 3 months or longer

TABLE 13
Captisol

	Route	Duration	Dose	Comments
Rat	Oral	1 month	10 ml/kg	12% solution, well tolerated
	Intravenous	1 month	4 ml/kg	12% solution, well tolerated
Primate	Oral	9 months	1 g/kg	10% solution, well tolerated
	Subcutaneous	12 months, with 3 weekly administrations	120 mg/kg	Well tolerated
Mouse	Oral	1 month	500 mg/kg	10% solution, well tolerated
	Subcutaneous	6 month	1200 mg/kg	NOAEL
		90 day	1200 mg/kg	NOEL

TABLE 14
Carboxymethyl Cellulose (CMC)

	Route	Duration	Dose	Comments
Primate	Oral	30 days	5% in water	Well tolerated
	Subcutaneous	Acute	10 ml/kg	Well tolerated
Rat	Oral	1 year	5% in water	Well tolerated

TABLE 15
Carboxymethyl Cellulose Calcium

	Route	Duration	Dose	Comments
Dog	Oral	90 days	1 ml/kg	Well tolerated; 1% solution

TABLE 16
Carboxymethyl Cellulose Sodium

	Route	Duration	Dose	Comments
Rabbit	Oral	1 month	.5 ml/kg	Well tolerated; 1% solution

TABLE 17
Cetyl Alcohol

	Route	Duration	Dose	Comments
Mouse	Intraperitoneal	1 month	100 mg/kg	Well tolerated

TABLE 18
Citrate Buffer

	Route	Duration	Dose	Comments
Dog	Intravenous	8 doses	30 ml/kg/day	Well tolerated
	Subcutaneous	30 days	10 ml/kg/day	Well tolerated
Rat	Oral	2 weeks	15 ml/kg	Well tolerated (50 mM)
		2 weeks	10 ml/kg	Well tolerated (50 mM)

TABLE 19
Citric Acid Buffer

	Route	Duration	Dose	Comments
Rat	Oral	2 weeks	15 ml/kg	Well tolerated (50 mM)
		2 weeks	10 ml/kg	Well tolerated (50 mM)

TABLE 20
Collagen Matrix

	Route	Duration	Dose	Comments
Primate	Implantation in humerus bone	6 months	Two strips/site (humerus right and left)	Well tolerated
Rabbit	Implantation	6 months	Single application, 5 ml/kg	Well tolerated

TABLE 21
Corn Oil

	Route	Duration	Dose	Comments
Dog	Oral	1 month	3.0 ml/kg	Well tolerated
Rat	Oral	20 doses	5 ml/kg	Well tolerated
		1 dose	10 ml/kg	Well tolerated
Mouse	Oral	1 month	2.5 ml/kg	Well tolerated
Rabbit	Oral	1 month	1 ml/kg	Well tolerated
Chick embryo	Oral	Once	.1 μl/g	Less mortality than 1.0 μl/g egg
	Injection into egg	Once	1 μl/g	Increase in mortality, decreased activity during rightig reflex, running time, visual discrimination, and olfactory aversion test

TABLE 22
Cremophore EL

	Route	Duration	Dose	Comments
Dog	Intravenous	1 month	2 ml/kg	Well tolerated
Rat	Oral	1 month	100 mg/kg	Well tolerated

TABLE 23
Cyclohexane

	Route	Duration	Dose	Comments
Rat	Oral	4 weeks	5 ml/kg/day	Clinical signs: intermittent convulsive after dosing, piloerection round back and emaciated appearance
	Dermal	30 days	1 ml/kg/day	Well tolerated
Rabbit	Oral	30 days	0.5 ml/kg/day	Well tolerated

TABLE 24
D-Glucose Anhydrous 30%/PEG 70% (v/v)

	Route	Duration	Dose	Comments
Dog	Oral	2 weeks	0.32 ml/kg	Well tolerated
	Intravenous	2 weeks	Bolus 0.24–0.33 ml/kg infusion 0.08–0.11 ml/kg/h	Well tolerated
Rat	Intravenous	3 weeks	Bolus 0.8–1.07 ml/kg infusion 0.266–0.356 ml/kg intravenous injection (into tail vein), followed by an intravenous injection for 6 h	Well tolerated

TABLE 25
Dextrose (0.5%)

	Route	Duration	Dose	Comments
Dog	Intravenous	90 days	150 ml/h	Well tolerated
Rat	Intravenous	1 dose	1.4 ml/animal	Well tolerated

TABLE 26
Diethyleneglycol Monoethyl Ether

	Route	Duration	Dose	Comments
Primate	Intravenous	1 month	.355 ml/kg	Well tolerated

TABLE 27
DMSO

	Route	Duration	Dose	Comments
Dog	Intravenous	1 month	1.25 ml/kg	Well tolerated
Rat	Oral	7 days	5 ml/kg	Well tolerated
		4 weeks	5 ml/kg	Well tolerated
	Intravenous	1 month	200 mg/kg	Well tolerated
	Intraperitoneal	1 month	5 ml/kg	Well tolerated
Guinea pig	Intravenous	1 month	.1 ml/kg	Well tolerated
Primate	Oral	Efficacity	3 ml/kg/day	Well tolerated
Mouse	Oral	4 weeks	5 ml/kg	Well tolerated
	Intraperitoneal	1 month	100 mg/kg	Well tolerated
		3 days	10 ml/kg	Well tolerated
Rabbit	Subcutaneous	1 month	1 ml/kg	Erythema, inflammation

