CUSTOM BIOGENIC SYSTEMS
2101 CONTROLLED RATE FREEZER
SET-UP & TECHNICAL MANUAL

Custom **BioGenic** **Systems**

www.custombiogenics.com
74100 Van Dyke ◆ Bruce Twp., MI 48065 ◆ USA
1.800.523.0072 ◆ Tel: 1.586.331.2600 ◆ Fax: 1.586.331.2588

Leading the World with Innovative Cryopreservation Technology Solutions

IMPORTANT INFORMATION

We at Custom Biogenic Systems are proud of our work, and appreciate your purchase of this product. With proper care, this equipment will be trouble-free for many years to come. Before setting up and using your new cryogenic storage unit, first check to see that all parts are accounted for and that no damage has occurred during shipping. Also, read this manual completely before proceeding to set-up. If at any time you are unsure of the procedures for set-up and use of this product, please contact CBS or your CBS sales representative.

NOTE: If equipment is used in a manner not specified by Custom Biogenic Systems, the protection provided by the equipment will be impaired.

PRODUCT WARRANTY

Custom BioGenic Systems warrants all manufactured cryogenic equipment to be free from defects in workmanship or materials for a period of one year.

Custom BioGenic Systems' liabilities under the warranty shall be limited to correcting or replacing defective workmanship or materials. A claimant under the warranty must notify Custom BioGenic Systems within (10) days after the discovery of the defect. Custom BioGenic Systems reserves the right, at their discretion, to correct the defect(s) in the field without return shipment to the factory.

This warranty does not cover defects on cryogenic equipment resulting from abusive handling and subsequent structural failure.

Serial Number_____

Model number_____

For Technical Assistance Call: 1.800.523.0072 (U.S. Only)
Phone: 586.331.2600   Fax: 586.331.2588
www.custombiogenics.com

LIQUID NITROGEN SAFETY

IMPORTANT: The following section on LIQUID NITROGEN SAFETY should be read carefully and be followed completely, but is by no means a complete volume on the safe use of cryogenic liquids. All personnel should have a complete knowledge of the correct procedures, as well as the hazards of working with liquid nitrogen. Failure to do so could result in serious injury or death. Always review latest Nitrogen, refrigerated liquid material safety data sheet

⚠ WARNING ⚠

LIQUID NITROGEN IS AN EXTREMELY COLD LIQUID (-196°C). BECAUSE OF THESE COLD TEMPERATURES, LIQUID NITROGEN WILL CREATE A FROST BITE IF THEY COME INTO CONTACT WITH SKIN. NEVER ALLOW DIRECT SKIN CONTACT WITH LIQUID NITROGEN OR SERIOUS FROST BITE WILL RESULT.

ALTHOUGH LIQUID NITROGEN ITSELF IS NON-TOXIC, WHEN RELEASED INTO A CONFINED SPACE IT CAN DISPLACE OXYGEN CAUSING ASPHYXIATION. ENTERING AN OXYGEN DEFICIENT ROOM CAN CAUSE UNCONSCIOUSNESS WITHOUT WARNING. ALWAYS CHECK AIR QUALITY UPON ENTERING A ROOM WHERE CRYOGENIC LIQUIDS ARE BEING USED, AND IF POSSIBLE, HAVE AIR RESPIRATORS AVAILABLE.

INTRODUCING EQUIPMENT WHICH IS AT ROOM TEMPERATURE INTO LIQUID NITROGEN IS ALWAYS SOMEWHAT HAZARDOUS. BEWARE OF SPLASHING AND "BOILING" WHICH MAY OCCUR. ALL PERSONNEL PERFORMING THESE OPERATIONS SHOULD BE FULLY INFORMED OF PROPER HANDLING PROCEDURES, AND SHOULD ALWAYS WEAR A FACE SHIELD AND PROTECTIVE CLOTHING.

LIQUID NITROGEN SHOULD NEVER BE USED IN COMBINATION WITH OTHER SUBSTANCES WITHOUT KNOWING WHAT THE RESULT WILL BE. WHEN IN DOUBT, CONTACT A COMPETENT AUTHORITY.

HANDLING LIQUID NITROGEN

Personnel handling liquid nitrogen should be thoroughly instructed as to the nature of these materials. Proper training is essential to safety, and will ensure the accident-free use of this equipment.

Because of its low temperature, liquid nitrogen will cause frost bite to the skin much in the same way as hot liquids can burn. For this reason, always wear the proper protective clothing when handling these materials. It is advised that during use, handlers of liquid nitrogen should protect themselves by wearing goggles or face shields, cryogenic gloves (large enough to allow quick removal) and a cryogenic apron. It is preferable that shoes worn at these times have high tops, as to not permit accidently spilled liquid from entering, as well as pant legs which come down over the tops of shoes for further protection.

Also because of the extremely low temperatures, liquid nitrogen should only be handled and transported in approved containers. Many materials become brittle and may shatter when put into contact with liquid nitrogen.

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TABLE OF CONTENTS

Introduction

Welcome to the Custom BioGenic Systems model 2101 Controlled Rate Freezing System. This system consists of a freezing chamber, computer, controlled rate freezing software, *optional* rolling cart, a sample rack, a sample probe and a liquid nitrogen transfer hose.

The software that is provided and comes pre-loaded on your 2101 controlled rate freezer computer operates using the same navigation and conventions as windows based operating systems (menus, basic commands, etc.)

This manual will provide you with the information you will need to operate, maintain, troubleshoot, and safely operate this equipment. It is of the utmost importance that you completely read and understand the material in this manual before attempting to install, operate or service this equipment.

Unpacking

Your 2101 Rate Freezer will arrive on a pallet in a box that is 30" x 30 " x 30" (L x W x H) on a pallet that is 48" x 40". Before unpacking check for any visual damage if there is visual damage be sure to sign the Proof of Delivery as damaged and notify Custom BioGenic Systems. Start by cutting the banding that is holding the box to the pallet. Open the box from the top and remove the foam that is surrounding the unit. Next carefully cut the box around the unit and pull the box off of the pallet. When the unit is the only thing seen on the top of the pallet carefully lift it off and set it in the desired location.

NOTE: It is recommended that two people lift the unit due to the weight and size of the unit.

Initial Inspection

Check to make sure that you have received your unit in its entirety. At a minimum you should receive the freezing Chamber, the controller, a freezer rack, a sample probe and a liquid nitrogen transfer hose. If you order optional equipment or any other items that were suppose to ship with this order make sure to check that those items were also received. If something that you ordered was not received please contact CBS immediately

Detected Damage

Once all items are removed from their packaging, check them for damage. Also check that the unit is as ordered. If damage is detected after unpacking the rate freezer, immediately report it to the shipping agent and re-pack the rate freezer for return to the factory as described in the following section.

Equipment Return

Before returning damaged or malfunctioning equipment to the factory for repair, contact the sales organization from which you purchased the equipment. A Return Merchandise Authorization (RMA) number MUST be obtained from the factory before returning equipment for any reason.

Installation Specifications

The rate freezer is intended to operate in the following environment:
Indoor use only
Installation Category II per IEC664
Pollution Degree Level II per IEC60601-1
Temperature: 10°C to 50°C operating per IEC60601-1
Humidity: Maximum relative humidity 80% for temperatures up to 31°C decreasing linearly to 50% relative humidity at 40°C.
Rate Freezer Power Requirement: 120VAC or 220VAC depending on destination country. Check indication on unit.
Liquid Nitrogen Supply Pressure: Must be between 18-22 psi 22 psi max.
Input Power: The chamber voltage depends on destination country and should be specified when ordered. Either 120 VAC or 220 VAC. The notebook PC has a universal power supply rated for 100-240 VAC.
Outputs: Outputs data to a printer. Printer is set up independently and supplied by the user.
No. of Channels: 2
Thermocouples: Type T, +50°C to -200°C
Range of Returnable Rates: Slowest rate possible is .01 degrees per minute. Fastest rate possible, with a 22 psi liquid supply, is 99 degrees per minute.

Bench Top Installation

The rate freezer should be set on a bench top in a vertical position to ensure proper operation. Ensure that you have the proper clearances for the liquid nitrogen connection.

Optional Storage Cart Installation

Same as above, except the rate freezer is set on the optionally purchased storage cart.

Connection

Make all of the following connections BEFORE turning on the notebook PC.

C B S

Power Connections

The rate freezer is designed to operate on either 120VAC or 220VAC (must be specified when unit is ordered), depending on the users needs. Check to make sure that the rate freezer voltage is the correct voltage for the local power system. The rate freezer is supplied with either a North American style plug or a European style plug, depending on the destination country. User supplied adapters may still need to be utilized to properly connect to main power.

The notebook PC has its own universal power supply that operates between 100-240VAC, and can be plugged into an available power outlet in the rear electrical panel. See 2.3.5 Optional Power Connections.

Thermocouple Connections

The rate freezer uses two different Type T thermocouples, labeled as CHAMBER and SAMPLE probes. The CHAMBER probe is factory installed and should not need to be adjusted. The SAMPLE probe connection is located on the inside of the chamber in the upper left hand corner of the fan guard. Insert the male end of the SAMPLE probe into the female jack in the fan guard. The thermocouple plugs are designed to only fit one way, so make sure that the male and female sides of the plug are lined up correctly.
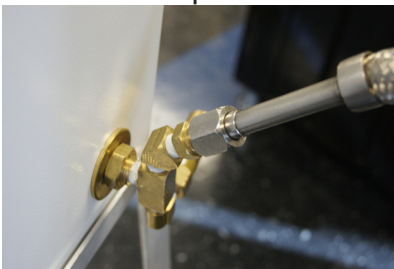
USB Connections

USB connection are connected at the factory make sure they are connected properly with a good connection.

Liquid Nitrogen Supply Connection

The liquid nitrogen supply connection is located on the right rear corner. This connector accepts a standard LN2 transfer hose.

Side view of the Controlled Rate Freezer showing the liquid nitrogen hose connection point.

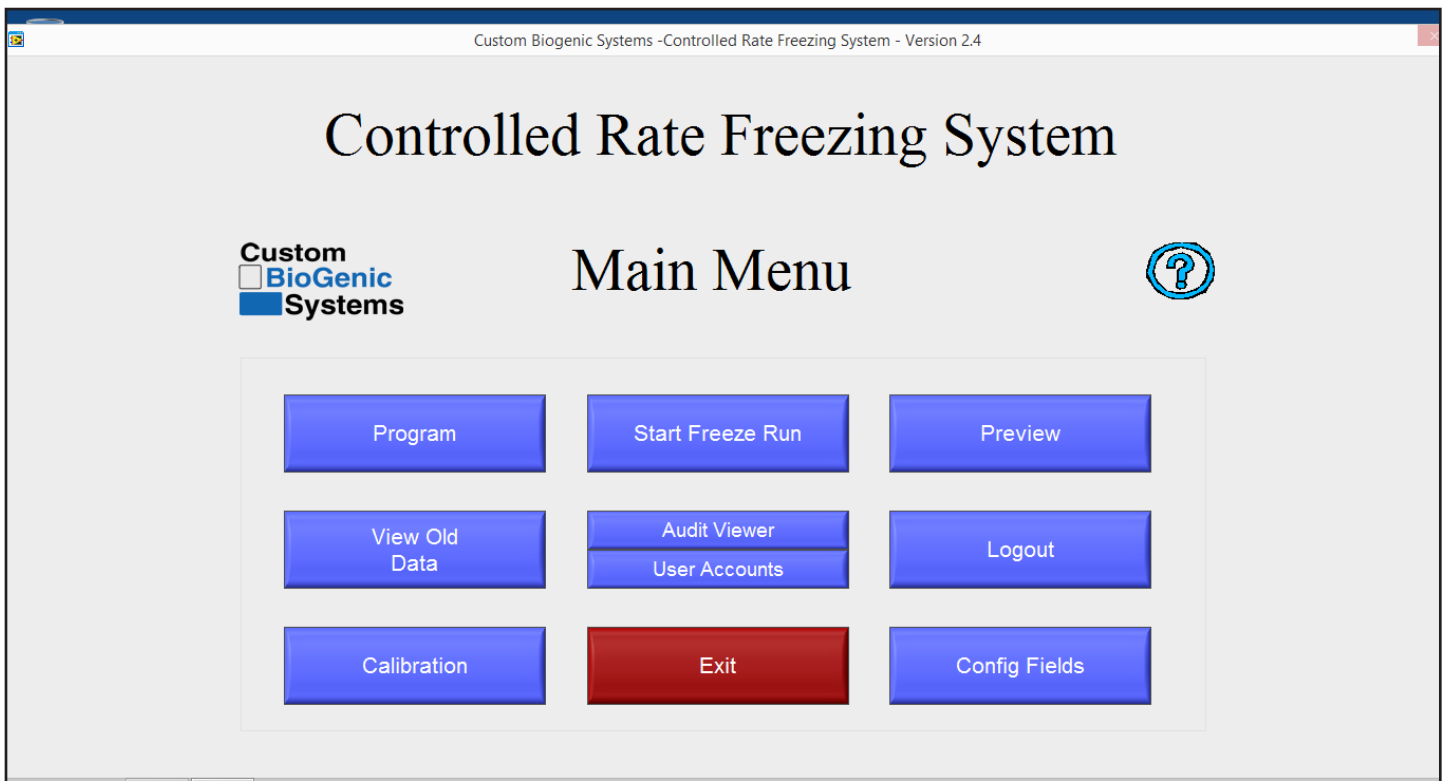Top view of the Liquid Nitrogen Supply tank showing the liquid nitrogen hose connection point.

Liquid Nitrogen Hose

Storage

For prolonged storage before installation, re-pack the rate freezer in the shipping container and store in a cool, dry area. We do not recommend storage of the rate freezer for more than six months. If longer storage time is required, contact the factory for additional storage information.

Custom Biogenic Systems -Controlled Rate Freezing System - Version 2.4

Controlled Rate Freezing System

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Main Menu

Program	Start Freeze Run	Preview
View Old Data	Audit Viewer / User Accounts	Logout
Calibration	Exit	Config Fields

CBS

Operating Instructions

A. <u>PROGRAM -</u> This menu button allows the user to program, edit, and save freezing profiles. This function is typically done after the profile is perfected in the preview menu.

