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Comparison of Safety Pharmacology End Points Used on Toxicology Studies Across Differing Cynomolgus Monkey Origins

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ABSTRACT

Background and Purpose: Demand for the use of cynomolgus macaque (CM; *Macaca fascicularis*) in biotherapeutic development has greatly increased. Due to the demand itself and other global factors (e.g., the COVID-19 pandemic), the continued use of CMs has necessitated exploring the use of potentially underutilized CM origins in new drug toxicology programs. However, as genetic and environmental variability between origins can complicate data interpretation, robust reference data must be generated to confidently determine what could be considered a drug effect. One origin of consideration is the insular Philippine CM population, whose use in regulatory toxicology studies has been minimal compared to Mauritius or mainland/Continental populations (Cambodian). In particular, safety pharmacology endpoints have not been greatly explored in the Philippine CM. To address the relative lack of data, safety pharmacology endpoints identified by ICH S7A were collected for Philippine CMs under common biotherapeutic toxicology study conditions and compared to Mauritius and mainland/Continental CMs. Assessments included snapshot electrocardiograms (ECGs), oscillometric blood pressure by the cuff, blood gases, and respiratory rate.

INTRODUCTION

In the actual context of drug development, many companies focus on the development of novel biotherapeutic drugs, e.g., gene therapy drugs, which require the use of cynomolgus macaque. The nonclinical regulatory framework for these novel drugs requires the evaluation of various endpoints for toxicology. Depending on the target of the pharmaceutical, additional safety pharmacology endpoints may also be required. Based on the nature of these drugs, a common approach is to evaluate the safety pharmacology endpoints in toxicology studies, which also contributes to the refinement of the experimentation and the reduction of animal used. However, even if we are able to reduce the number of animals in an overall nonclinical development program, the procurement of CM remains a challenge since the COVID pandemic, which necessitated exploring other CM origins. The results of select safety pharmacology endpoints, such as electrocardiograms (ECGs), oscillometric blood pressure by cuff, blood gases, and respiratory rate endpoints, that can be commonly added to a toxicology study, are compared in this presentation from animals of Philippine origin to those Mauritius and mainland/Continental origins.

MATERIAL AND METHODS

Data was collected from at least 20 male and 20 female Philippine, Mauritius, and mainland/Continental CMs, aged 1 to 4 years, prior to receiving any test article.

Animals were housed in a temperature- and humidity-controlled environment with target ranges between 18 and 29 degrees Celsius, and 30 and 70%, respectively. A 12-hour light/dark cycle was set, and animals were kept in stainless steel metal cages that complied with the Animal Welfare Act and recommendations set forth in the Guide for the Care and Use of Laboratory Animals (National Research Council 2011). Animals were fed PMI LabDiet® Fiber-Plus® Monkey Diet 5049 biscuits, and water were provided ad libitum.

All data were collected from awake animals restrained in a procedure chair. Electrocardiographic data were collected using the Ponemah Physiology Platform (Data Sciences International) via externally placed electrodes, blood pressure data were collected using the Suntech Vet20 blood pressure device, blood gas data were collected using CG8+ I-STAT cartridges, and respiratory rate was collected visually.

Average, standard deviation, minimum value, maximum values and percentiles (5% and 95%) were determined. The data distribution was also evaluated by determining the percentage of the total population evaluated per ranges established to cover the full range of the data set.

RESULTS

Table 1. Mean sex respiratory parameters obtained from at least 40 cynomolgus macaque per origin

	Respiratory Rate (bpm)			sO2 (%)			pO2 (mmHg)			pCO2 (mmHg)		
	Cambodian	Philippine	Mauritius	Cambodian	Philippine	Mauritius	Cambodian	Philippine	Mauritius	Cambodian	Philippine	Mauritius
Average	12.4	13.2	12.4	97.5	97.6	97.3	94	100	94	31	31	27
SD	2.28	1.44	1.58	1.51	0.71	0.69	14.1	8.0	7.4	3.3	2.7	2.6
Min	8.0	10.0	10.0	90	95	96	52	80	75	20	24	22
Max	22.0	18.0	15.0	100	99	98	168	118	106	41	36	32
Percentile 5%	9.9	10.1	10.0	98	98	97	94	101	95	31	31	27
Percentile 95%	16.0	15.0	15.0	95	97	96	70	84	81	25	25	23

