

Operation and maintenance instructions:

CDB01 Ancillaries

This instruction describes three add-ons to the CDB01-system 1) A passive powder sampler 2) Extensions to a Wet-In-Place cleaning system 3) A linear actuator.

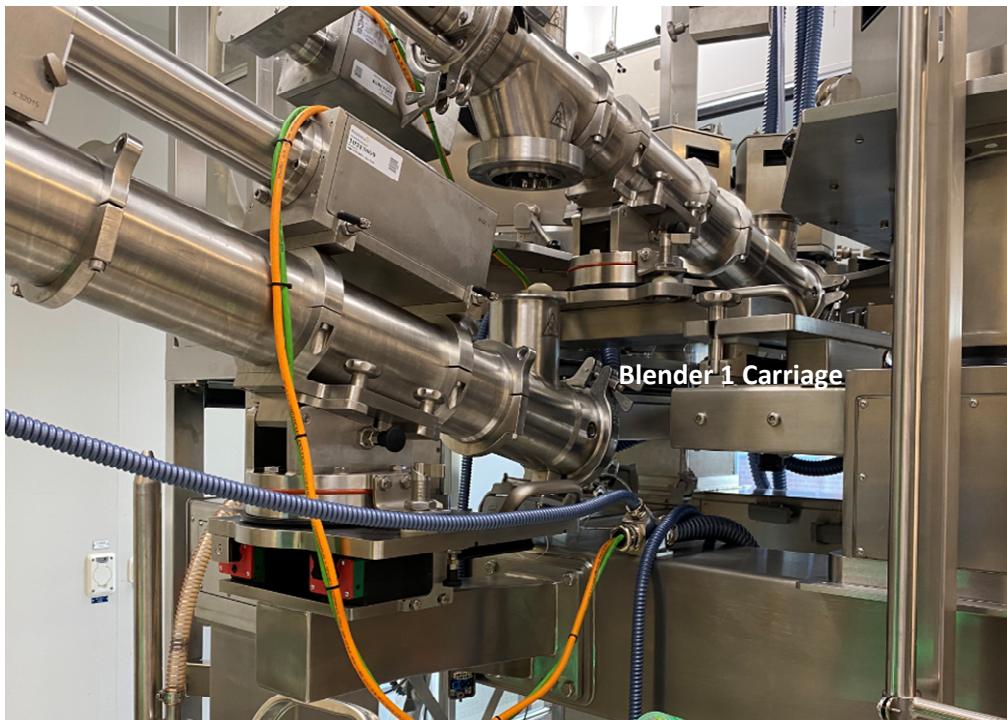
The basic function is that powder is processed through blenders of the CDB01 and into a tablet press. The Passive sampler is situated between blender 1 & 2. The WIP wets down the CDB01 once production is finished. The linear actuator is used to move blender 1 in preparation for disassembly and cleaning.

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(d), (g) General Description

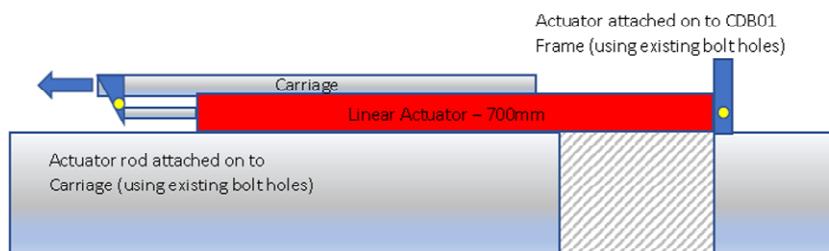
This part of the manual sets out the instructions for a linear actuator, in accordance with Appendix 1.7.4 of the Machinery Directive. Each section of this manual corresponds to the specified list of contents in 1.7.4.2 and the same descriptions and lettered bullets are used as in 1.7.4.2.



The linear actuator is used to move the carriage of Blender 1 on the CDB01 unit, during disassembly of the CDB01 rig for cleaning. The blender consists of a stainless steel tube enclosing a rotating shaft with blending blades, powered by an external electrical drive. The complete unit is designed to be removed for cleaning and weighs around 80kg.

For it to be removed, the blender has to be disconnected from up and downstream equipment and slid out to a position where it can be lifted out using a pillar lift. Details for this whole procedure are given in section 6.6 of document “LDMS_001_00105069” – user instructions for lift PoC09, and also section 6.2 of the CDB01 user instructions. To aid removal, the blender is mounted on a low-resistance slide system. However, a further ergonomic assessment suggested that the working position and force requirements are such that injury risk to complete the withdrawal and replacement processes would be intolerable.