B. <u>VIEW OLD DATA -</u>This menu button allows users to view and print previously saved freeze runs. The default print out consists of information header and the graph. **See page 22 Advanced Setup for other printing options.**

C. <u>CALIBRATION-</u>This menu button allows the user to access the thermocouple calibration screen.

NOTE: Calibration is done for the supplied probes at the factory. It is recommended that calibration be done at least once a year or if a probe is replaced.

Calibration should only be attempted by CONFIDENT users. This means that, although calibration is relatively simple, it should not be attempted until the user has read the manual and is comfortable with the machine.

Reminder: In the upper right corner of the calibration screen is a blue question mark. Click on it for an exact explanation of calibration for the thermocouple probes and the chart recorder. If the steps in the explanation are followed, the calibration will be easy and successful.

For a more detailed explanation on how to calibrate your 2101 Rate freezer please refer to pages 23-30.

D. <u>START FREEZE RUN -</u>This menu button brings up the profile and freeze name selection screen.

E. <u>AUDIT FUNCTIONS -</u> This menu button brings up the audit trail details after enabling User Accounts / Security

F. <u>USER ACCOUNTS -</u> This menu button allows the user to configure multiple users and passwords, and also to enable or disable security. There are also different levels of access that can be assigned to each user. Click on the blue question mark in the upper right hand corner to see a description of the access levels.

NOTE: The user names and passwords set up within the Rate Freezer Software have nothing to do with Windows user names and passwords. They are separate and independent.

G. <u>EXIT -</u> Closes software.

H. <u>Preview -</u> This menu button allows the user to preview a previously programmed profile, or to see a graph of the rates in their programming as they make changes. This function is intended to simplify the creation of freezing profiles.

I. <u>LOGOUT -</u> This menu button is only usable when security is enabled in the user accounts menu. It allows users to logout of the system.

J. <u>CONFIG FIELDS -</u> This menu button allows the user to define the labels only for the database fields that can be saved for each freeze run. This information is entirely optional and is used for database searching of freeze run information.

Turn On Computer

1. Push and release the POWER button on the computer [not shown].

2. The computer will ask you to log in. The user name is RateFreezer and the password is custombio.

3. Once you have logged in Click the Icon labeled Rate Freezer to launch the application.

21 CFR PART 11

21 CFR Part 11 Security Functions.

Introduction:

21 CFR Part 11 is a component of the CGMP regulations in parts 210 and 211 (21 CFR Parts 210 and 211) governing electronic signatures and records in all program areas.   Entities that choose to keep electronic records and signatures that may be submitted to the FDA must follow these guidelines.

It is important to note that as of time of writing there is no certifying body for this guideline therefore no vendor can claim to be 21 CFR Part 11 Certified.

The 2101 Controller Software is designed to address each ruling in 21 CFR Part 11.   A list of the directives and an explanation on how the controller meets the directive is listed in Appendix A.

Enabling Security / 21 CFR Part 11.

The Security / 21 CFR Part 11 module is disabled by default.
In order to enable the process perform the following steps:

1.   From the main menu select User Accounts.
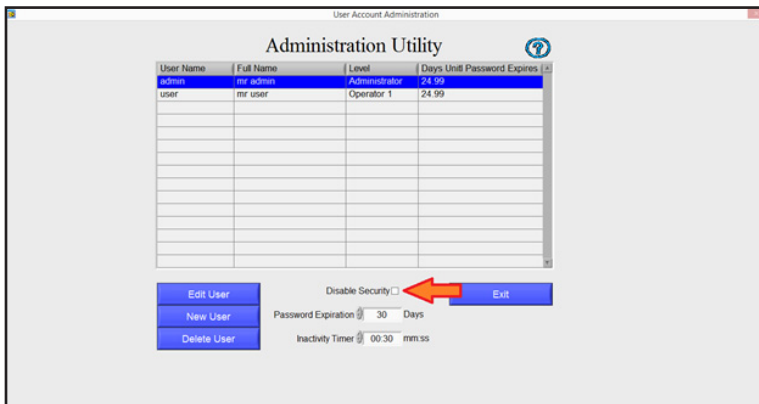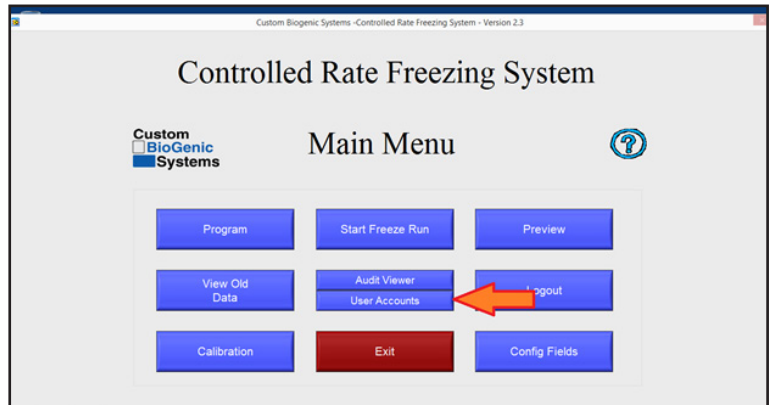
2.   Un-check the box disable security

3. Log in as the Administrator:

i. The first time you log in the user name and password are as follows:

User name: default
Password: administrator

Note that both the user name and password are lower case.

ii. At this time you should create a new administrator account and delete the default administrator account.

Creating a new account

To create a new User:

1. Ensure that you are logged in as the Administrator
2. From the Main menu select User Accounts
3. Click New User
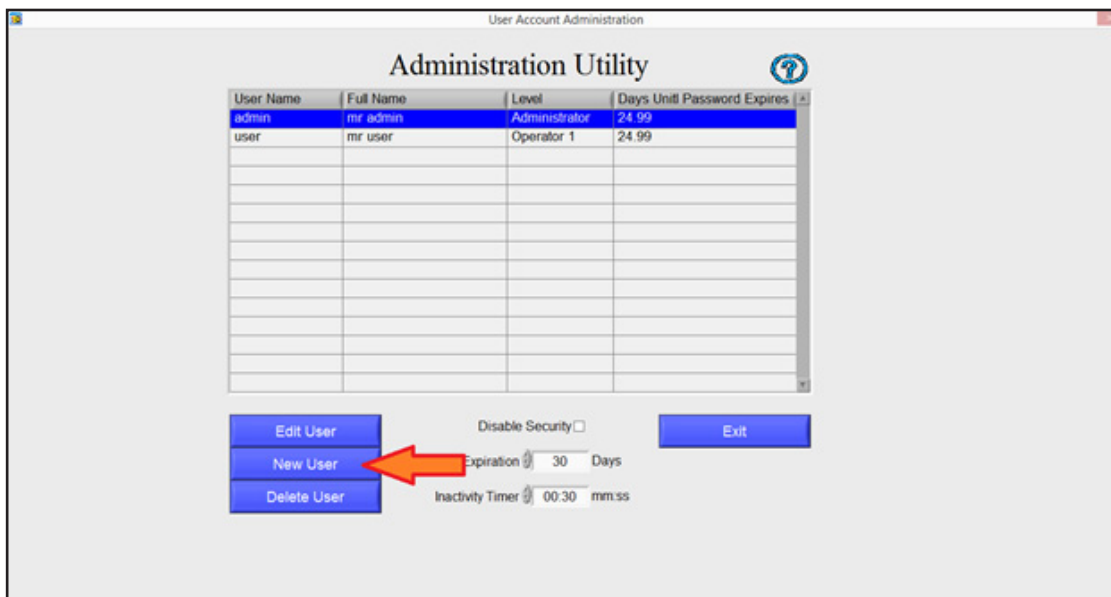
4. Enter the User Name and Full Name
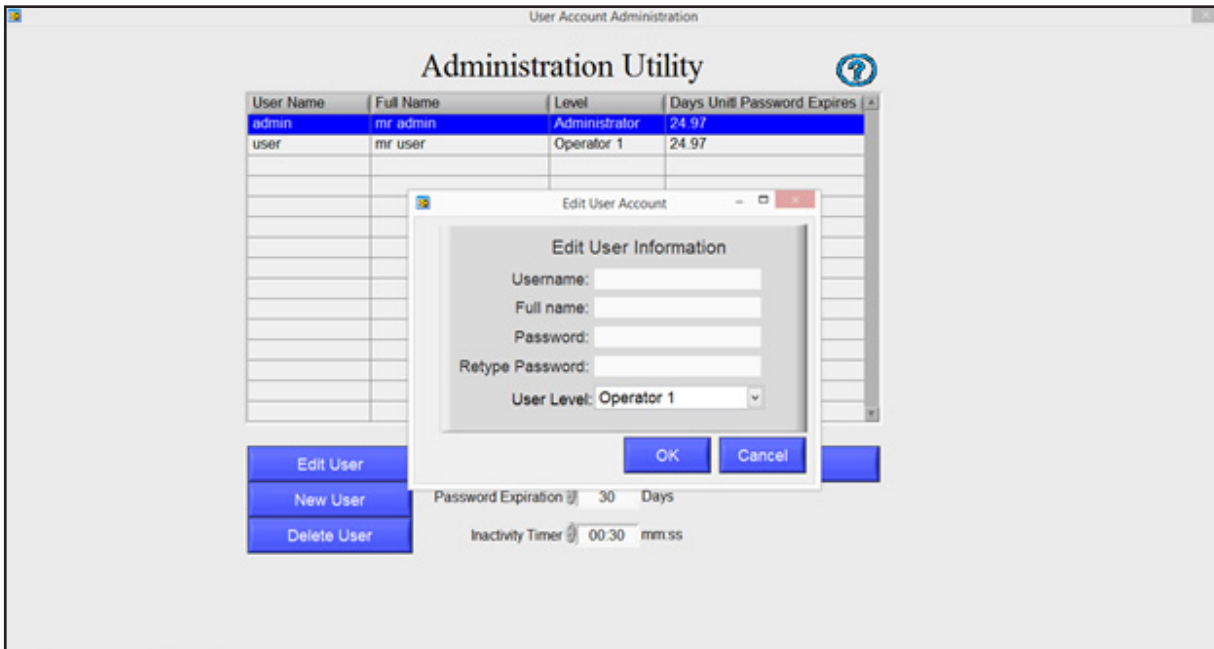
5. Enter a Password then Retype the password
6. Select the User Level

The first time that you are use the system, ensure that you create a new Administrator Account

There are 4 possible User Levels:

i. Operator 1- Has access to Program, Start Freeze Run, Preview and View Old Data
ii. Operator 2 – Has access to Start Freeze Run, Preview, View Old Data
iii. Operator 3 – Has access to Preview Only
iv. Administrator – Has access to all system functions.*

*Only Administrators can view the audit log and access security functions.

Note: When the new user logs in for the first time they will be required to change their password.
       Your SOP should prevent the sharing of passwords with other users or the Administrator.

Edit a User

To Edit a User

1. Ensure that you are logged in as the Administrator
2. From the Main menu select User Accounts
3. Click Edit User
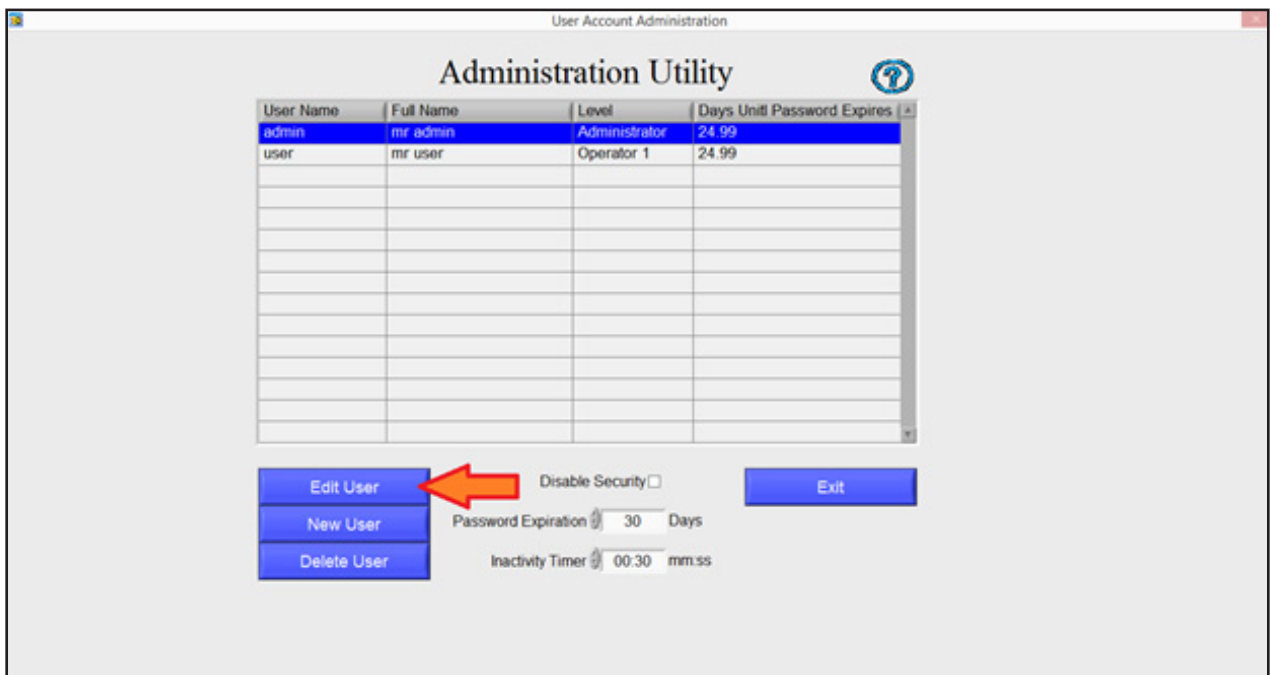
4. Change the information as necessary