TABLE 28
Dulbecco's Modified PBS

	Route	Duration	Dose	Comments
Rat	Oral	4 weeks	.1, .8, and 1.2 mg/kg	Well tolerated
	Intravenous	1 month	1 ml/kg/day	Well tolerated

TABLE 29
Ethanol

	Route	Duration	Dose	Comments
Dog	Oral	6 months	400 ml/kg	Hepatopathy, myopathy, CNS changes
		90 days	5 ml/kg	5% solution; Well tolerated
		1 month	5 ml/kg	7.5% solution; Well tolerated
	Intravenous	Once	1 ml/kg	30% solution; CNS depression, ataxia
Rat	Oral		5 ml/kg	Depression
		1 month	175 g/kg	Depression, decreased RBC
		12 months	1000 mg/kg	Fatty liver
		7 days	10 ml/kg	10% solution; Well tolerated
		4 weeks	2 ml/kg	70% solution; hypokinesia, dyspnea regurgitation, distended lungs/ileum and swollen abdomen
		90 days	8 ml/kg	10% solution; well tolerated
	Intravenous	12 months	250 g/kg	Nephrosis, ATN, bladder changes, weight loss
Primate	Oral	9 months	250 mg/kg	Behavioral changes
Mouse	Oral	6 months	2500 mg/kg	Well tolerated
		1 month	2.5 ml/kg	5% solution; well tolerated
	Intraperitoneal	Acute	5 ml/kg	5% solution; well tolerated
	Cutaneous	13 weeks	100 μl/animal/day	70% solution; well tolerated

TABLE 30
Gelucire 44/14

	Route	Duration	Dose	Comments
Rabbit	Cutaneous	Acute	0.5 ml	Not irritant
	Ocular	Acute	0.1 ml	Slight irritant
Rat	Oral	28 days	600, 1500, 2400 mg/kg/day	NOEL: 2400 mg/kg/day
		7 days	600, 1500, 2400 mg/kg/day	NOEL: 2400 mg/kg/day
		Acute	No dilution	LD_{50}: >2004 mg/kg/day
Dog	Oral	3 months	400, 1000, 2500 mg/kg/day	NOAEL: >2500 mg/kg/day
		14 days	400, 1000, 2500 mg/kg/day	

TABLE 31
Glucose

	Route	Duration	Dose	Comments
Dog	Oral	ADME	2/10 ml/kg/day	5% solution; well tolerated
Rat	Oral	26 weeks	.71–8.6 ml/kg	10% solution; well tolerated
		Prelim	5 ml/kg	5% solution; well tolerated
	Subcutaneous	2 weeks	.75 ml/kg	5% solution; well tolerated
Primate	Oral	13 weeks	.78–9.3 ml/kg	10% solution; well tolerated
		ADME Card. Vas.	5 ml/kg	5% solution; well tolerated

TABLE 32
Glycerol

	Route	Duration	Dose	Comments
Rat	Oral		1000 mg/kg	Well tolerated
		1 month	15 g/kg	Reduced adrenal weights
		1 month	1000 mg/kg	Well tolerated
	Subcutaneous		10 mg/kg	Well tolerated
Guinea pig	Oral	1 month	500 mg/kg	Well tolerated
Mouse	Oral	90 days	500 mg/kg	Depression and reduced respiration
	Intravenous	1 month	100 mg/kg	Well tolerated
	Subcutaneous	Acute	10 mg/kg	Well tolerated
	Intraperitoneal	1 month	250 mg/kg	Well tolerated
Rabbit	Intravenous		10 mg/kg	Well tolerated

to updating and maintaining such a free access website database for at least the next 5 years, through 2011.

Formulation for drugs, and in a less sophisticated manner, all test materials for evaluation in intact animal systems (whether done for efficacy/pharmacology testing or for toxicology) is a field of expertise of its own. Although there are a few books on formulation of human drugs (Racz 1989, for example), no such volume known to the authors exist for preclinical formulations.

Although the development of pharmaceutical formulations for marketed clinical products is done in a rigorous manner, what is employed for nonclinical testing is much more pragmatic. The reader is referred to Racz (1989), Yalkowsky (1999), and Weiner and Kotkoskie (1999) for more detail than is offered here as to the principles of vehicle and formulation component selection.