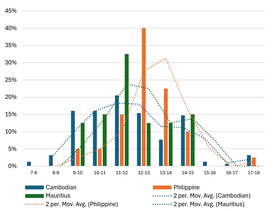

Figure 1. Respiratory distribution

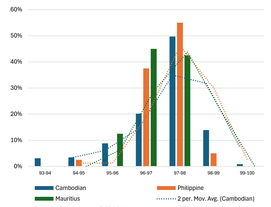

Figure 2. Oxygen saturation distribution

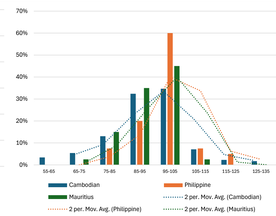

Figure 3. Partial pressure of oxygen distribution

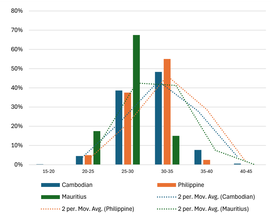

Figure 4. Partial pressure of carbon dioxide distribution

Table 2. Mean sex cardiovascular parameters obtained from at least 40 cynomolgus macaque per origin

	Heart Rate (bmp)			QTc[Bazetts] (msec)			Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)		
	Cambodian	Philippine	Mauritius	Cambodian	Philippine	Mauritius	Cambodian	Philippine	Mauritius	Cambodian	Philippine	Mauritius
Average	244	255	244	321	334	325	146	161	163	95	103	107
SD	24.5	14.3	17.9	14.8	14.0	25.9	24.1	15.8	18.3	17.0	12.5	14.0
Min	158	229	199	253	299	253	62	129	128	40	79	71
Max	306	290	276	382	359	382	220	200	208	129	133	128
Percentile 5%	198	229	204	300	307	266	109	130	132	63	80	73
Percentile 95%	284	277	273	344	358	370	191	197	196	123	124	126

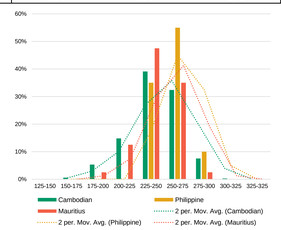

Figure 5. Heart rate distribution

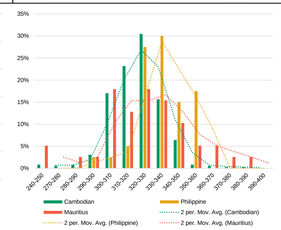

Figure 6. QTcB distribution

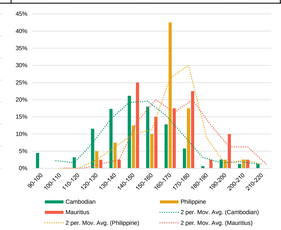

Figure 7. Systolic blood pressure distribution

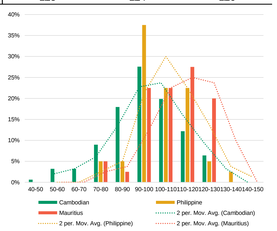

Figure 8. Diastolic blood pressure distribution

Table 3. Mean sex body temperature obtained from at least 40 cynomolgus macaque per origin

	Body temperature (℃)		
	Cambodian	Philippine	Mauritius
Average	39.5	39.2	39.2
SD	0.53	0.38	0.49
Min	37.7	38.1	38
Max	40.9	39.7	40
Percentile 5%	38.5	38.4	38.2
Percentile 95%	40.1	39.7	39.9

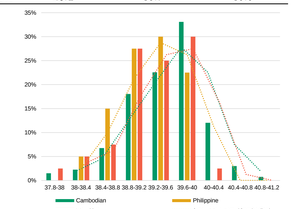

Figure 9. Body temperature distribution

Mean sex-combined results and their distribution were generally comparable across origins, for Philippine (P), Mauritius (M), and mainland/Continental (C).

CONCLUSIONS

In the assessment of safety pharmacology endpoints in regulatory toxicology studies, data generated from Philippine cynomolgus macaques were found to have no meaningful difference in cardiovascular, respiratory or body temperature values when compared to Mauritius or mainland/Continental cynomolgus macaques. The lack of difference helps to validate Philippine CMs as a viable test system for biotherapeutic toxicology assessment, warranting consideration for more detailed safety pharmacology assessments (e.g., jacketed or implanted telemetry studies).