Delete a User

To Delete a User

1. Ensure that you are logged in as the Administrator
2. From the Main menu select User Accounts
3. Click Delete User
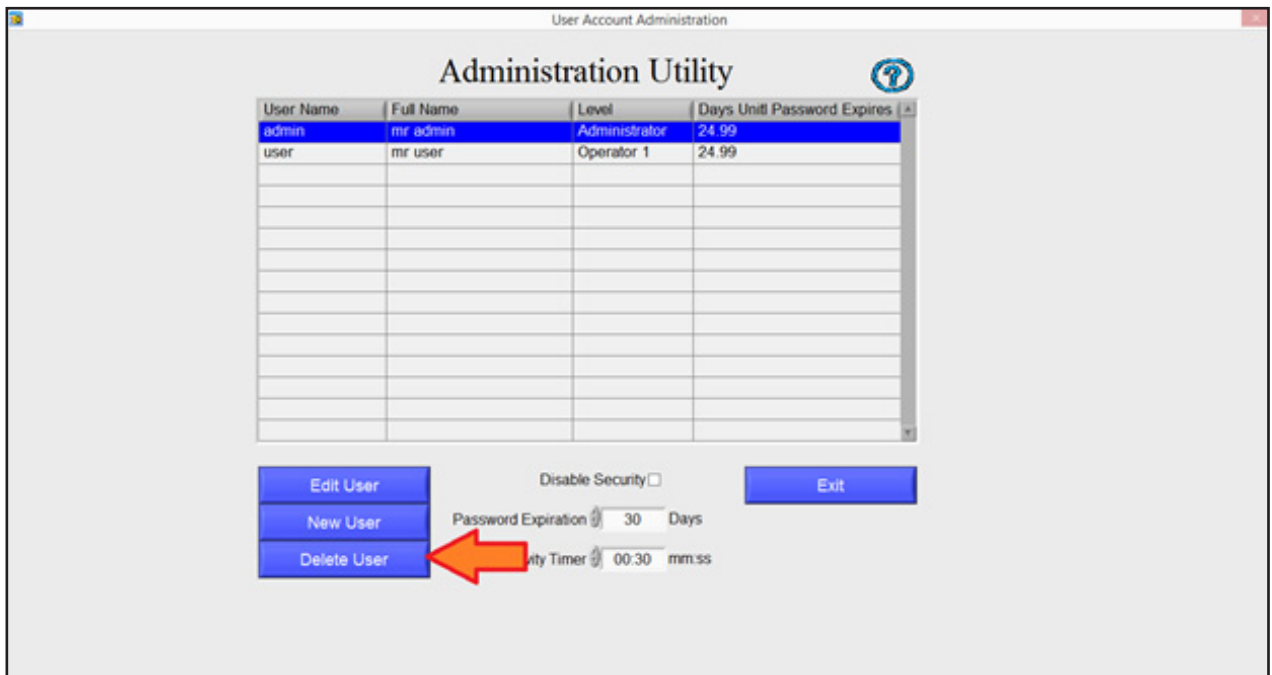
Setting the Inactivity Timer

According to the 21 CFR Part 11 ruling the system must allow you to set an inactivity timer. Once this time limit is reached the user is logged out and must log in again.

To set the Inactivity Timer do the following:

1. Ensure that you are logged in as the Administrator.
2. Select User Accounts
3. Set the Inactivity Time to the desired number of minutes and seconds – The default is 30 seconds.
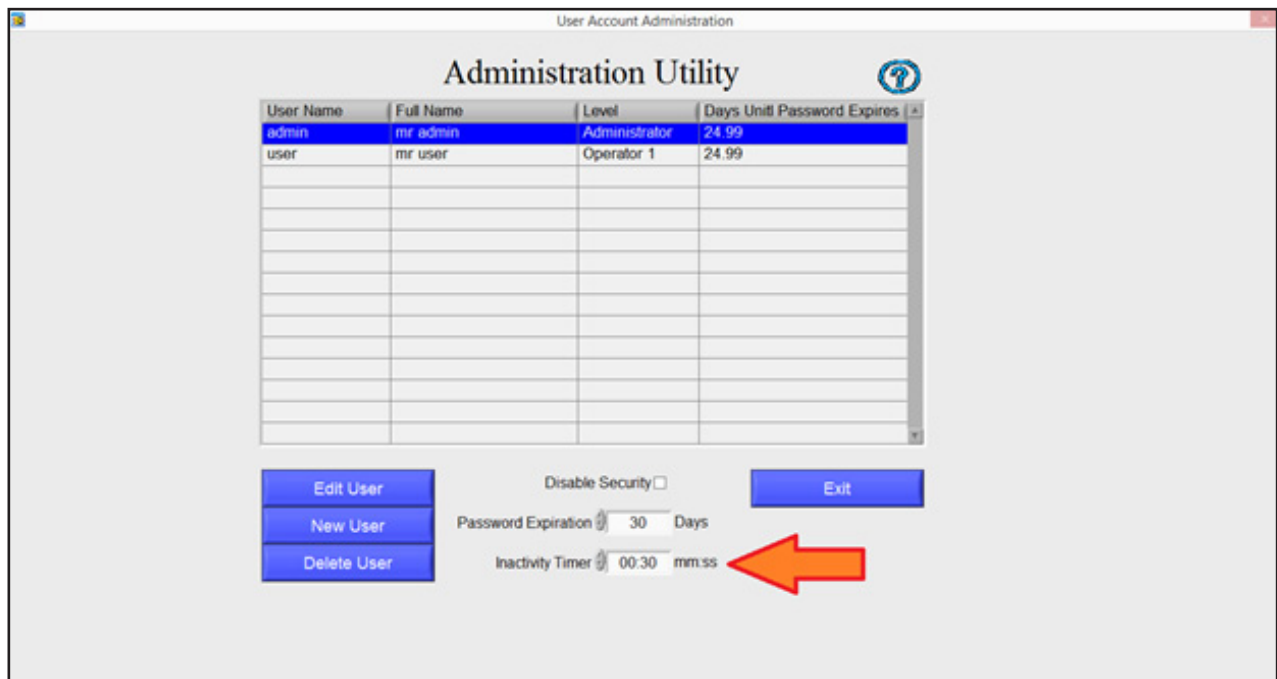
Note: The Inactivity Timer applies to ALL users.
The Inactivity Timer will not engage during a run cycle.

Setting the Password Expiration

According to the 21 CFR Part 11 ruling, Passwords must expire (and therefore be changed) a minimum of every 90 Days.

To set the expiration period do the following:

4. Ensure that you are logged in as the Administrator.
5. Select User Accounts
6. Set the Password Expiration to the desired number of days – The default is 30
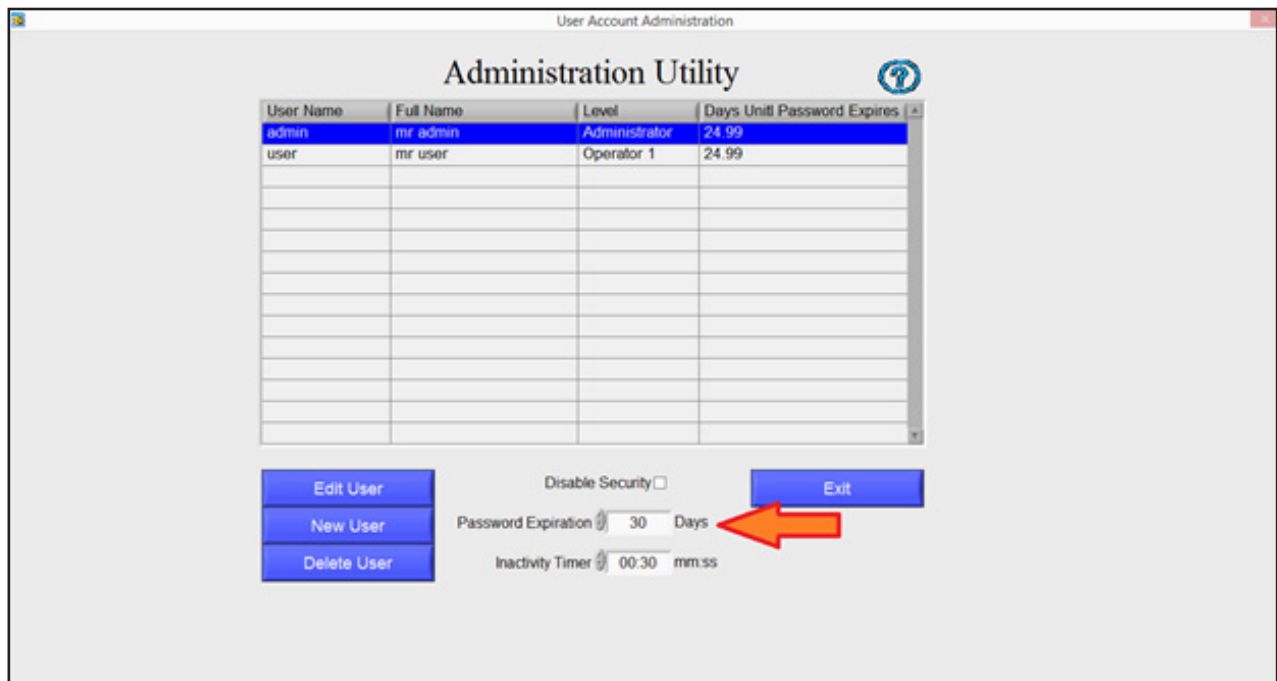
Note: The Password Expiration applies to ALL users.
        The grid displays the number of days before a Password will expire.

Viewing the Audit Trail

According to the 21 CFR Part 11 ruling the system must keep a complete history of all security related inter-actions with the system. The Audit Trail provides a record of all changes made to the Controlled Rate Freezer by users.

To View the Audit Trail:

1.   Ensure that you are logged in as the Administrator
2.   From the Main Menu click Audit Viewer
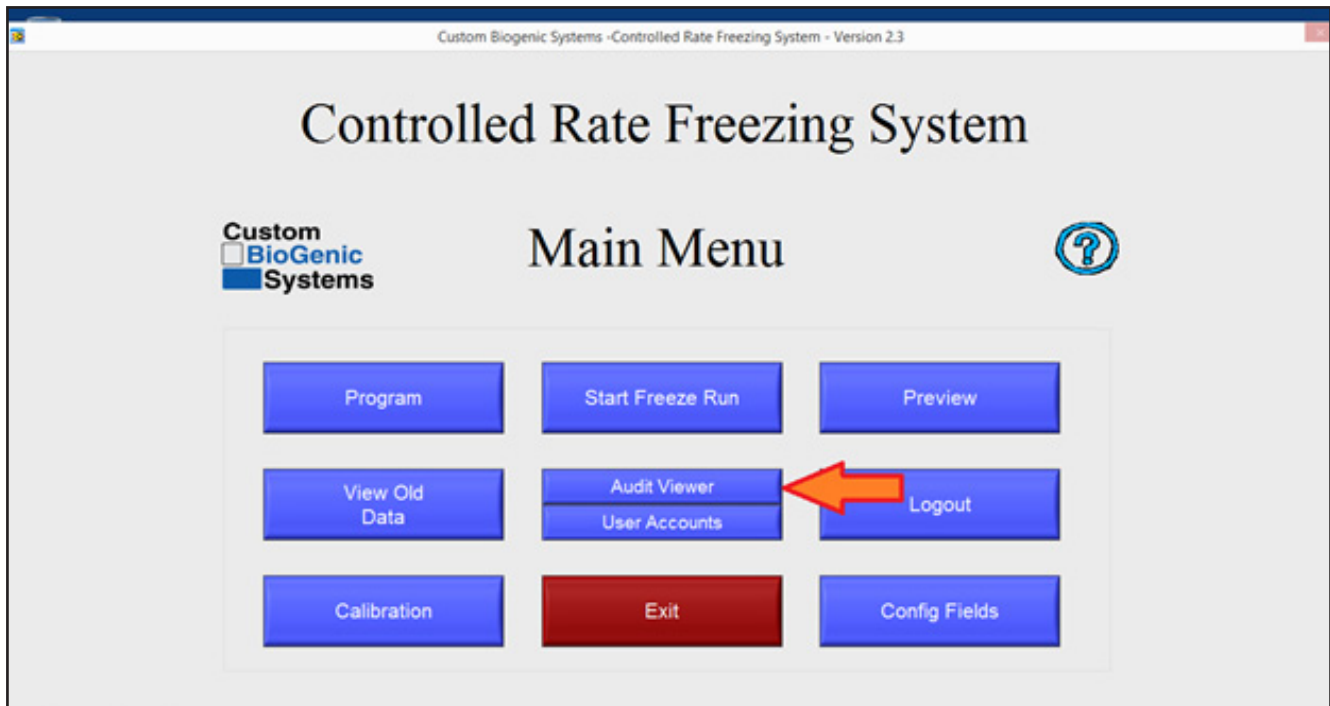
The system will now display a list of the events in the system.

You can filter this list by date as follows:

1. Click on the Event Query Type drop down, change from All Events to "In Date Range".
2. The Start Time Stamp and End Time Stamp will now be enabled.
3. Enter the Start Time and Date and End Time and Date, Alternatively you can click the calendar icon to select the time and date.
4. The Audit Trail will automatically be filtered as you make your selection.

Printing the Audit Trail:

The Audit Trail can be printed from the same screen by clicking the Print Button. The system will print the records that are currently displayed in the grid.

NOTE: The Audit Trail may contain information about users and passwords.
Care must therefore be taken when printing this log to ensure that it is not accessible by unauthorized persons.