TABLE 33
Gum Tragacanth

	Route	Duration	Dose	Comments
Mouse	Oral	2 weeks	10 ml/kg	.5% solution; well tolerated

TABLE 34
Hydroxypropyl Beta-cyclodextrin

	Route	Duration	Dose	Comments
Dog	Intravenous	1 month	10 ml/kg	40% solution; well tolerated
Rat	Intravenous	1 month	10 ml/kg	40% solution; well tolerated

TABLE 35
Hydroxypropyl Cellulose

	Route	Duration	Dose	Comments
Rat	Oral	90 days	1000 mg/kg	Well tolerated

TABLE 36
Hydroxypropyl Methylcellulose

	Route	Duration	Dose	Comments
Dog	Intraperitoneal	28 days	200 mg/kg	Well tolerated
Rat	Oral	1 dose	10 ml/kg	.2%; well tolerated
		1 dose	10 ml/kg	.5%; well tolerated
			10 ml/kg	.5%; well tolerated
	Intraperitoneal	1 dose	5 ml/kg	.5%; well tolerated
Mouse	Oral	10 doses	10 ml/kg	.2%; well tolerated
		1 dose	10 ml/kg	.5%; well tolerated
	Intraperitoneal	Acute	50 mg/kg	Well tolerated
		Acute	5 ml/kg	.5%; well tolerated

TABLE 37
Isopropyl Alcohol

	Route	Duration	Dose	Comments
Rabbit	Dermal	1 month	1000 mg/kg	Well tolerated

TABLE 38
Isopropyl Myristate

	Route	Duration	Dose	Comments
Rabbit	Dermal	1 month	500 mg/kg	Well tolerated

TABLE 39
Labrafil MI944

	Route	Duration	Dose	Comments
Dog	Oral	1 month	2 mg/kg	Well tolerated

TABLE 40
Labrasol

	Route	Duration	Dose	Comments
Rat	Oral	Acute	20, 22.4, 25.1, 28.21 and 31.60 g/kg	LD_{50} = 22 g/kg; nontoxic
		ADME	10, 150 mg/kg/day	
		Segment II: embryofetal development	1000, 2000, or 3000 mg/kg/day	NOEL: 3000 mg/kg/day with no indication of a teratogenicity
		14 days	100, 300, 1000, 3000 mg/kg/day	NOAEL: 3000 mg/kg/day
		6 months	300, 1000, and 3000 mg/kg/day	NOEL: 300 mg/kg/day; NOAEL: 3000 mg/kg/day
	Intravenous	28 days	10 mg/kg/day	
	Cutaneous	Patch test	.02 ml/animal	Well tolerated
		Acute		Very well tolerated
	Ocular			Slight irritant
Dog	Oral	13 weeks	0, 300, 1000, and 3000 mg/kg/day	NOEL: 1000 mg/kg/day; NOAEL: 3000 mg/kg/day
		14 days	100, 300, 1000, and 3000 mg/kg/day	In high-dose group, moderate suppurative inflammation of the lungs. No adverse affects on survival and clinical observations
		3 months	300, 1000, 3000 mg/kg/day	NOEL: 1000 mg/kg/day; NOAEL: 3000 mg/kg/day
Rabbit	Cutaneous	Patch test	0.5 ml	Well tolerated
	Ocular	Acute	0.1 ml	Slight irritant

TABLE 41
Lactose

	Route	Duration	Dose	Comments
Primate	Inhalation	2 weeks	1 L/min/animal	Well tolerated

TABLE 42
Lanolin

	Route	Duration	Dose	Comments
Rabbit	Dermal	90 days	1000 mg/kg	Well tolerated

TABLE 43
L-Ascorbic Acid

	Route	Duration	Dose	Comments
Rat	Oral	90 days	500 mg/kg	Hematologic changes, weight loss

TABLE 44
Lauroglycol

	Route	Duration	Dose	Comments
Rabbit	Cutaneous	Acute	No dilution	Moderately irritant
	Ocular	Acute	No dilution	Slightly irritant
Rat	Oral	Acute		LD_{50}: >2003 mg/kg/day

TABLE 45
Maltitol Solution

	Route	Duration	Dose	Comments
Rat	Intraperitoneal	1 month	500 mg/kg	Well tolerated

TABLE 46
Maltol

	Route	Duration	Dose	Comments
Guinea pig	Oral	1 month	75 mg/kg	Well tolerated
Rabbit	Oral	1 month	100 mg/kg	Well tolerated

TABLE 47
Mannitol

	Route	Duration	Dose	Comments
Primate	Oral	2 months	10 ml/kg	Well tolerated

TABLE 48
Methyl Cellulose

	Route	Duration	Dose	Comments
Rat	Oral	1 month	10 ml/kg	.5%; well tolerated
		1 month	5 ml/kg	.5%; well tolerated
		14 doses	10 ml/kg	1%; well tolerated
		1 dose	10 ml/kg	2%; well tolerated
Guinea pig	Oral	12 doses	4 ml/kg	.5%; well tolerated
Primate	Oral	1 month	10 ml/kg	.1%; well tolerated
		1 month	10 ml/kg	.5%; well tolerated
		2 weeks	5 ml/kg	.5%; well tolerated
		1 month	5 ml/kg	1%; well tolerated
Mouse	Oral	90 days	10 ml/kg	.5%; well tolerated
Rabbit	Oral	1 month	4 ml/kg	.5%; well tolerated
Dog	Oral	2 weeks	10 ml/kg	.5%; well tolerated

