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Standardization and Harmonization of Altasciences Historical Control Database Development Using Certara SEND Explorer® for Integrated Toxicological Evaluation

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BACKGROUND

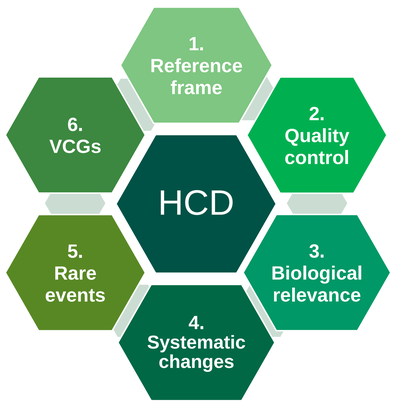
History of Nonclinical Historical Control Data (HCD)

- HCD is gathered from animals treated under similar conditions across multiple studies without exposure to the test article, which provides baseline reference information and frequency of spontaneous findings in untreated or vehicle-treated animals, such as clinical pathology, organ abnormalities, or tumor incidences.
- The use of HCD in safety assessments dates back to the mid-20th century when regulators began requiring robust methods to interpret study findings. It has now become integral to successful drug development.

Early Utilization (1950s - 1970s)	• Initially employed to contextualize unexpected findings in control animals (e.g., standardized lab strain)
Emergence of Guideline (1980s - 1990s)	• Regulators (USFDA/OECD/ICH) acknowledged the value of HCD, especially in evaluating low-frequency events (e.g., spontaneous tumor)
Standardization and Best Practices (2000s)	• Statistical methodologies improved the analysis and interpretation of HCD; regulators emphasize using concurrent controls to reduce variability, **with HCD as a supplemental tool**
Modern Applications and Challenges (2010s - now)	• Digital data systems enable more comprehensive HCD; regulators stress **transparency in HCD** generation, selection, and potential for misuse

Figure 1. History of Use of Nonclinical HCD in Drug Safety Assessments

Broad Applications of HCD in Drug Safety Assessment



1. Providing a biological reference frame for a measurement
2. Evaluation of toxicological bioassays for quality and performance control
3. Assessment of biological relevance of observed potentially adverse findings (e.g., statistical significance)
4. Continuous monitoring of the control animal data in future studies (e.g., genotypic/phenotypic changes)
5. Investigating the full range of data on toxicological endpoints of interest (e.g., rare observations)
6. Creating Virtual Control Groups (VCGs) based on specific study design criteria

Figure 2. Current Applications of HCD in Preclinical Drug Development

PURPOSE

Current Challenges of HCD and Study Objective

- Since the introduction of SEND as an FDA requirement for toxicology data standardization, utilization of HCD has been significantly facilitated during drug development and regulatory review. **However, in the current practice, the collection, use, and interpretation of HCD are not harmonized due to a lack of global consensus.**
- Our goal is to develop a high-quality and harmonized HCD repository (2022-24) using a transparent approach for Altasciences' three preclinical test facilities in North America to meet these challenges and regulatory requirements.

METHODS

Workflow of Altasciences' HCD Development

Altasciences and Certara worked strategically to generate site-specific HCD repository (regulatory rodent and non-rodent species) using the SEND Explorer® (Warehouse V11), which is fully implemented at Altasciences for continuously collecting, analyzing, distribution of data via SEND Explorer visualization, and reporting large sets of control animal data from general toxicology studies.