Create a Program
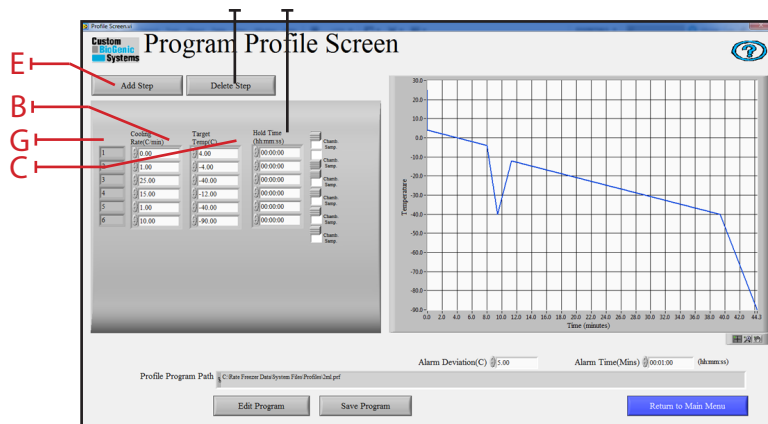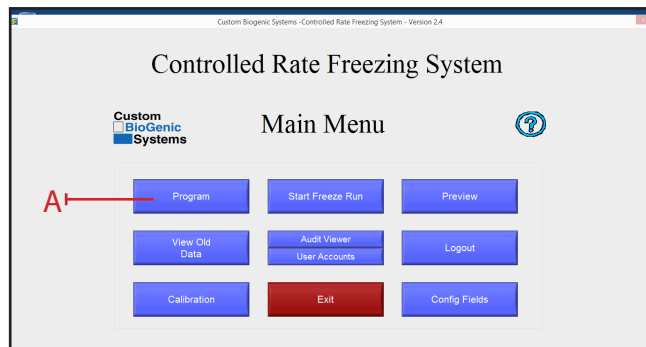
1. At the main menu click on the program button [A].

2. Clicking the program button [A] will open a new window called PROGRAM PROFILE. The program profile screen is where you will enter the steps of the program. The step number [G] will automatically be created when entered.

3. Click the pointer on the cooling rate area [B] and enter a desired cooling rate

4. Click the pointer on the target temperature area [C] and enter desired target temperature

5. Click the pointer on the hold time area [D] and enter the desired time (HH:MM:SS)

6. Click on add a step area [E] to add a program step.

7. Click on delete a step [F] to remove entire last step.

8. Verify all information is correct

9. Continue steps 3-6 until program is complete

NOTE: The recommended method for starting a freezing cycle is to program a wait function. Enter a 0 (zero) as the cooling rate by clicking the cooling rate area [B] (see program profile above). Enter a target temperature in area [C](see program profile above). This function will pre-cool the chamber and hold the chamber temperature at the programmed target temp [C](see program profile above). A 0(zero) degree rate will hold indefinitely at the programmed target temp [C](see program profile above).
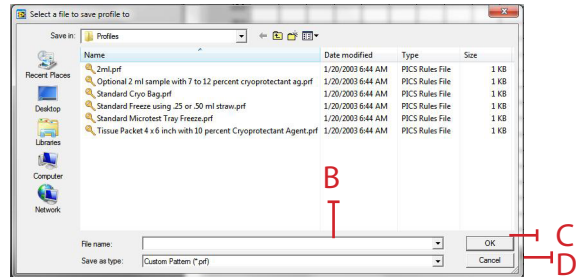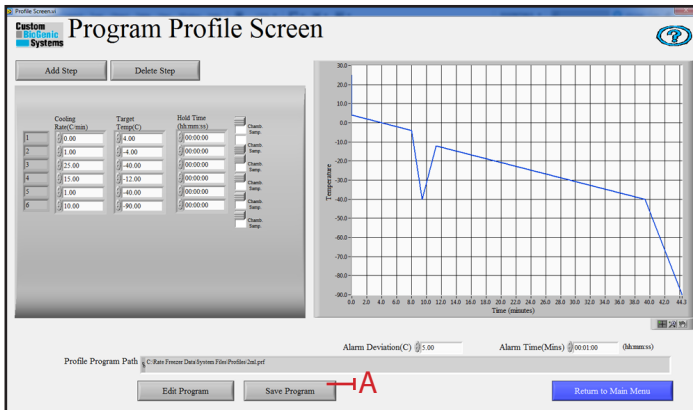
NOTE: If you do not desire a wait pre-cool function go to step 1 of the create a program section of this manual.

NOTE: If you desire a negative number for the target temperature you **must** enter a minus sign for temperatures below zero. (Example: -50 degrees C.)

NOTE: This software does not require an "end of program" command.

Save a Program

After you have created a program, you may save, edit, or delete it. To save a program:

1. Create a program (see page 17; steps 1-8)

2. Click on the SAVE PROGRAM button [A].

3. Type the name you wish to give to this program in the save profile window [B].

4. Click on the OK button[C]. The program is now saved in the computer.

NOTE: If you do not wish to save the new program click the CANCEL button [D].

Edit a Program
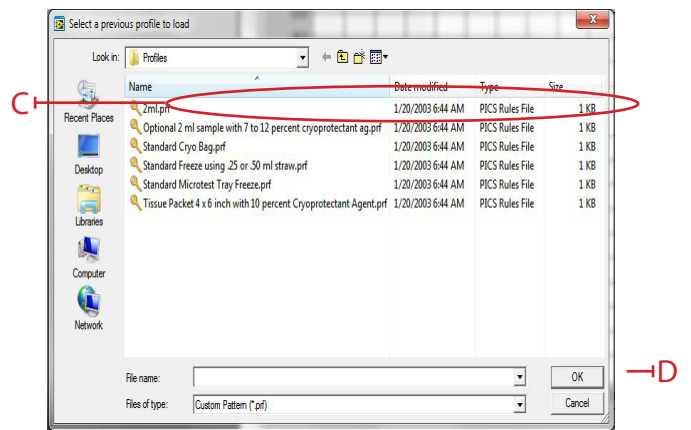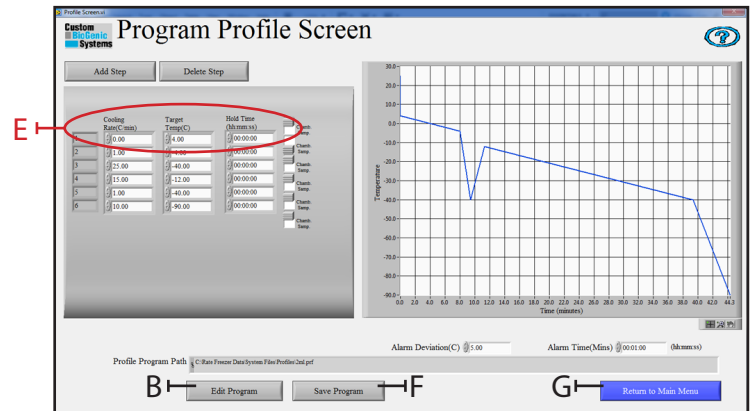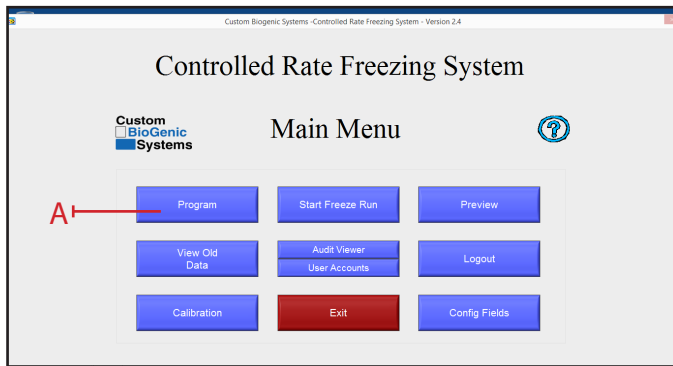
Custom BioGenic Systems has provided you with six preset programs that you can use as templates for many common freezing processes. (Both User-created and preset programs can be edited.)

1. At the main menu screen press the PROGRAM button [A].

2. At the program profile screen click the EDIT PROGRAM button [B]

3. Locate the program to be edited [C} and click OK [D] to open it.

4. Move the pointer to the step you wish to change and click on that area [E].

5. Use the backspace or delete keyboard keys to delete the value you wish to change.

6. Enter a new value.

7. Repeat steps 4-7 until you have made all the changes you desire.

8. If you wish to save your changes click the save program button [F]. (see page 18 for saving instructions)

9. If you do not wish to save your changes click the return to main menu button [G].

Operating Instructions

Run a Program
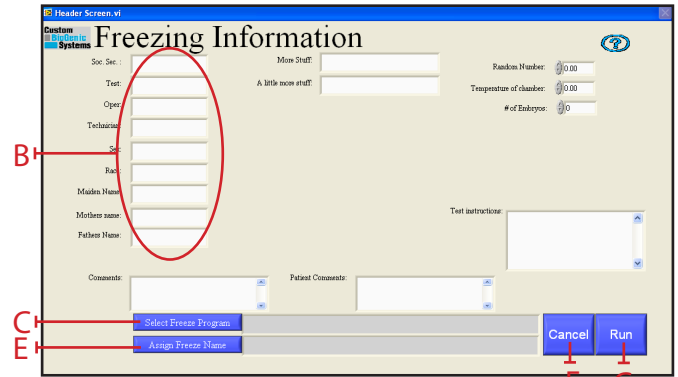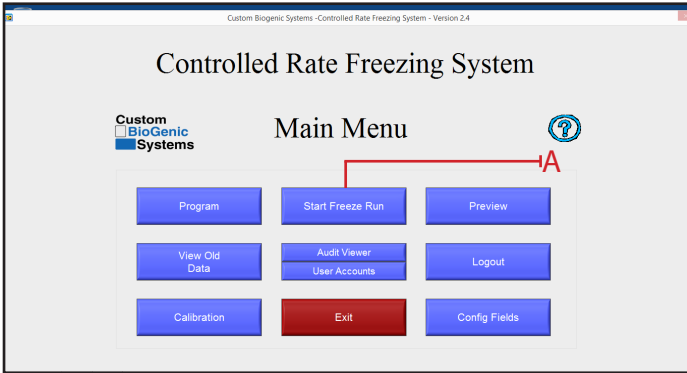
Every time you run a program you create a unique set of data. In many cases you will wish to save this data using a unique file name; if you don't your old program data will be overwritten by the latest data.

1. At the MAIN MENU screen click the START FREEZE RUN button [A].

2. At the FREEZING INFORMATION screen fill in the optional fields [B] with the information you desire.

> **NOTE:** The freezing information [B] is a form that is customized to each customer's need.
> The information entered will differ according to use and customer.

3. Click the SELECT FREEZE PROGRAM button [C].

(Use config fields on the main screen to customize fields)
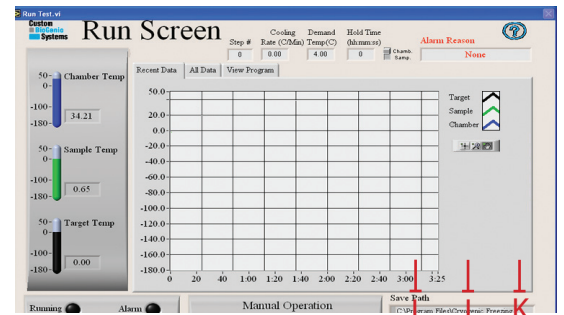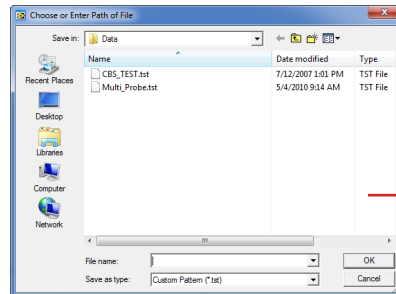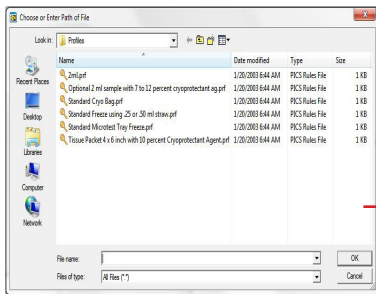
4. Select a program profile from the window and click OK [D].

5. Click ASSIGN FREEZE NAME [E].

6. Assign the freeze a name and click OK [H]

7. To start a freeze click RUN [G].

8. To cancel a freeze click CANCEL [F]

9. To begin the freeze run click RUN [I].

10. At the end of a freeze run click RUN WARM [J] (this will automatically warm the chamber up to 25ºC for shut down)

11. Click EXIT [K] after freeze run is complete

CBS

Operating Instructions

Preview a Profile
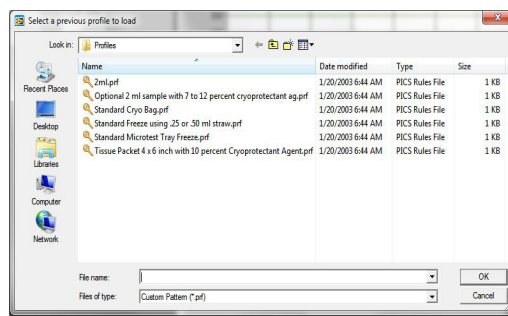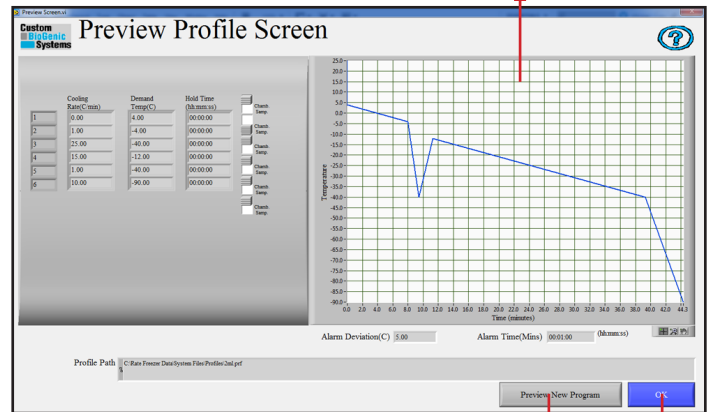
NOTE: Custom BioGenics recommends that you preview a program before running it. By doing this you can often identify incorrect information by previewing the program as a graph.