TABLE 49
Mineral Oil

	Route	Duration	Dose	Comments
Rat	Oral	1 month	5 ml/kg	Well tolerated
Mouse	Oral	1 month	250 mg/kg	Well tolerated
Dog	Oral	1 month	2.5 ml/kg	Well tolerated

TABLE 50
PBS (Phosphate-Buffered Saline)

	Route	Duration	Dose	Comments
Rat	Oral	1 month	10 ml/kg	Well tolerated
	Intravenous	1 dose	1 ml/kg	Well tolerated
	Subcutaneous	1 month	1 ml/kg	Well tolerated
	Slow bolus	11 doses	1 ml/kg	Well tolerated
Mouse	Subcutaneous	6 month	10 ml/kg	Well tolerated
Primate	Oral	2 weeks	10 ml/kg	Well tolerated
		2 weeks	1.6 ml/kg	Well tolerated
	Subcutaneous	1 week	.2 ml/kg	Well tolerated
		9 months	1 ml/kg	Well tolerated

TABLE 51
Peanut Oil

	Route	Duration	Dose	Comments
Rat	Oral	1 month	10 g/kg	Well tolerated
		12 months	10 g/kg	Well tolerated
		90 days	10 g/kg	Well tolerated

TABLE 52
PEG 300

	Route	Duration	Dose	Comments
Guinea pig	Intravenous	1 month	1 ml/kg	Well tolerated
Mouse	Oral	ADME	10 ml/kg/day	Well tolerated
Rabbit	Oral	1 month	500 mg/kg	Well tolerated

TABLE 53
PEG 400

	Route	Duration	Dose	Comments
Guinea pig	Oral	1 month	1000 mg/kg	Well tolerated
Mouse	Oral	4 weeks	10 ml/kg/day	Well tolerated
	Intraperitoneal	1 month	500 mg/kg	Well tolerated
		3 days	10 ml/kg	35%; well tolerated
		1 month	2.5 ml/kg	40%; well tolerated
Rat	Oral	10 doses	1.67 mg/kg	Well tolerated
		1 dose	2 ml/kg	Well tolerated
		1 dose	5 ml/kg	Well tolerated
		4 weeks	5 ml/kg/day	Well tolerated
		1 month	5 ml/kg	Well tolerated
	Intravenous	1 dose	.5 ml/kg	Well tolerated
		4 weeks	0.5 ml/kg	Well tolerated
	Intraperitoneal	1 month	5 ml/kg	35%; well tolerated
	Cutaneous	13 weeks	2.5 ml/kg	Well tolerated
		104 weeks	2.5 ml/kg	Well tolerated
Minipig	Cutaneous	2 weeks	2.5 ml/kg	Well tolerated

TABLE 54
Petrolatum

	Route	Duration	Dose	Comments
Rabbit	Dermal	1 month	1 mg/kg	Well tolerated

TABLE 55
Poloxamer

	Route	Duration	Dose	Comments
Rat	Oral	1 month	10 ml/kg	7.5%; well tolerated
Mouse	Oral	1 month	10 ml/kg	Well tolerated

TABLE 56
Povidone

	Route	Duration	Dose	Comments
Rat	Intramuscular	90 days	1 ml/kg	1%; well tolerated

TABLE 57
Propylene Glycol

	Route	Duration	Dose	Comments
Rat	Oral	1 month	2.5 ml/kg	Well tolerated
		2 weeks	2 ml/kg	Well tolerated
	Subcutaneous	4 weeks	2.5 ml/kg	Well tolerated
Minipig	Cutaneous	26 weeks	2.5 ml/kg	Well tolerated
Mouse	Oral	1 month	10 ml/kg	50%; well tolerated
	Intraperitoneal	1 month	2.5 ml/kg	40%; well tolerated
Dog	Oral	1 month	2.5 ml/kg	Well tolerated
		Prelim	2 ml/kg	Well tolerated

TABLE 58
Rameb 7.5%

	Route	Duration	Dose	Comments
Primate	Intranasal	1 month, 3 doses per day	82.8 mg/ml (with treatment) 74.7 mg/ml (as placebo)	Well tolerated

TABLE 59
Sesame Oil

	Route	Duration	Dose	Comments
Rat	Oral	1 month	1 ml/kg	Well tolerated
Mouse	Oral	1 month	.25 ml/kg	Well tolerated
Rabbit	Oral	1 month	.5 ml/kg	Well tolerated
Dog	Oral	1 month	1 ml/kg	Well tolerated

TABLE 60
Sodium Acetate Trihydrate Buffer

	Route	Duration	Dose	Comments
Primate	Intravenous	Card.vas.	1 ml/kg	Well tolerated

