

## Dosing & Documentation Errors in Preclinical GLP Infusion Studies

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### Summary

A typical preclinical GLP infusion study presents tens of thousands of opportunities for human error and omission in dosing and documentation. Applying automation to this dated (1970s) infusion model reduces the possibility for errors by 99% and eliminates paper documentation.

This infusion study model is rife with repetitive tasks involving precise numbers (e.g., dose rates, volumes, and durations). Despite extensive in-study Quality Assurance audits, these errors can escape detection because infusion pumps do not have readily accessible logs to corroborate the data recorded by study technicians.

Possibilities for Dosing and Documentation Errors per Study	
Manual	Orchestra™ Semi-automated
201,200	299

The costs of dosing and documentation errors are severe. Study data may be called into question by FDA

and regulatory agencies, CROs may repeat studies at their own expense, and offending employees can be terminated.

Such a system with high potential for human error and high stakes is ripe for automation. Solomon Scientific studied dosing and documentation errors in preclinical GLP studies while developing the Orchestra™ automated infusion system. The dosing and documentation errors most likely to occur in manual infusion studies are...

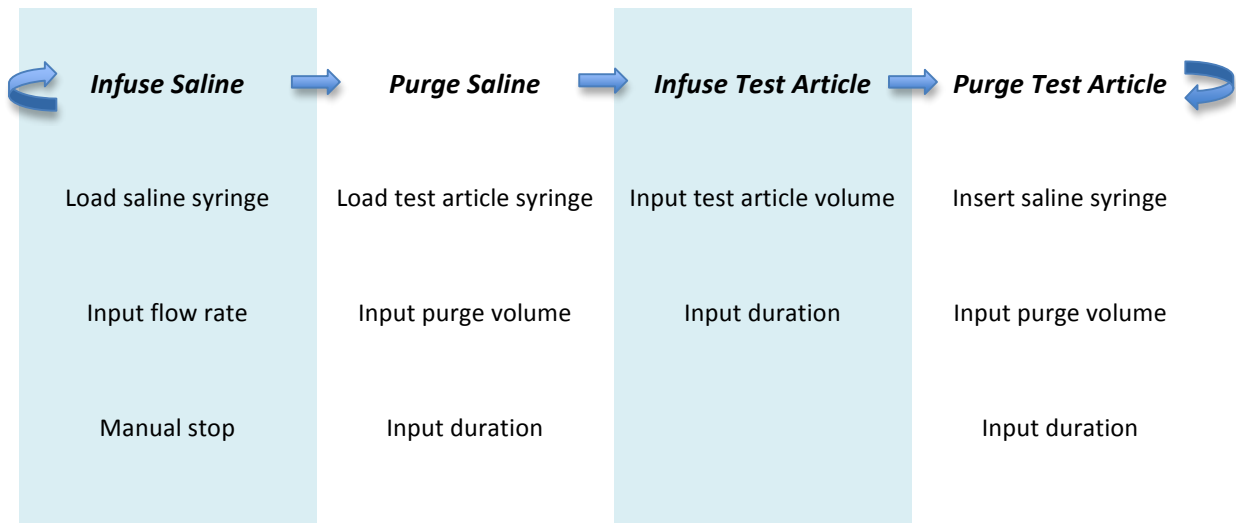
1. Keystroke errors on infusion pump keypad
2. Incorrect syringe loaded on pump
3. Incorrect animal identification
4. Dose spreadsheets
5. Inaccurate and omitted documentation



Infusion pump

## The Infusion Study Protocol

The protocol for preclinical GLP infusion studies is universal across research facilities in North America and Europe. Some minor process variations exist, but the process below for intermittent infusions largely illustrates the protocol. A common rat infusion study might comprise two hundred rats, each paired with a pump, infused daily over thirty days (as illustrated in the multiple tables below).



## Opportunities for Dosing and Documentation Errors

### *Keystroke Errors on Infusion Pump Keypad*

During infusion studies, a technician manually inputs values for rates, volumes, and durations into each pump's keypad, often several times daily. These inputs regulate infusion of test article and saline (maintenance) syringes for dosing, purging, and maintaining positive flow when not dosing. Input errors may result from reading or remembering incorrect values from paper dose sheets or result from "fat fingering" (a keypad "typo"). The total quantity of numeric keystrokes daily for the entire intermittent process is approximately nineteen per animal (depending on the pump and protocol). The calculations in this paper account for the numeric and decimal keystrokes.

Keystroke Errors on Infusion Pump	
Pumps (animals)	200
x Days	30
x Keystrokes*	19
<b>Total potential errors</b>	<b>114,000</b>

\* saline flow rate = .XX (3 keystrokes); saline purge volume = .XX (3);  
 saline purge duration = XX (2); test article volume = X.XX (4);  
 test article duration = XX (2); test article purge volume = .XX (3)  
 test article purge duration = XX (2)

### *Incorrect Syringe Loaded on Pump*

There are two daily syringe changes required in the intermittent infusion protocol. A test article syringe is loaded on the pump to administer the test article dose. A saline fluid syringe is loaded to complete (purge) test article delivery and to maintain positive flow for catheter patency between doses. Dosing errors, possibly undetected by QA audits, occur when the wrong syringe is loaded.

Incorrect Syringe Loading Errors	
Pumps (animals)	200
x Days	30
x Syringe changes/day	<u>2</u>
<b>Total potential errors</b>	<b>12,000</b>

### *Incorrect Animal Identification*

Most of the infusion process requires correct animal identification. The technician must execute each step detailed in the dose sheet (see below) directed to the proper animal. Additionally, the technician must direct each step to the correct pump paired with the proper animal.