1. At the main screen press the PREVIEW button [A].

2. At the preview profile screen select a profile to load and click OK [B].

3. Watch the screen [C] display the freezing protocol.

4. When you have finished previewing the protocol hit the OKAY button [D] to return to the main menu.

5. To preview a different program click PREVIEW NEW PROGRAM [E].

Calibration

1. Unplug the chamber from the power source. The controller (computer) will continue to operate on battery power.
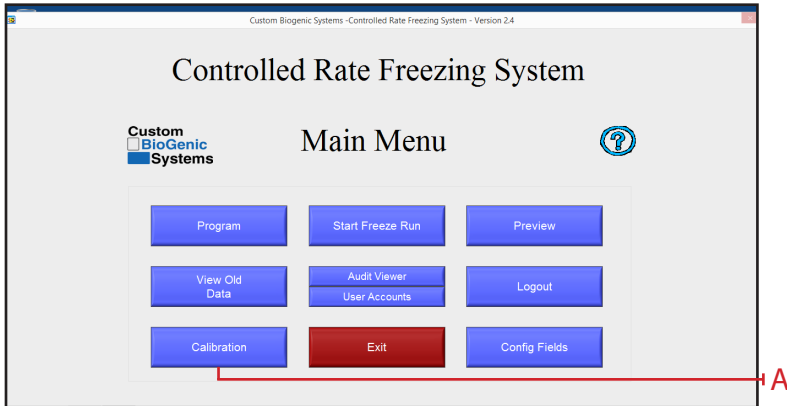
2. At the main screen click the CALIBRATION button [A].
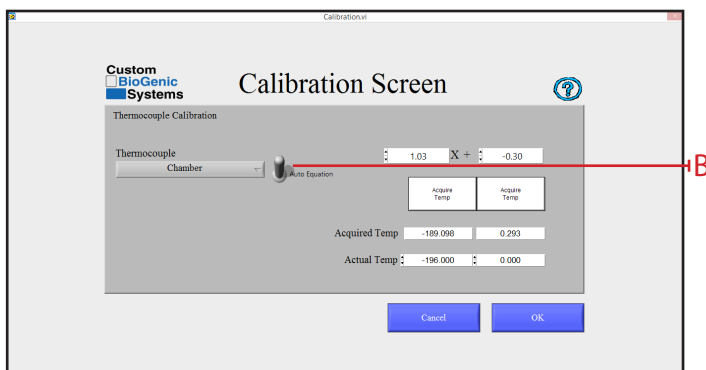
3. On the calibration screen, verify the toggle switch is in the Auto Equation position [B]. If not, click on switch to change to the Auto Equation position.

4. The unit is now ready to be calibrated.

Chamber Probe Calibration

4 Phillips Head Screws
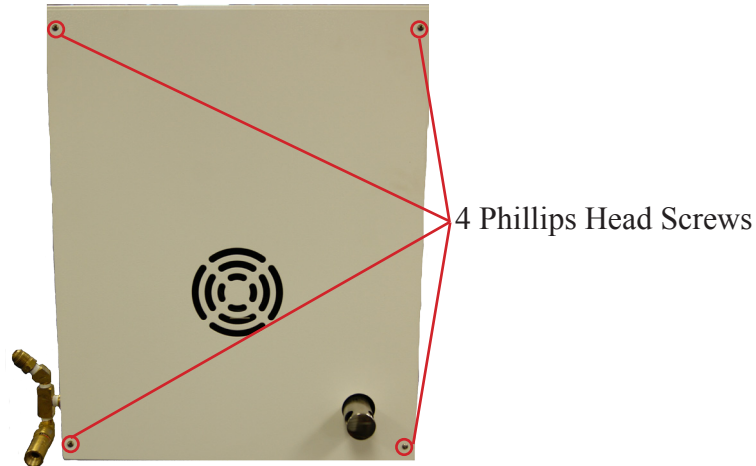
1. Remove back cover of freezing chamber by removing 4 phillips-head screws. [A]
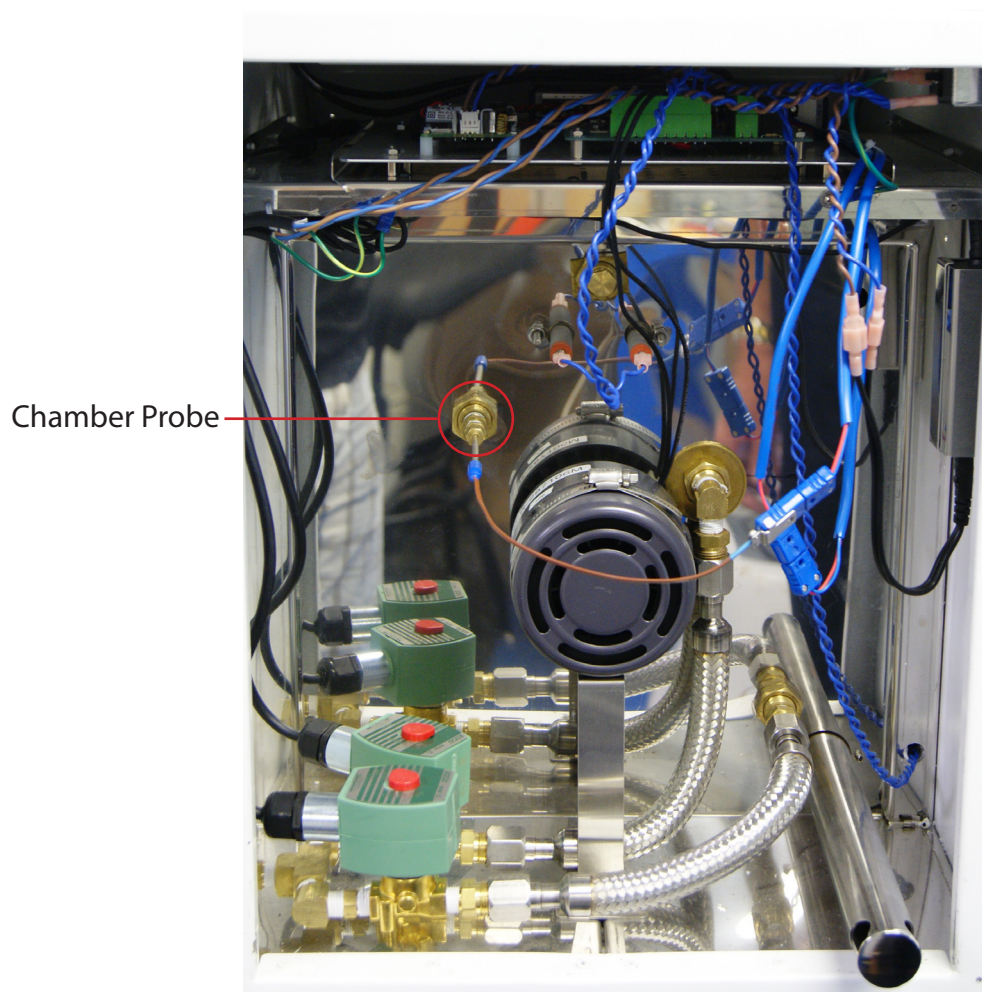
Chamber Probe

2. Locate and remove chamber probe by loosing the brass fitting using 3/8" wrench. [B]
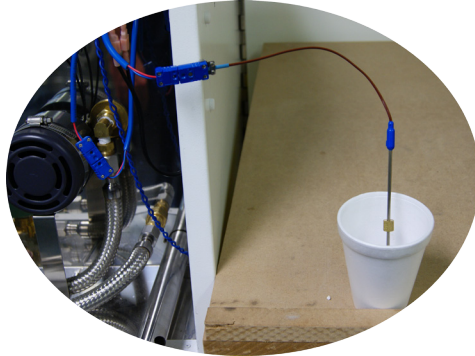
3. Place chamber probe into ice bath and allow 10 - 15 seconds for chamber probe temperature to stabilize.
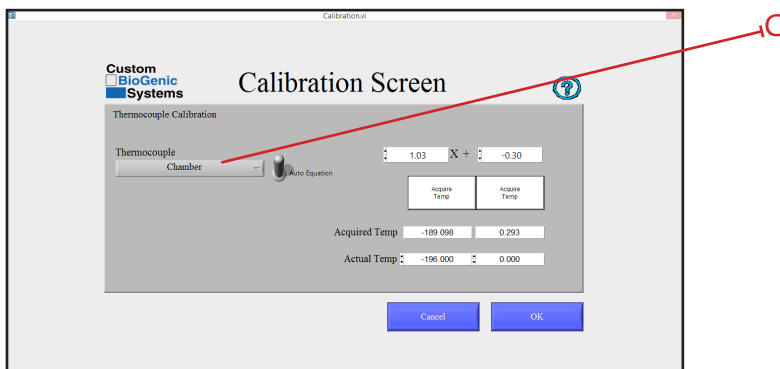
4. Click on the drop down box that is under the header of Thermocouple and select chamber. [C]
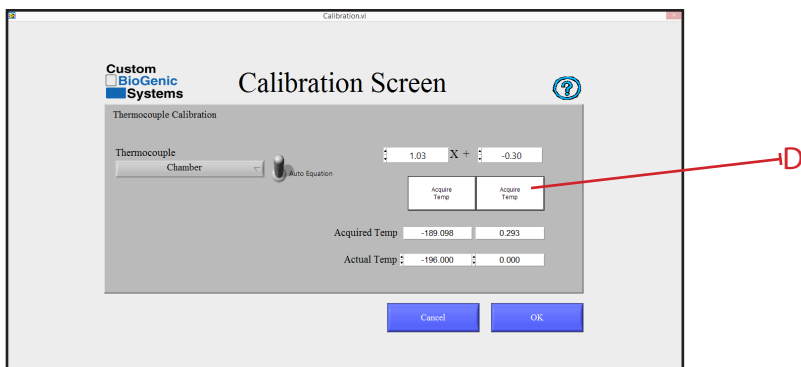
5. Click on the white box that is labeled Acquire Temp. [D]
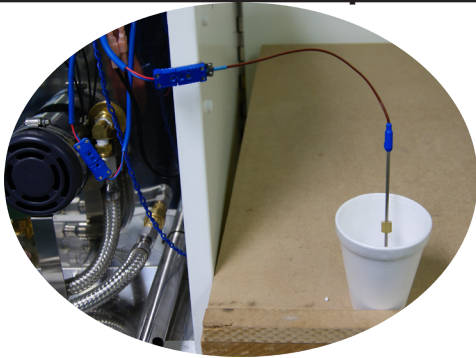
6. Remove the chamber thermocouple from the ice bath, allow probe to dry before placing in a container of liquid nitrogen. Allow 10 - 15 seconds for chamber probe temperature to stabilize.
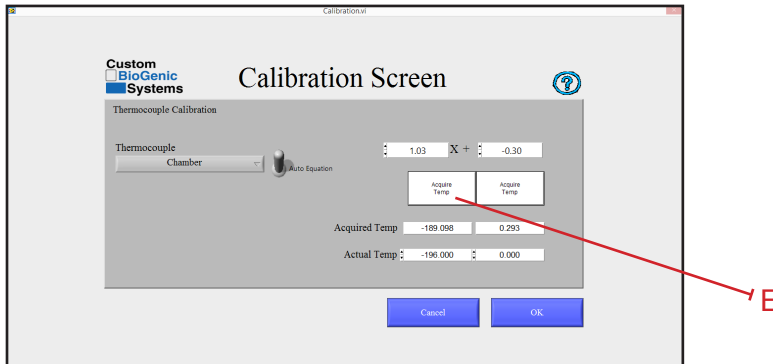
7. Click on the white box that is labeled Acquire Temp. [E]

8. Remove the probe from liquid nitrogen and allow the probe to return to room temperature.

Chamber Probe
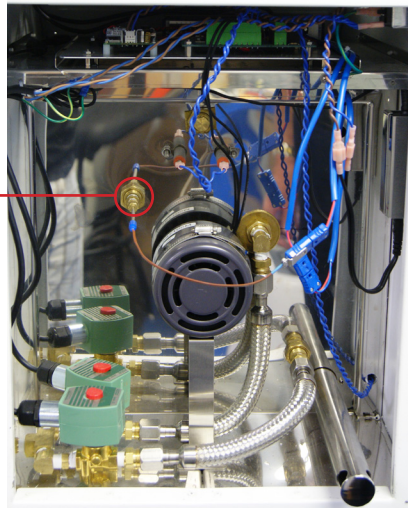
9. Locate and replace the chamber probe by tightening the brass fitting using 3/8" wrench. [F]

4 Phillips Head Screws
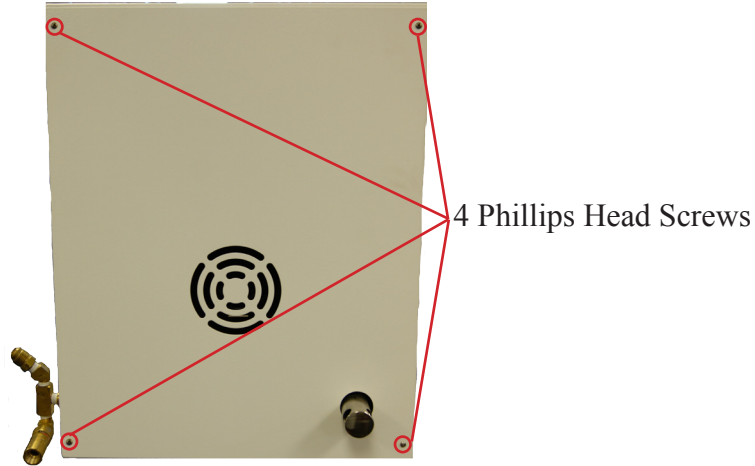
10. Replace the back cover of freezing chamber by tightening the 4 phillips head screws. [G]