- Step 1 — **Collection:** historical studies of control animal data uploaded from Provantis or Pristima to SEND Explorer® to build HCD database (HCDB)
- Step 2 — **Analysis:** HCDB filtered with criteria (comply with guidelines) including but not limited to test facility, animal species/strain, age ranges, dosing duration, route of administration, and GLP compliance, followed by statistical analysis and visualization
- Step 3 — **Report:** Toxicological endpoints reported with a consistent Altasciences' format for a time window (3-5 years) around the investigated study to increase the acceptance of HCD in regulatory assessments

Figure 3. A Simplified Illustration of the Altasciences' HCD Development Process

KEY RESULTS

Altasciences HCD Database (Species and Study Types)

Pathology-focused parameters: reference interval (2.5th-97.5th percentiles) for quantitative parameters (i.e., clinical pathology, organ weight) and background incidence rate (%) for qualitative parameters (i.e., microscopic findings)

Table 1. Altasciences HCD Database Development to Support Regulatory Nonclinical Toxicology Study

Species/Study duration	7-28 days	Up to 13 weeks	≥13 up to 26 and 39 or 52 weeks	Carcinogenicity studies	Specialized (CNS or Ocular)
Nonhuman primates (NHP) (Cambodia/Mauritius/Vietnam/China)	√	√	39 weeks	N/A	√
Dog (Beagle)	√	√	52 weeks	N/A	√
Minipig (Nanopig/Göttingen™)	√	√	39 weeks	N/A	√
Rat (SD/Wistar)	√	√	26 weeks	2 years	N/A
Mouse (CD-1)	√	√	26 weeks	2 years	N/A
TgRasH$_2$ Mouse	N/A	N/A	N/A	26 weeks	N/A
Rabbit (DB/NZW)	√	√	√	N/A	√

CASE EXAMPLES

Utilization of Altasciences HCD in Toxicology Studies

Case Study 1: Clinical pathology reference intervals in SD rats (8-12 weeks, oral gavage, fasted, inert vehicle; Seattle site)
Rationale: Additional tool for animal selection and/or treatment comparison
Hematology *(selected data for demonstration only)*

Table 2. Selected Hematology Reference Intervals in SD Rats

Test	Unit	Males			Females		
		Count(n)	Range*	Median	Count(n)	Range*	Median
Red Blood Cell Count	^6/µL	88	6.14-8.77	7.89	86	6.39-8.31	7.51
Hemoglobin	g/dL	88	13.1-16.6	15.1	86	12.6-16.0	14.6
Hematocrit	%	88	39.2-49.2	44.9	86	36.9-6.2	42.2

*2.5 to 97.5th percentile

Case Study 2: Spontaneous microscopic findings in Beagle dog testes (27-88 weeks, study duration 1-9 months, various administration routes)
Rationale: 28-day (PO) canine cannabinoid receptors-related testicular findings

Table 3. Spontaneous Testicular Microscopic Findings in Beagle Dog

Tissues	Sex	Male	Female
Findings	Dose (mg/kg)	0	0
	No. of Animals	67	65
Testes Degeneration		1 (1%)	N/A

Case Study 3: Most common anatomic background findings in Cynomolgus NHP post-IV administrations

Altasciences Pathology Services Historical Control Data (Seattle; 2022-2024)
Species/Origin: Macaca fascicularis (Cynomolgus Macaque)/Cambodian
Age: 2-6 years
Study Duration: up to 9 months
ROA: IV

Table 4. Common Microscopic Background Findings in Cynomolgus NHP (Cambodian) Post-IV Administrations

Tissues	Sex	Male	Female
Findings	Dose (mg/kg)	0	0
	No. of Animals	83	81
Heart Infiltration, Mononuclear Cells		27 (33%)	30 (37%)
Kidneys Infiltration, Mononuclear Cells		22 (27%)	25 (31%)
Injection Site(s) Hemorrhage Infiltration, Mononuclear Cells		6 (7%) 4 (5%)	9 (11%) 2 (2%)

SUMMARY AND CONCLUSIONS

Benefits of Integrate Altasciences HCD in Drug Development Programs
We demonstrated a transparent and harmonized approach for collecting, evaluating, and reporting HCD in regulatory general toxicology studies to improve data quality and reliability and streamline study analysis by reducing the likelihood of false positives or negatives. **Importantly, it meets regulatory requirements by providing evidence-based comparisons for safety assessments.**

REFERENCES: OECD, 2008; Kluxen et al., 2021 and 2024