Incorrect Animal Identification Errors	
Pumps (animals)	200
x Days	30
x Animal IDs/day	<u>3</u>
<b>Total potential errors</b>	<b>18,000</b>

### *Dose Spreadsheet*

Infusion study staff create computer spreadsheets (e.g., in MS Excel) to generate the daily infusion instructions for each animal. The manual generation of these spreadsheets creates additional opportunity for human error. Technicians update these spreadsheets weekly to reflect animal weight updates and the resulting changes in the weight-based doses. The number of computer keyboard keystrokes is calculated to be nineteen.

Dose Spreadsheet Errors	
Pumps (animals)	200
x PC keystrokes per animal*	19
x Weekly updates	<u>4</u>
<b>Total potential errors</b>	<b>15,200</b>

\* saline flow rate = .XX (3 keystrokes); saline purge volume = .XX (3);  
saline purge duration = XX (2); test article volume = X.XX (4);  
test article duration = XX (2); test article purge volume = .XX (3)  
test article purge duration = XX (2)

*Documentation Errors*

In addition to the many routine events which technicians must document (e.g., test article and saline administered) there are many non-routine pump events which they must document (e.g., pump alarms). QA cannot audit fully much of this data because it is recorded by human hand (often corroborated by a second technician), and there is no electronic record artifact. With tens of thousands of events to document and myriad daily paper forms, errors and omissions occur.

Documentation	
Pumps (animals)	200
x Days	30
x Data entries/day*	7
<b>Total potential errors</b>	<b>42,000</b>

\* Seven entries are: saline flow rate, saline purge volume, saline purge duration, test article volume, test article duration, test article purge volume, test article purge duration

Total Potential Dosing & Documentation Errors	
Pump keystrokes	114,000
+ Incorrect syringe loading	12,000
+ Incorrect animal identification	18,000
+ Dose spreadsheet	15,200
+ Documentation	42,000
<b>Total potential errors</b>	<b>201,200</b>

## Use of Automation to Reduce Opportunities for Dosing and Documentation Errors

The Orchestra™ automated infusion system is a validated system which is GLP and Part 11 compatible. Using custom software and wireless networking, the system automates most of the repetitive tasks which give rise to dosing and documentation errors. Applying this level of semi-automation significantly reduces opportunities for human error. One computer manages up to three hundred infusion pumps on an 802.15.4 wireless network. The automation features described below are designed to limit potential human error in dosing and documentation

Total Potential Dosing & Documentation Errors— Manual vs Semi-automated		
	Manual	Orchestra™ Semi-automated
Software programming keystrokes*	n/a	99
+ Pump keystrokes	114,000	0
+ Incorrect syringe loading	12,000	0
+ Incorrect animal identification	18,000	200
+ Dose spreadsheet	15,200	0
+ Documentation	48,000	0
<b>Total potential errors</b>	<b>201,200</b>	<b>299</b>

\* dead volume = X.X (3)  
 + [4 syringe menu choices x 8 groups]  
 + [test article rate = X.XX (4) x 8 groups]  
 + [saline rate = X.XX (4) x 8 groups]  
 + 200 pump-animal pairings  
 = 299

### Automated Inputs Reduce Keystrokes

At the beginning of each study, data is entered into the Orchestra™ software for storage and use during the entire study. This reuse of data obviates much of the repetitive work in a manual infusion study. For example, each animal is in a dose group. The target volume for the group coupled with each animal's weight provides the dose for each animal. The system retrieves animal weights from the LIMS (Laboratory Information Management System) and broadcasts dose info to each pump. Thus, the technicians need not program the pumps with numeric values during the entire study.



### *Pump Sensor Detects Proper Syringe Loading*

The Orchestra™ system requires assignment of a different syringe size for test article and for saline. Human-use syringe pumps are equipped with syringe size sensors. The infusion software communicates with the syringe size sensor to identify if the proper syringe (i.e., test article or saline) is loaded on the pump. The system blocks the pump from infusing an errant syringe.

### *Animals and Pumps Are Paired in the Software*

As mentioned, users enter study parameters into the Orchestra™ software which will remain active throughout the study. One of these parameters is the pairing of animal identifications to pump serial numbers. This step is a robust method to prevent the use of an incorrect animal identification. When dosing data is prepared by the software, it is broadcast to the appropriate pump-animal pairing thereby precluding the technician from inputting dose data to an incorrect animal.

### *Dose Calculation*

Initial study data required by the software comprises animal identification, animal weight, group, group dose rate, and target dose volumes. Periodically (usually weekly) updated animal weights are imported (preferably from LIMS) to derive new dosing data for each animal. The new dosing data is calculated by the software and broadcast to each pump. Thus, study staff do not create dose spreadsheets and do not use printed manual dose sheets.

### *Documentation is Automatically Recorded*

Orchestra™ has a sophisticated data recording system which gathers data electronically according to GLP and Part 11 requirements, virtually eliminating all paper from the process. Any human intervention requires login credentials which are then time-stamped. Any changes to the data leave an audit trail and show the original entry.

## **Conclusion**

A typical preclinical GLP infusion study presents tens of thousands of dosing and documentation error and omission possibilities. Application of an automated infusion system eliminates 99% of the opportunities for these errors by removing most of the repetitive human activity (which also reduces labor costs). Every step of the infusion process is recorded electronically and every manipulation to the system requires login credentials. The system has been fully validated and is compatible with all GLP and Part 11 regulations.