Sample Probe Calibration
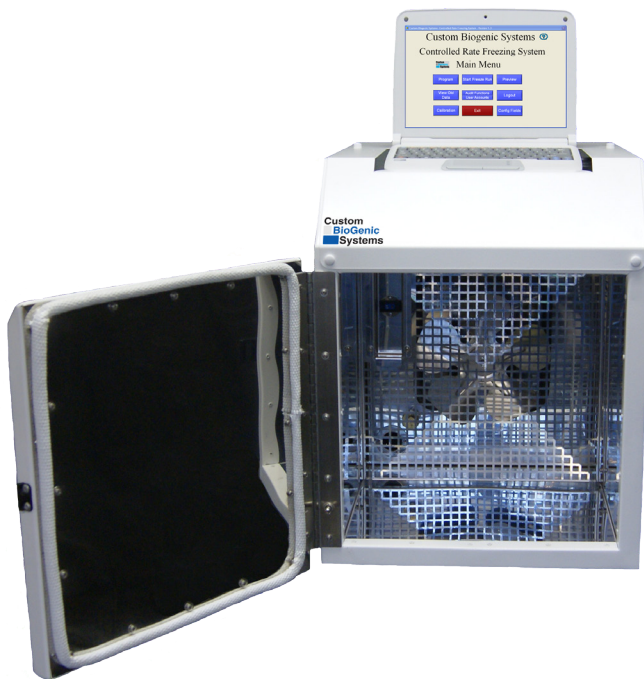
1.   Open the chamber door. [A]
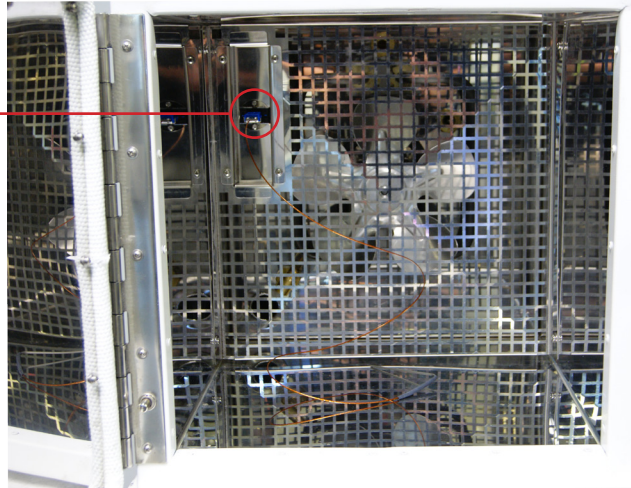
Sample Probe

2. Plug in the sample probe into the sample probe socket. [B]

3. Place sample probe into ice bath and allow 10 - 15 seconds for sample probe temperature to stabilize.

C
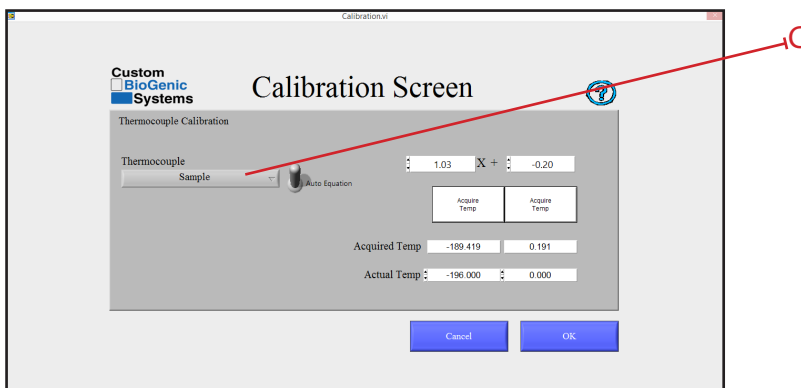
4. Click on the drop down box that is under the header of Thermocouple and select sample. [C]
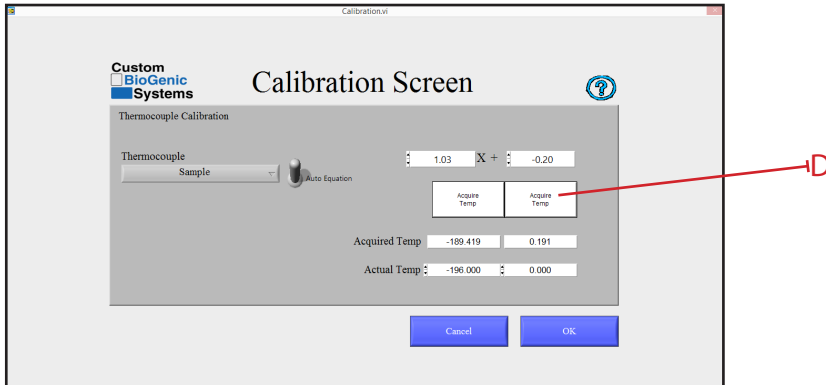
5. Click on the white box that is labeled Acquire Temp. [D]

6. Remove the sample thermocouple from the ice bath, allow probe to dry before placing in a container of liquid nitrogen. Allow 10 - 15 seconds for sample probe temperature to stabilize.

Calibration Screen
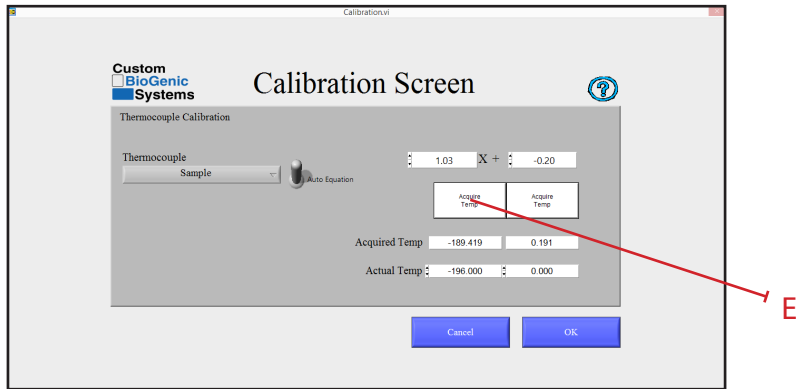
7. Click on the white box that is labeled Acquire Temp. [E]

8. Remove the probe from liquid nitrogen and allow the probe to return to room temperature.

9. Plug chamber into power source and resume normal operation

Logout of the System
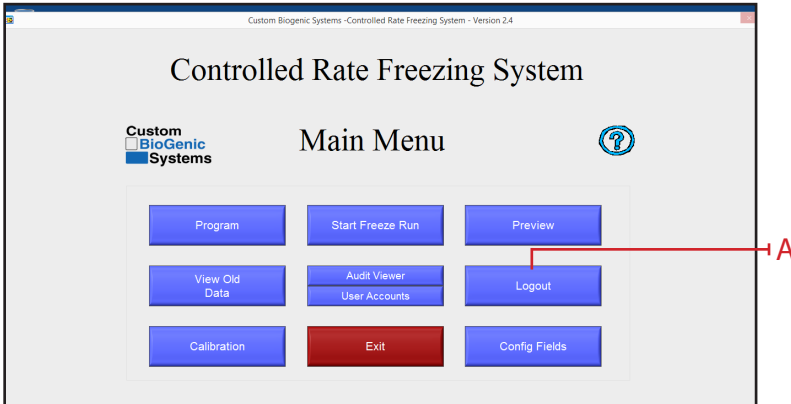
1. At the main menu screen click the LOGOUT button [A].

> **NOTE:** Logging out of the system brings up the Log On screen so another user can enter their login and password if desired.

Exiting of the System
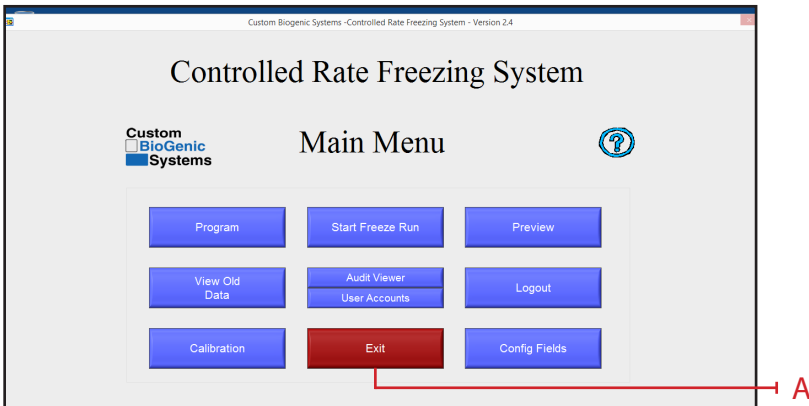
1. At the main menu screen click the EXIT button [A].

> **NOTE:** Exiting the system shuts down the software

Theory Of Operation

This Cryogenic Rate Freezer freezes at pre-defined, user programmable rates. This means that the user has total freedom when it comes to programming their freezing profiles. A few good practices when programming and running profiles is: 1) THE CHAMBER TEMPERATURE SHOULD BE USED FOR CONTROLLING THE FREEZING OF THE SAMPLE. This means that, due to the principles of Thermodynamics, any mass (such as a sample) that is within the chamber HAS to follow that chamber's temperature profile. 2) THE SAMPLE TEMPERATURE SHOULD ONLY BE USED TO AUTOMATICALLY CONTROL THE ADVANCEMENT OF STEPS WITHIN A PROFILE, NOT TO CONTROL THE ENTIRE FREEZING PROCESS. 3) PLACING THE SAMPLE PROBE WITHIN THE SAMPLE WILL ALWAYS YIELD THE MOST ACCURATE AND REPEATABLE GRAPH LINE. If it is not possible to place a probe inside a sample due to the sensitivity of the material, an equivalent dummy sample can be used. This just involves using the same type of sample receptacle (i.e. vial, bag, straw) that has an equivalent mixture of whatever is being frozen, minus the actual sample material (See page 35&36 for probe placement). In this way the user can be confident they're getting the most accurate and repeatable results possible, without compromising an actual sample.

The Notebook Computer

The 2101 Controller is a Windows Based Computer running specific drivers and software in order to actuate the Controlled Rate Freezer in a manner that is reproducible and consistent. The controller is configured in a specific way to prevent other software from interrupting or slowing processing cycles while executing directives to the National Instruments DAC's.
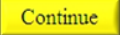
Installation of 3rd party Software or connection to the internet may cause the controller to deviate from it's intended function and is therefore prohibited. Connecting to the internet or executing 3rd Party Software will void the Warranty.

Rationale:

1. The Controller is configured from a Windows Image that has been tuned to ensure that no interference occurs with the Control Rate Freezer Software.

2. The Controlled Rate Freezer has passed verification and validation tests that will be invalidated if 3rd Party Software is installed on the device.

3. The Controller has been validated and verified with a specific version of windows and specific drivers. Updating the windows version or drivers will invalidate the verification and validation tests as there is no guarantee that future updates or driver changes will not change the function of the controller.

4. The controller has no access to the internet which reduces exposure to viruses.

5. An exception is made for printer drivers and USB memory Sticks used with the 2101 controller.

6. It is recommened that USB Memory Sticks used with the 2101 controller are periodically scanned for Viruses and only used for the purpose of moving run files from the rate freezer to the USB Memory Sticks.

The Hold Function

Another important aspect of the Cryogenic Rate Freezer is the fact that ANY STEP WITHIN A PROFILE THAT IS PROGRAMMED WITH A ZERO DEGREE RATE AUTOMATICALLY GETS INTERPRETED BY THE SOFTWARE AS A "HOLD" FUNCTION. This means that if the step is programmed to cool at 0° per minute, the machine will attempt to cool to the set point as fast as possible and then hold there until the [Continue] button is pressed, regardless if any hold time is programmed in. This is typically done during the first step in a profile based on how the user prepares the samples for insertion into the chamber. EXAMPLE: A user is freezing 2ml vials of fluid. They keep the samples in an ice bath until they are ready to insert them into the chamber. An ice bath is typically no warmer than +4°C, so the user programs the first step in the profile to cool at 0° per minute down to +4°C. The ZERO DEGREE RATE causes the chamber to cool to and hold at +4°C. The user then loads the samples into the chamber, presses the [Continue] button, and the freezing profile advances to the next step. It will then continue to advance through the programmed steps as long as another ZERO DEGREE RATE is not encountered.

Alarm Deviation

The alarm deviation consists of two things. 1) The temperature difference between the CHAMBER and TARGET values that has to exist for a TRACKING ALARM to occur, and 2) The amount of time that these two values are not equal before a TRACKING ALARM occurs. The default settings are 5°C for 1 minute. This means that if the CHAMBER temperature is deviated 5°C or more from the TARGET temperature, for 1 minute, a TRACKING ALARM occurs. These values can be changed in the PROGRAM menu.

Reviewing Data

Data can be viewed as it is being acquired, and after the freeze run has completed. When viewing data during a freeze run, there are two tabs at the top of the graph labeled RECENT DATA and ALL DATA. The RECENT DATA view is selected by default and shows only the most recent portion of the freeze run. The ALL DATA view is used to see the entire run up to the current time.

> **IMPORTANT:** The RECENT DATA view should be selected for the majority of the run. The ALL DATA view is used to periodically check the entire run up to the current time. If the ALL DATA view is left selected during the entire run, the time that is logged will become offset from "real time".

Due to the fact that the software is continually updating and displaying a growing number of data points, the same loop of code takes longer and longer to execute as time goes on. This manifests itself as a time loss as compared to real time. It has been observed to be 10-15 seconds of loss per hour. While it does not adversely affect the operation of the Cryogenic Rate Freezer, this time loss does exist, but only builds up when the ALL DATA view is selected for an entire freeze run. The vast majority of users will not be concerned with this effect.

When viewing data after a freeze run, click on the [View Old Data] button on the main menu to select a file to view. Use the DATA VIEWING FUNCTIONS [A], indicated by the small magnifying glass, cross hair, and hand icons located to the right of the graph to view the data. Clicking on these icons reveals zoom, selection, and manipulation modes. The DATA VIEWING FUNCTIONS are also available during a freeze run. ⊢A

Advanced Setup

The following options require the modification of an INI file located in the hard drive of the notebook PC, C:\Program Files\Cryogenic Rate Freezer\release custom biogenic systems\data\crfs**. DO NOT ATTEMPT TO MODIFY THIS FILE UNTIL THIS ENTIRE MANUAL IS READ AND UNDERSTOOD.**

After the INI file is modified correctly, press ctrl+S to save the INI file in its modified form. Only then will the changes take effect.

Printing Options

There are several printing options that can be enabled through the modification of the INI file. These are as follows:

SHORT = info header and graph, default setting.

LONG = info header, graph, and every data point taken from the thermocouples during the run.

> **WARNING:** This option produces hundreds of pages of data and is usually only needed for validation purposes. If it needs to be used, make sure to switch the option back to SHORT or GRAPH to avoid printing hundreds of pages of data every time a freeze run graph is printed.

GRAPH = graph only printouts.