TABLE 61
Sodium Chloride 0.9%

	Route	Duration	Dose	Comments
Rat	Intravenous	7 doses	1 ml/kg	Well tolerated
		1 dose	1 ml/kg	Well tolerated
		14 doses	10 ml/kg	Well tolerated
		3 doses	4 ml/kg	Well tolerated
	Subcutaneous	1 dose	0.1–0.4 ml	Well tolerated
		1 month	4 ml/kg	Well tolerated
		56 doses	2 ml/kg	Well tolerated
	Slow bolus	1 dose	1 ml/kg	Well tolerated
		1 dose	10 ml/kg	Well tolerated
Mouse	Intravenous	1 dose	10 ml/kg	Well tolerated
	Subcutaneous	1 dose	10 ml/kg	Well tolerated
Rabbit	Intravenous	1 dose	.1 ml/kg	Well tolerated
	Intraperitoneal	1 dose	.1 ml/kg	Well tolerated
Dog	Oral	1 dose	.282 ml/kg	Well tolerated
	Intravenous	1 dose	10 ml/kg	Well tolerated
		1 dose	2 ml/kg	Well tolerated
		2 weeks	5 ml/kg	Well tolerated
	Subcutaneous	1 month	.025 ml	Well tolerated
	Slow bolus	1 dose	.3 ml/kg	Well tolerated
Primate	Subcutaneous	1 month	.67 ml/kg	Well tolerated
		56 doses	.5 ml/kg	Well tolerated

TABLE 62
Sodium Phosphate

	Route	Duration	Dose	Comments
Dog	Oral	2 weeks	10 ml/kg	70 mM; well tolerated
Rat	Oral	2 weeks	10 ml/kg	70 mM; well tolerated

TABLE 63
Tartaric Acid

	Route	Duration	Dose	Comments
Rat	Oral	39 week	.5 ml/kg	Well tolerated
		2 weeks	3 ml/kg	Well tolerated
Rabbit	Oral	Prelim. Segmt. II	3 ml/kg/day	Well tolerated
		Segmt. II	3 ml/kg/day	Well tolerated

TABLE 64
Transcutol

	Route	Duration	Dose	Comments
Cat	Intravenous	1 month	2 ml/kg	Well tolerated
Rabbit	Dermal	Skin irritation	.5 ml over 2 cm^2 area	50%; nonirritant
		28 days	0, 300, 1000, 3000 mg/kg/day	Undiluted; NOEL >1000 mg/kg/day
	Ocular	Eye irritation	0.1 ml	30%; Slight irritation
		Eye irritation	0.1 ml	Undiluted; slight irritation
Rat	Oral	90 days	0%, 0.25%, 1%, and 5%	NOEL is 1%
		Acute	5.0 g/kg	LD_{50} > 5000 mg/kg
		Fertility and embryotoxicity range-finding study	500, 1000, 2000, 4000 mg/kg/day	NOEL > 500 mg/kg/day
Mouse	Oral	Acute		6.6 g/kg tested toxic
	Oral	Chronic (12 months)		NOEL: 850–1000 mg/kg
Dog	Oral	90 days		NOAEL: 1500 mg/kg/day

DISCUSSION

Although some of the vehicle options and choices presented here may seem unusual, it should be noted that what is reported here represents what is used from the discovery phase of drug development through early nonclinical safety assessment, and in many cases, all the way through to use in marketed products (the reader is invited to inspect the FDA's [Food and Drug Administration] inactive ingredient list, at www.fda.gov/cder/drug/iig/inact.pdf, to verify this point). Lactose as a formulation component for inhalation may seem contralogical, yet marketed products employ it for dispersion of drug powder and metered dose inhaler (MDI) dosage formulation.

TABLE 65
Trisodium Citrate Dihydrate

	Route	Duration	Dose	Comments
Dog	Oral	52 weeks	10 ml/kg/day	Well tolerated
Rat	Oral	Segm. III	10 ml/kg/day	Well tolerated
		39 weeks	10 ml/kg/day	Well tolerated
		4 weeks	10 ml/kg/day	Well tolerated
Mouse	Intravenous	13 weeks	10 ml/kg/day	Well tolerated

TABLE 66
Tween 20

	Route	Duration	Dose	Comments
Rat	Oral	1 month	250 mg/kg	Well tolerated
		90 days	500 mg/kg	Diarrhea
Mouse	Oral	1 month	10 mg/kg	Well tolerated

TABLE 67
Tween 80

	Route	Duration	Dose	Comments
Dog	Oral	90 days	5 ml/kg	as 1% of formulation; Well tolerated
Rat	Oral		350 mg/kg	Well tolerated
		4 weeks	5 ml/kg	1%; well tolerated
		7 days	10 ml/kg	1%; well tolerated
	Intravenous		100 mg/kg	Well tolerated
Mouse	Intraperitoneal	1 month	10 ml/kg	2%; well tolerated
	Intranasal	3 days	10 μl/nostril	.2%; well tolerated
Primate	Oral	Efficacy	5 ml/kg	1%; well tolerated

TABLE 68
Xylitol

	Route	Duration	Dose	Comments
Primate	Intranasal	1 month	1200 μl/day for control and high in test formulations: concentration 200 and 400 μl/day for respectively low- and intermediate-dose level	Well tolerated at 1200 μ1/day