Audit Trial Functions

The audit trail is an advanced feature that allows the tracking of freeze runs, new users added, users deleted, users edited, and profile changes. It also keeps track of invalid log ins and locks the system out after repeated failed attempts. It only operates if security is "Enabled" in the user accounts menu. The audit trail is saved as an un-modifiable file and builds up indefinitely until the hard drive runs out of space. It is possible to disable the audit trail while still retaining user account functionality. Consult factory for details.

Sample Probe Placement

Sample probe placement is very important. The position of this probe determines the accuracy and repeatability of the sample trace line on the viewer screen .

Vial Probe Placement

Probe tip must be equal distance from each side of the vial and from the bottom of the vial.

Probe Tip

Bag Press Probe Placement
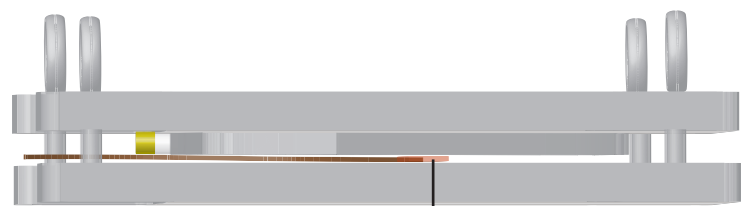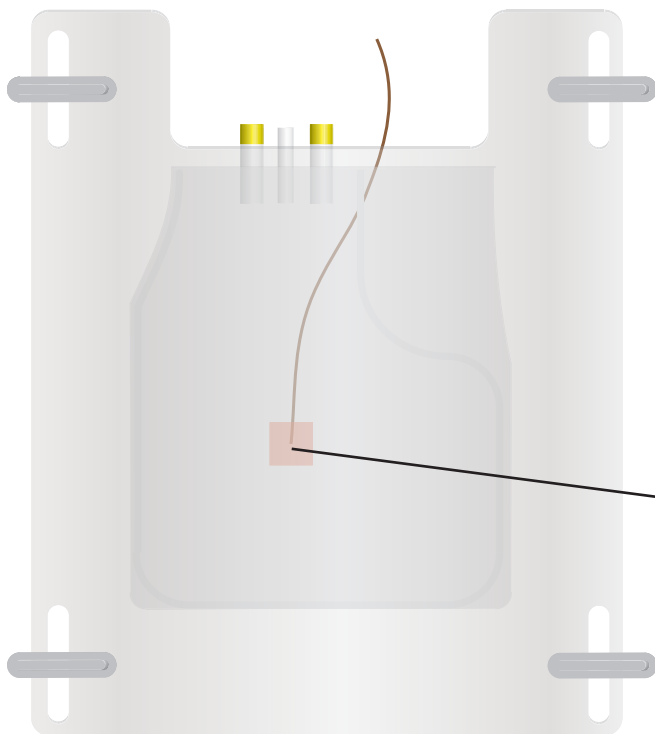
Plastic probe end must be positioned in the center of the fluid that is inside the bag. making sure there is no contact with air bubbles that may be present in the bag.

Canister Probe Placement
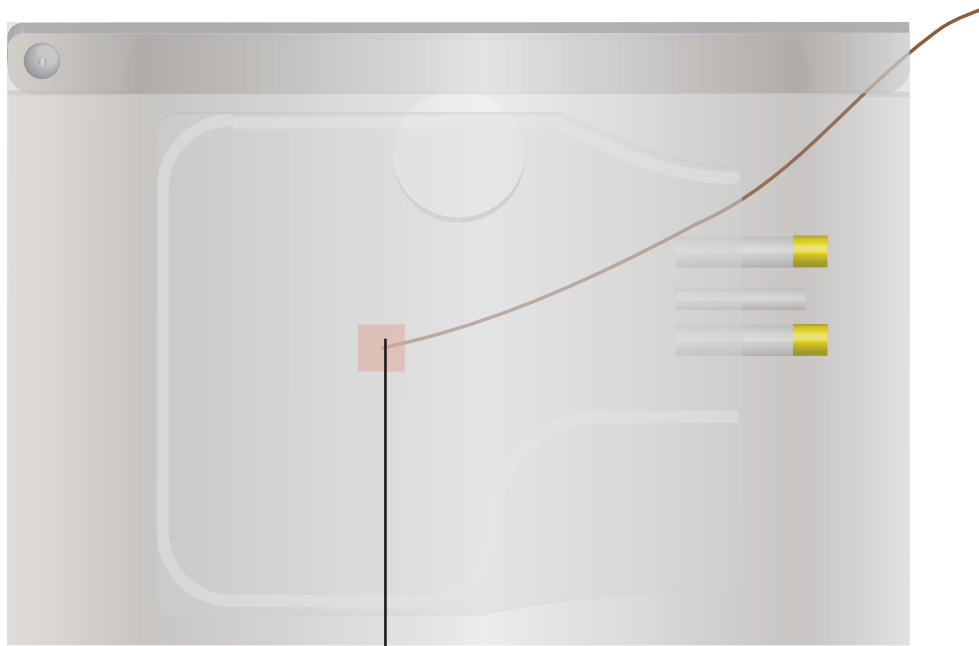
Plastic probe end must be positioned in the center of the fluid that is inside the bag. making sure there is no contact with air bubbles that may be present in the bag.

Proper Run

TROUBLESHOOTING GUIDE: ALARMS

CONDITIONS	CAUSES	SOLUTIONS
Sample Probe Alarm	◆ One (or both) of the thermocouple's conductors are broken or disconnected. This can occur anywhere between the tip of the probe and the NIDAQ Modules.	◆ This alarm is NOT self correcting, and only goes away once the cause has been fixed and the software re-started. Isolate the open (or broken) connection(s). The most common cause is within the thermocouple connection jacks, anywhere between the tip of the probe and the NIDAQ modules. Start by shorting the Female sample probe jack located in the upper left corner of the fan guard. If the alarm goes away, you know the problem is in the probe. If it doesn't go away, continue your way back towards the NIDAQ modules, checking the connections.
Chamber Probe Alarm	◆ One (or both) of the thermocouple's conductors are broken or disconnected. This can occur anywhere between the tip of the probe and the NIDAQ modules.	◆ This alarm is NOT self correcting, and only goes away once the cause has been fixed and the software re-started. Isolate the open (or broken) connection(s). The most common cause is within the thermocouple connection jacks, anywhere between the tip of the probe and the NIDAQ modules. Start by shorting the Male Chamber probe jack located in the rear 2100 housing. If the alarm goes away, you know the problem is in the probe. If it doesn't go away, continue your way back towards the NIDAQ modules, checking the connections.

C B S

TROUBLESHOOTING GUIDE: ALARMS

CONDITIONS	CAUSES	SOLUTIONS
Tracking Alarm	◆ The chamber temperature has been deviated from the target temperature for the programmed amount of time and temperature deviation.	◆ This alarm is self correcting, which means that the alarm will reset once the values come back into range. Verify proper LN2 supply operation, i.e. correct pressure(18-22 psi, 22 psi max),and use of the shortest possible transfer hoses. Also, alarm time and deviation are saved along with the steps in a freezing profile. The default values are 5 degrees of deviation for 1 min. These may need to be adjusted depending on the installation of the user's LN2 supply and freezing program. Adustments to the Default values can be made on the Program Screen.

C-B-S

2101 RATE FREEZER PART I.D.

Description	Part Number
1) 2101 Frame Assembly	3122-F601
2) 2101 Plumbing Assembly	SEE PAGE 41
3) 2101 Rear Service Cover	3101-F137
4A) Fan Motor 120 Volt	M001-0004
4B) Fan Motor 240 Volt	M001-0003
5) 10.2" Asus Computer	E001-0375
6A) Chamber Heater 110 Volt	H001-0001
6B) Chamber Heater 220 Volt	H001-0002
7) 8" Fan	F001-0008
8) 2101 Fan Guard	3101-F141
9) 2101 Probe Pocket	3101-F142
10) Female Lid Temp Thermocouple Assembly	5617-E601
11) 2101 Door Assembly	3116-F601
12) 2101 Hinge Assembly	3118-F601
13) Chamber Door Gasket	G001-0004
14) 2101 Exhaust Tube Assembly	3117-F601

C B S
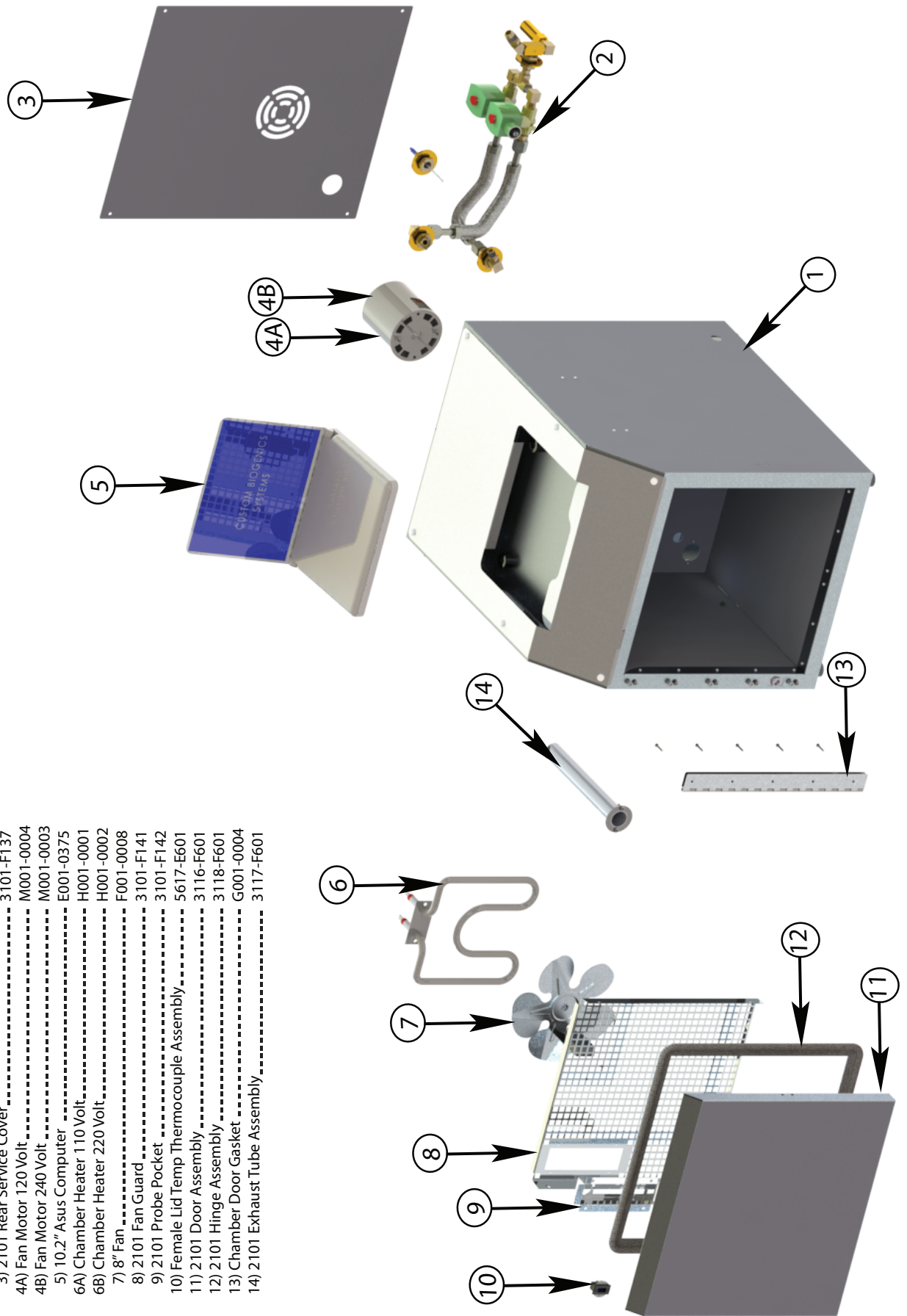
2101 RATE FREEZER PLUMBING PART I.D.
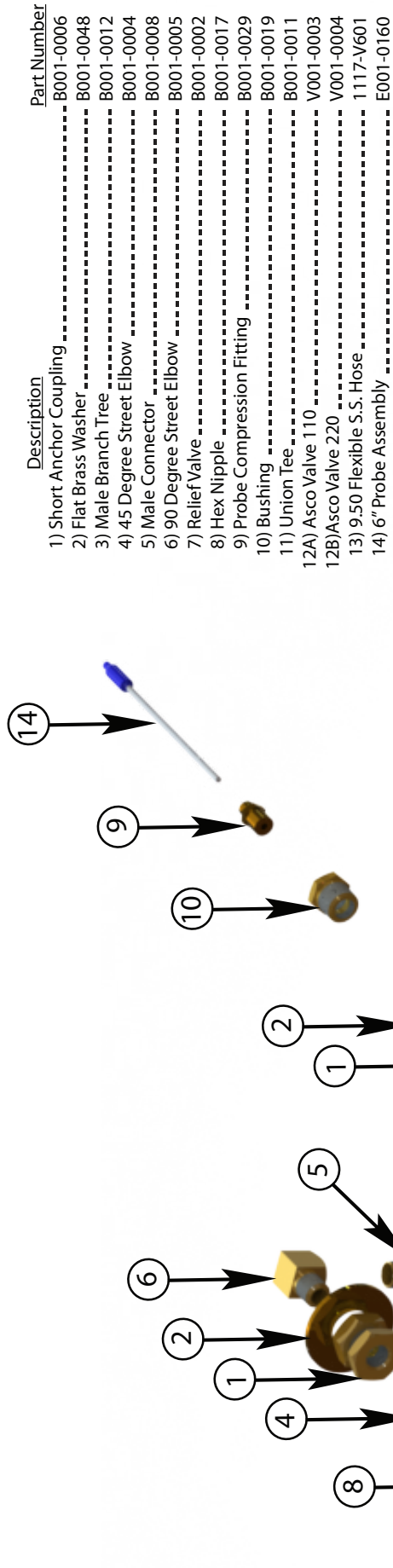
	Description	Part Number
1)	Short Anchor Coupling	B001-0006
2)	Flat Brass Washer	B001-0048
3)	Male Branch Tree	B001-0012
4)	45 Degree Street Elbow	B001-0004
5)	Male Connector	B001-0008
6)	90 Degree Street Elbow	B001-0005
7)	Relief Valve	B001-0002
8)	Hex Nipple	B001-0017
9)	Probe Compression Fitting	B001-0029
10)	Bushing	B001-0019
11)	Union Tee	B001-0011
12A)	Asco Valve 110	V001-0003
12B)	Asco Valve 220	V001-0004
13)	9.50 Flexible S.S. Hose	1117-V601
14)	6" Probe Assembly	E001-0160

C B S

1.   Specific Response to 21 CFR Part 11.100 General Requirements:

21 CFR Part 11 Rule	2101 Controlled Rate Freezer
(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.	The 2101 Controlled Rate Freezer specifically does not allow passwords to be re-used. The 2101 Rate Freezer does not allow user names to be used more than once. The 2101 Controlled Rate Freezer forces users to change their passwords once they have been assigned by the Administrator. This ensures that an individual password cannot be known by another user. As part of the Standard Operating Procedure the Administrator should not assign the same user name to multiple users of the system. As part of the Standard Operating Procedure users should not share their user name and password combination with other users.
(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.	As part of the Standard Operating Procedure the Administrator should verify the identity of the assigned user before providing user with signature pair (user name and password).
(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures. (1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857. (2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.	As part of the Standard Operating Procedure the Administrator should notify the appropriate Agency of their intent to use Electronic Signatures.

2.	Specific Response to Sec. 11.200 Electronic Signature Components and Controls.

(a)	Electronic Signatures that are not based upon biometrics shall:

21 CFR Part 11 Rule	2101 Controlled Rate Freezer
(1) Employ at least two distinct identification components such as an identification code and password. (i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual (ii) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.	A User Name and Password pair is required for access to the system. This constitutes an electronic signature. The user must enter their password after the initial log in action for subsequent changes. A user name and signature pair is required for access following a nonconsecutive controlled session in the system. i.e. If the user logs out of the system after a session both components of the signature are required to sign in.
(2) Be used only by their genuine owners; and	The genuine owner is the only person with knowledge of the owners credentials.
(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.	Only the assigned genuine owner can access the system. The user is forced to change their password when the account is created. In this way only the user is aware of their credentials.
(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.	N/A

3.   Specific Response to Sec. 11.300 Controls for Identification Codes / Passwords

21 CFR Part 11 Rule	2101 Controlled Rate Freezer
Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include: (a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.	Both User Name and Passwords cannot be re-used. The user name cannot be the same as the password. A password cannot be used more than once. Users are forced to change their password the first time an account is created. The user must then continue to change their password a minimum of every 90 days. This rule ensures that no two users can have the same password.
(b) Ensuring that identification code and password is-suances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).	User Signatures Expire after a set period.
(c) Following loss management procedures to elec-tronically deauthorize lost, stolen, missing, or other-wise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or per-manent replacements using suitable, rigorous controls.	Administrators can revoke user signatures if neces-sary.
(d) Use of transaction safeguards to prevent unauthor-ized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organiza-tional management.	Invalid Login Attempts are recorded in a unique Log File
(e) Initial and periodic testing of devices, such as to-kens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner	N/A The System does not use Tokens or Cards as part of the security implementation.

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Further Security / Design Specifications:

21 CFR Part 11 Rule	2101 Controlled Rate Freezer
1. The System must provide complete access to complete records and documents in human readable form.	The system provides reports and dialogs in human readable form
2. The System must be able to retrieve active and historical data, metadata, audit trail and signature information.	The system provides the ability to retrieve data by using the Audit Trail Function which provides a complete history of changes made to run files, runs in progress and user account access and change history.
3. The system must maintain the integrity and security of electronic quality records and any associated electronic signatures for the retention period of the record.	All data is stored permanently on the hard drive in an encrypted proprietary format.
4. The system must be capable of detecting invalid or altered records.	Files that have been tampered with are rendered invalid.
5. If applicable the system must be able to derive original results from raw data retained as a quality record.	When a program profile is created and executed run file is created. This run file is viewable at a later date in human readable form. In addition program profiles can be recalled and re-run as necessary.
6. If applicable the system must maintain the integrity and security of electronic quality records and any associated electronic signatures when data is migrated.	N/A - Data is not migrated. A password is required to access any data in the system. The audit trail is stored in the database and is password protected.
7. If applicable the system must maintain the integrity and security of electronic quality records and any associated electronic signatures for the retention period of the record if required by the predicate rule.	All user security records and the audit trail is retained for the life of the system.
8. The system must prohibit access by unauthorized users	The user must enter a user name and password as an electronic signature pair to access the system.
9. A minimum of two components must be entered for access	The user must enter their uniquely assigned user name and their unique password.
10. The system must require individual account access except for read-only access.	There is no access to the system without a user name and password.

C-B-S

21 CFR Part 11 Rule	2101 Controlled Rate Freezer
11. The system must prevent the re-use of user accounts.	A user account cannot be assigned to more than one user as the passwords are known only to the assigned user. As part of the SOP users should be prevented from sharing their password with other users.
12. The system must prevent the use of automated logins or login scripts by individual users.	By Design the system will not allow automated logins or scripts.
13. The system must define system access and security levels for authorized individuals, System and Data Administrators with capability to delete records must be kept separate from the other users using the system.	There are designated Operators and Administrators. Operators exist at three levels with diminishing levels of functional access.
14. The system must provide controls, time outs	The 2101 is a controlled process that should not be interrupted while a freeze run is in progress. When the system is not running a cycle the system will log off the user after a determined period of time.
15. The system must define an unauthorized attempt threshold and report upon detection of reaching this threshold to appropriate authority.	Invalid logins are recorded in the audit trail. A user is logged out after 6 attempts.
16. Users must be required to change their system access password every 90 days	Passwords can be set to expire at a minimum of every 90 Days.
17. If applicable, remote or interfaced systems must be authenticated prior to transfer or processing of data.	Freeze Run logs can be accessed by a Viewer. The user must enter a password before viewing any data retrieved from the system.
18. If applicable remote or interfaced systems must be authenticated prior to transfer or processing of data.	Not Applicable – The 2101 is a closed system.
19. If applicable device checks must be in place to determine the validity of the source of data input or operational instructions, as appropriate	Not Applicable – The 2101 is a closed system.
20. Changes to an electronic quality record must be documented.	Any changes to the system are logged in the Audit File.

C-B-S

21 CFR Part 11 Rule	2101 Controlled Rate Freezer
21. Change to an electronic quality record must not obscure previously recorded information.	The Audit Trail Concatenates and does not overwrite.
22. The system must provide an obvious indication of changes made to an electronic quality record	The Audit Trail shows the original and changed values.
23. System must capture human initiated creation and changes to an electronic quality record in an audit trail at the time of electronic commitment	All changes are recorded at the time of change with proof of authentication via active logged in users.
24. The system must provide a link between the audit trail and associated electronic records for the retention period of the record.	The name of the run file is indicated in the Audit Trail.
25. The Audit Trail must capture the following: a. The User ID b. Date and Time of Action c. User Action Taken d. Create Modify or Delete e. Reason for change maybe documented separately. Time Stamp must be legible.	The Audit Trail captures all of the data a – e. The Time stamp is recorded in a legible format, in addition the complete user name is recorded.
26. The system must provide access for review of audit trail information. Records that are critical and or subject to alteration must be reviewed on a periodic basis and or part of the routine batch release to ensure data integrity.	The Administrator can review Audit Trail Records. As part of the SOP regular reviews of the Audit Trail should be scheduled.
27. The system must automatically generate audit trail information.	The 2101 system automatically generates the Audit Trail without user intervention.
28. The System must protect audit trail information so that it cannot be modified or disabled through normal means.	The Audit Trail is encrypted in the database and cannot be deleted through normal means.
29. The system must provide a separate computer system logon event and e-signature application event.	The e-Signature is unique and separate from the computer system logon.

21 CFR Part 11 Rule	2101 Controlled Rate Freezer
30. The system must provide a link between electronic signatures and electronic records, including associated metadata, that cannot easily be refuted for the retention period of the record.	The Audit Trail includes the user name data and time of the events. Individual database files are tagged with the user name and date time stamp.
31. The electronic signature manifestation must be subject to the same controls as the associated electronic record.	The Audit Trail is protected by Security and Encryption.
32. The system must prevent the re-use of an electronic signature by another individual.	The electronic signature is protected by the users password.
33. The system must require a unique combination of two components for an electronic signature. The first component of an electronic signature must be unique to one person and cannot be reassigned to, reused by, or shared with another person. The second component of an electronic signature must be associated with the first component and cannot be entered by electronic means.	Users are assigned a unique user name. The user must change their password during the first sign on.

User Names cannot be duplicated or re-used within the system.

Passwords must be unique and are required to be changed at a minimum every 90 days. |
| 34.   The System must present the following information in the manifestation of an electronic signature in human readable form.

a.   Printed Full Name of the signer   No
b.   Date of signature execution   Yes
c.   Accurate time of signature execution Yes
d.   Meaning of the signature   No | The Audit Trail records items a – d for each event within the system. |
35. The system must present the manifestation of the electronic signature on all printed and displayed forms of its associated electronic record.	The Audit Trail provides this information when printed.
36. The system must maintain the security and integrity of the electronic signature	The system protects the security and integrity of electronic signatures via encryption and controlled access.
37. Users must be required to change their electronic signature passwords (or second component) at least every 90 days	As part of standard operating procedures the software will prevent the use of an electronic signature after 90 days (if set to 90 days). The Administrator must reactivate the signature and must change the password in order to meet this requirement
38. The system must define a period of inactive time after which the session must be considered non-continuous. For multiple signings in a continuous session, the initial signing must require all components, independent of the system login and subsequent signings must require the second component at a minimum. Non-continuous signing sessions must require entry of both components for each signing.	The system requires a user login after a period of inactivity.

The user must reenter their password for actions that qualify as Auditable events.

The user must login in with both factors after being logged out. |

21 CFR Part 11 Rule	2101 Controlled Rate Freezer
39. Users must be required to change their signature passwords upon first use following administrator password assignment.	The system requires the user to change their password on the first use of the user name.
40. The system must define an "authorized attempts" threshold for applying an electronic signature and report upon detection of reaching this threshold to appropriate authority.	The system will only allow 6 log in attempts. Once this level is reached the user is locked out of the system. This activity is reported to the Administrator via the login attempts report .
41. The system must prevent automated execution of electronic signature	The user must manually enter the password.
42. If applicable, if a physical token is used for electronic signature, it must lack at least one signature component	N/A
43. Encryption must be provided for records exchanged over an open system.	All Data is encrypted
44. Digital Signature Standards must be used	All Data is encrypted. As part of Standard Operating Procedure all files should be treated as electronic records under HIPAA regulations, i.e. they should be stored in a secure location and not distributed. In cases where control of files has been lost the files are still encrypted.
45. There must be security at both the sending and receiving systems.	The Run files are encrypted and require a password to be decrypted and viewed.
46. The final revision / editions of paper and electronic quality records must have the same electronic content.	Actual Run data cannot be manipulated beyond colors and line representation when using the data viewer. The data component cannot be modified.
47. Traceability between an electronic quality record and paper record including any alterations must exist.	Actual Run data cannot be manipulated beyond colors and line representation when using the data viewer. The data component cannot be modified. Changes to programs are logged in the audit file.

CLEANING & MAINTENANCE

Cleaning

Use a mild, non-abrasive household type cleaner for cleaning all surfaces of the unit except for the notebook PC. A mixture of 40% bleach, 60% water may be used inside the chamber of the unit for decontamination or heavy cleaning purposes. Check with Custom BioGenic Systems before using any cleaners not mentioned above. A lint-free cloth or compressed air of no more than 20 p.s.i. may be used to clean the laptop. The use of any chemicals, cleaners, or methods not mentioned above will void the warranty.

Maintenance
(The following should be performed at least once annually)

1) Test all alarm functions for proper operation.

2) Check accuracy of the chamber probe and sample probe. If calibration is required, see calibration starting on page 23.

3) Check for leaks at all connection points of the liquid nitrogen lines.

4) Be sure that all electrical wires are free of damage and plugs are firmly in place.

SOLENOID VALVE MAINTENANCE

IMPORTANT: This should be done *only as required,* and is not a necessary part of maintenance. Solenoid valve(s) may be opened to inspect for cleanliness and to check seals for wear. Wipe seals with a clean, lint-free cloth. Distilled ammonia may be used to wipe seals if needed.

The solenoid valves may be opened and cleaned if they are not working smoothly. If this is done, use the diagram below to reassemble the valves properly. If the valve is found to be defective, it must be replaced, as replacement parts are not available individually.

1. Valve Body
2. Plunger
3. Flange
4. Valve Coil Locknut
5. Coil
6. Spec. Plate
7. Valve Cap
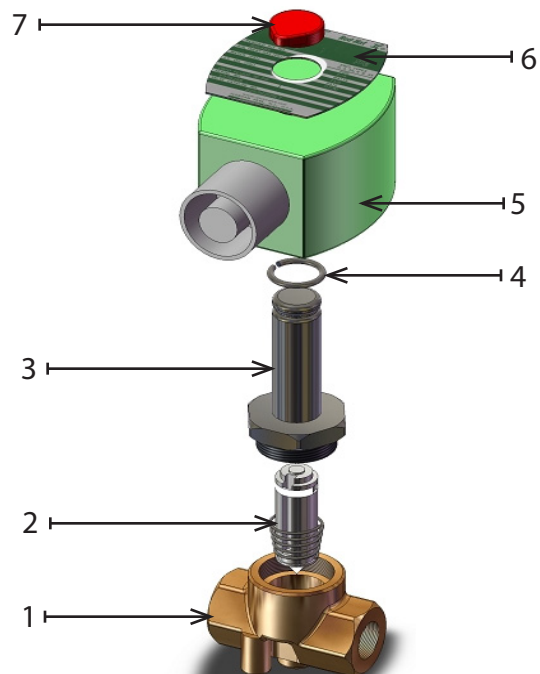
NOTES

Custom
BioGenic
Systems

74100 Van Dyke
Bruce Township, Michigan
48065 U.S.A.

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