TABLE 69
Summary of vehicle information

Excipient/vehicle	Data in Table no.	CAS no.	Chemical name	Formula	Key toxicity review articles	Animal species evaluated
2-Hydroxypropyl-β-cyclodextrin	NA	128446-35-5			Gould (2005)	Rat, primate, mouse, rabbit, dog
Acacia	3	9000-01-5	Acaciae gummi		TOXSYS; Anderson (1986); Bachmann (1978)	Rat, primate
Acetate, Sodium	4	127-09-3	Acetic Acid Sodium Salt	$C_2H_3NaO_2$	TOXSYS	Rat
Acetic Acid	5	64-19-7	Ethanolic Acid	$C_2H_4O_2$	Cragg (2001); Schonwald, (2004) "Irrigating Solutions"	Rat, mouse
Acetone	6	67-64-1	2-Propanone	CH_3COCH_3	Meditext (2006)	Rat, mouse, guinea pig, rabbit
Acetylmethylamine in water	NA	79-16-3	n-Methylacetamide	C_3H_7NO	NA	
Alginic Acid	7	9005-32-7	Norgine	$(C_6H_3O_6)n$	JECFA, 49th (1997)	Rat
Anecortave Acetate	8	7753-60-8		$C_{23}H_{30}O_5$	Jockovich (2006); Talsma (2004)	Rat
Benzoic Acid	9	65-85-0	Benzoic Acid	$C_7H_6O_2$	TOXSYS; Nair (2001); David et al. (2001)	Rat
Beta-Cyclodextrin	10	7585-39-9	Beta-Dextrin	$C_{42}H_{70}O_{35}$	TOXSYS; Toyoda (1997); Waner (1995); Marttin (1998); Challa (2005)	Rat, primate
BHT	NA	128-37-0	Butylated Hydroxytoluene	$C_{15}H_{24}O$	Lanigan (2002); Nakagawa (1984); Briggs (1989)	
Canola Oil	11	120962-03-0	Canbra Oil		Evangelista (2004)	Dog
Capryol 90	12	31565-12-5	Propylene glycol monocaprylate	$C_{11}H_{22}O_3$	Li (2005); Cho (2004)	Rat, dog, rabbit
Captisol	13	182410-00-0	Beta-cyclodextrin sulfobutyl ether, sodium salt (CDSBE)	$C_{42}H_{70}$-nO_{35} · (C4H8SO3Na)n	TOXSYS	Rat, primate, mouse

Carboxymethylcellulose (CMC)	14	9000-11-7	Acetic acid; 2,3,4,5,6-pentahydroxyhexanal	$C_8H_{16}O_8$	Mehlman (2001) "Carboxymethylcellulose"	Primate, rat
Carboxymethylcellulose Calcium	15	9050-04-8	Calcium CMC		TOXSYS	Dog
Carboxymethylcellulose Sodium	16	9004-32-4	Carmellose Sodium		Bar (1995); Freeman (2003); Cavender (2001) "Sodium Carboxymethyl Cellulose"; Bachmann (1978)	Rabbit
Cavasol W7	NA	128446-35-5	2-Hydroxypropyl cyclo heptaamylose		Wacker Fine Chemicals (2006)	
Cetyl Alcohol	17	36653-82-4	Hexadecan-1-ol	$C_{16}H_{34}O$	TOXSYS; Bevans (2001) "Alcohols"	Mouse
Citrate buffer	18	77-92-9	Sodium citrate-citric acid buffer		Schonwald (2004) "Acidifying and Alkalinizing Agents"	Dog, rat
Citric Acid Buffer	19	77-92-9		$C_6H_8O_7 \cdot H_2O$	Cragg (2001) "Citric Acid"	Rat
CMC with dimethicone	NA	9004-32-4 9006-65-9	Carboxy-methylcellulose Sodium Trimethyl-trimethylsilyloxy-silane	$C_6H_{18}OSi_2$	NA	
Coconut Oil	NA	8001-31-8	n/a		Shadnia (2005); National Toxicology Program (2001)	
Collagen Matrix	20	9007-34-5	Collagen Human		McCarthy (2002); Clark (1989)	Primate, rabbit
Corn oil	21	8001-30-7	Corn germ oil, glyceridic		TOXSYS; Wu (2004); Dupont (1990); DeWitt (2005)	Dog, rat, mouse, rabbit, chick embryo

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TABLE 69
Summary of vehicle information *(Continued)*

Excipient/vehicle	Data in Table no.	CAS no.	Chemical name	Formula	Key toxicity review articles	Animal species evaluated
Cremophore EL	22	61791-12-6	Polyoxyl castor oil		TOXSYS; Gelderblom (2001); Ramadan (2001); Lorenz (1977)	Dog, rat
Cyclohexane	23	110-82-7	Hexahydrobenzene; hexamethylene; hexanaphthene	C_6H_{12}	Kreckmann (2000); Malley (2000); Gad (2005) "Cyclohexane"	Rat, rabbit
DAM PEG (Polyethyllene Glycol)	24				NA	Dog, rat
Dextrose	25	50-99-7	D-Glucose, anhydrous; dextrosol	$C_6H_{12}O_6$	Buard (2003)	Dog, rat
Diethyleneglycol-monoethylether	26	111-90-0			Hardin (1983,1984)	Primate
DMSO	27	67-68-5	Dimethylsulfoxide	C_2H_6OS	TOXSYS; White (1983); Augustine (2000); Ali (2001); Schonwald (2004) "Irrigating Solutions"	Dog, rat, guinea pig, primate, mouse, rabbit
Dulbecco's modified PBS	28				NA	Rat
EDTA	NA	60-00-4	Ethylenediamineetra-acetic acid	$C_{10}H_{16}N_2O_8$	TOXSYS; Heimbach (2000) Lanigan (2002); Cavender (2001) "Ethylenedi-aminetetraacetic Acid"	
Ethanol	29	64-17/5	Ethyl Alcohol	C_2H_6O	TOXSYS; Church (1997); Bevan (2001) "Ethanol"	Dog, rat, primate, mouse
Gelucire 44/14	30	121548-04-7	PEG-32 glyceryl laurate		Yan (2005); Kawakami (2004)	Rabbit, rat, dog
Gelucire 50/13	NA	121548-05-8	G-50-13		Sharma (2006)	

Glucose	31	50-99-7	dextrose	$C_6H_{12}O_6$	Robertson (2003)	Dog, rat, primate
Glycerol	32	56-81-5	Glycerine	$C_3H_8O_3$	TOXSYS; Anderson (1999); Cosmetic Ingredient Review (2004) Glycerols;	Rat, guinea pig, mouse, rabbit
Gum tragacanth	33	9000-65-1			Anderson (1989); Bachmann (1978); Hagiwara (1991)	Mouse
Gum xanthane	NA	11138-66-2		$(C_{35}H_{49}O_{29})_n$	NA	
Hydroxypropyl Beta-cyclodextrin	34	94035-02-6		(C_{42} H_{70}-n O_{35})	Gerloczy (1994)	Dog, rat
Hydroxypropyl Cellulose	35	9004-64-2	Methocel		TOXSYS; Cavender (2001) "Hydroxypropyl Cellulose	Rat
Hydroxypropyl methylcellulose	36	9004-65-3	Benecel MHPC, Hypromellose		TOXSYS; Geerling (2001); Maki (2000); Rosen (1987); Mehlman (2001) "Hydroxypropyl Methylcellulose"; Obara (1992)	Dog, rat, mouse
Isopropyl Alcohol	37	67-63-0	Sec-propyl alcohol	C_3H_8O	TOXSYS; Tyl, (1994); Bevan (2001) "Isopropanol"; Sivilotti (2004); Burleigh-Flayer (1998); Church (1997); Allen (1998)	Rabbit
Isopropyl Myristate	38	110-27-0	Crodamol IPM	$C_{17}H_{34}O_2$	TOXSYS; Komatsu (1979); Campbell (1981)	Rabbit

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TABLE 69
Summary of vehicle information *(Continued)*

Excipient/vehicle	Data in Table no.	CAS no.	Chemical name	Formula	Key toxicity review articles	Animal species evaluated
Labrafil M1944	39	62563-68-2	Labrafil		TOXSYS; Beckwith-Hall (2002)	Dog
Labrasol	40	85536-07-8	Polyglycolyzed Glycerides		Hu (2001)	Rat, dog, rabbit
Lactose	41	63-42-3(anhy)	O-β-D-Galactopyranosyl-(1->4)-α-D-glucopyranose	$C_{12}H_{22}O_{11}$ (anhyrous)	TOXSYS; Baldrick (1997); Ahmad (2004)	Primate
Lanolin	42	8006-54-0	Lanolin		Kligman (1983)	Rabbit
L-Ascorbic Acid	43	50-81-7	Cevatine, Cevex, Cevital	$C_6H_8O_6$	Bendich (1990); Dykes (1975); Temple (2004)	Rat
Lauroglycol	44	27194-74-7	Lauric acid, monoester with propane-1,2-diol		Liu (2006)	Rabbit, rat
Maltitol Solution	45	9053-46-7	Liquid Maltitol	$C_{12}H_{24}O_{11} + C_6H_{14}O_6$	Walker (1978); Modderman, JP (1993)	Rat
Maltol	46	118-71-8	3-Hydroxy-2-methyl-4H-pyran-4-one	$C_6H_6O_3$	Hironishi (1996); Murakami (2006)	Guinea pig, rabbit
Mannitol	47	69-65-8	D-Mannitol	$C_6H_{14}O_6$	TOXSYS; Horvath (1982); Lina (1996)	Primate
Methane Sulfonic Acid	NA	75-75-2	Methylsulfonic acid	CH_4O_3S	TOXSYS; Shertzer (2001)	
Methyl Cellulose	48	9004-67-5	Cellulose Methyl Ester		TOXSYS; Mehlman (2001) "Methylcellulose"; Bachmann (1978); Sellers (2005)	Rat, guinea pig, primate, mouse, rabbit, dog
Miglyol 810	NA	85409-09-2	Caprylic, capric triglycerides		TOXSYS; Traul (2000); Sellers (2005)	

Mineral Oil	49	8012-95-1	Liquid paraffin		TOXSYS; Dalbey (2003); Trimmer (2004); Nash (1996)	Rat, mouse, dog
Neobee 1053	NA	73398-61-5	Medium Chain Triglycerides		NA	
N-methylpyrrolidone (Pharmasolv)	NA	872-50-4	1-Methyl-2-pyrrolidinone	C_5H_9NO	TOXSYS; Solomon (1996); Trochimowicz (2001); Lee (1987)	
PBS (phosphate-buffered saline)	50				NA	Rat, primate, mouse
Peanut oil	51	8002-03-7	Arachis oil, Fletcher's		TOXSYS; Cosmetic Ingredient Review (2001)"Peanut"	Rat
PEG 300	52	25322-68-3	Polyethylene glycol 300	$HOCH_2(CH_2OCH_2)nCH_2OH$	TOXSYS; Cavender (2001) "Polyethylene Glycols"; Patel (2005)	Guinea pig, mouse, rabbit
PEG 400	53	25322-68-3	polyethylene glycol 400	$(C_2H_4O) \cdot nH_2O$	TOXSYS; Hermansky (1995); Patel (2005)	Rat, minipig, guinea pig, mouse
Petrolatum	54	8009-03-8	Yellow soft paraffin		TOXSYS	Rabbit
Poloxamer	55	9003-11-6	Lutrol	$HO(C_2H_4O)a(C_3H_6O)bH$	Frim (2004); TOXSYS; Grindel (2002)	Rat, mouse
Polysorbate 80	NA	9005-65-6	Polyoxyethylene (20) sorbitan monooleate		TOXSYS; NTP (1992)	
Povidone	56	9080-59-5	2-Methoxy-6-methyl-phenol	$C_8H_{10}O_2$	Beji (2006)	Rat
Propylene glycol	57	57-55-6	1,2-Dihydroxypropane	$C_3H_8O_2$	TOXSYS; Cosmetic Ingredient Review (1999) "Propylene Glycol"; Cavender (2001) "Propylene Glycol"	Rat, minipig, mouse, dog

(Continued in next page)

TABLE 69
Summary of vehicle information *(Continued)*

Excipient/vehicle	Data in Table no.	CAS no.	Chemical name	Formula	Key toxicity review articles	Animal species evaluated
Rameb 7.5%	58		Randomly Methylated Beta-cyclodextrins		Challa (2005)	Primate
Sesame Oil	59	8008-74-0	Sesame Oil		TOXSYS; Farber (1976); Genovese (1999)	Rat, mouse, rabbit, dog
Sodium Acetate Trihydrate buffer	60	6131-90-4			NA	Primate
Sodium Chloride	61	7647-14-5	Salt, Halite	NaCl	Meneely (1953); Meneely (1958); Teitelbaum (2001); Caraccio (2004) "Over the Counter Products"	Dog, rat, primate, mouse, rabbit
Sodium Phosphate	62	7558-80-7			Moore (1988); Pierce (2001)	Dog, rat
Solutol® HS15/purified water	NA	70142-34-6	Polyethylene glycol-15-hydroxystearate		Coon (1991); Ruchatz (1998)	
Succinate, Sodium	NA	150-90-3	Succinic Acid Sodium Salt	$C_4H_4Na_2O_4$	TOXSYS; MSDS; Cragg (2001) "Succinic Acid"	
Tartaric Acid	63	87-69-4	*d*-Tartaric acid; 2,3-dihydroxy-butanedioic acid	$HOOC(CH_2O)_2$ COOH	Sourkes (1950); Cragg (2001) "Tartaric Acid"	Rat, rabbit
Transcutol	64	111-90-0	2-(2-Ethoxyethoxy)-ethanol	$C_6H_{14}O_3$	Liu (2006)	Cat, rabbit, rat
Trisodium citrate dihydrate	65	6132043		$C_6H_5Na_3O_7 \cdot 2H_2O$	NA	Dog, rat, mouse
Tween 20	66	9005-64-5	Polysorbate 20 NF		TOXSYS; Bartsch (1976)	Rat, mouse
Tween 80	67	9005-65-6	Armotan pmo-20, Tween(R) 80		TOXSYS; Daher (2003); Fisherman (1974); Sellers (2005)	Rat, primate, mouse, dog
Xylitol	68	87-99-0	Xylite	$C_5H_{12}O_5$	TOXSYS; Takahashi (1999)	Primate

Note. NA- Not currently Available.

For all formulations, the ability to accurately administer an aliquot of what has been prepared, with each aliquot being of uniform content, is a primary requirement. With fewer exceptions (i.e., capsule fills), this means achieving a solution or (second choice) stable suspension.

Although the first choice for any systemic route is always a modification of an aqueous based vehicle, the physiochemical characteristics of the test material dictate available options (Yalkowsky 1999; Racz 1989). One starts with either a polar or nonpolar solvent to begin with, depending on which achieved adequate dissolution of the test material, and works from there.

Although it is common in much of the pharmaceutical industry to stick to those components that have already seen use in other drugs from as early a point in development as possible, such is nowhere near a universal case.

In hopes of making the database presented here as accessible as possible and to broaden its content, GCS has set up an online version with free access (go to www.gadconsulting.com), which provides an online mechanism to submit new data, and will maintain and update the electronic site for at least 5 years after publication of this article (until 2011).

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