Following this assessment, a powered linear actuator was specified to automate the withdrawal process. The system consists of an electrically powered linear actuator connected to the blender and support frame using existing mounting points, and a two hand operating controller to allow a single user to operate the system.

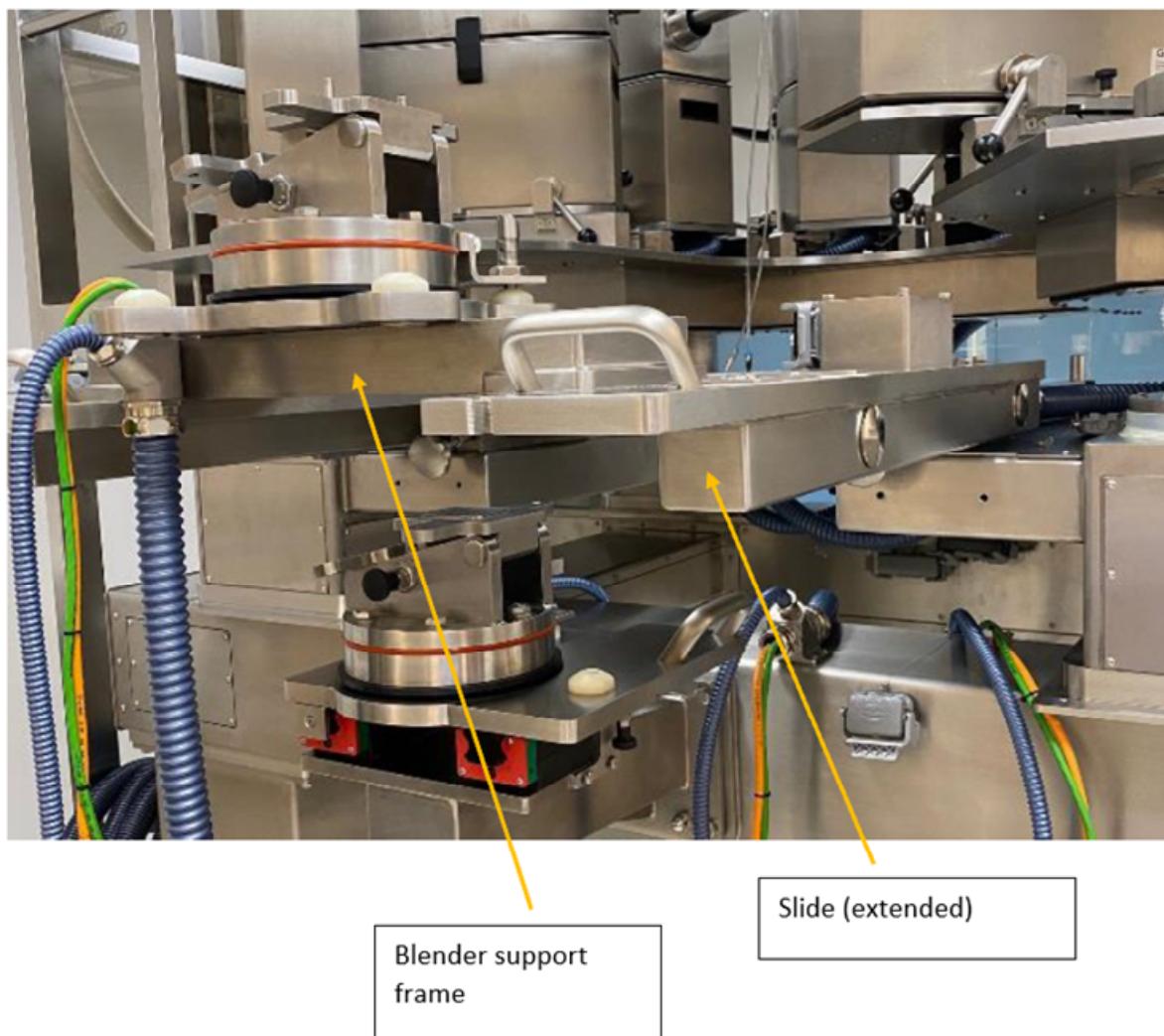


(f) Actuator Location



The actuator is mounted adjacent to the blender slide. The drive motor is at the rear of the CDB01, lying horizontal to the frame with the actuating rod facing forward to connect to the carriage at the point where the existing handle is located.

(f) Actuator Location





The actuator is mounted to
the body of the CDB01 via a
single M10 pivot bolt

(f) Actuator Location

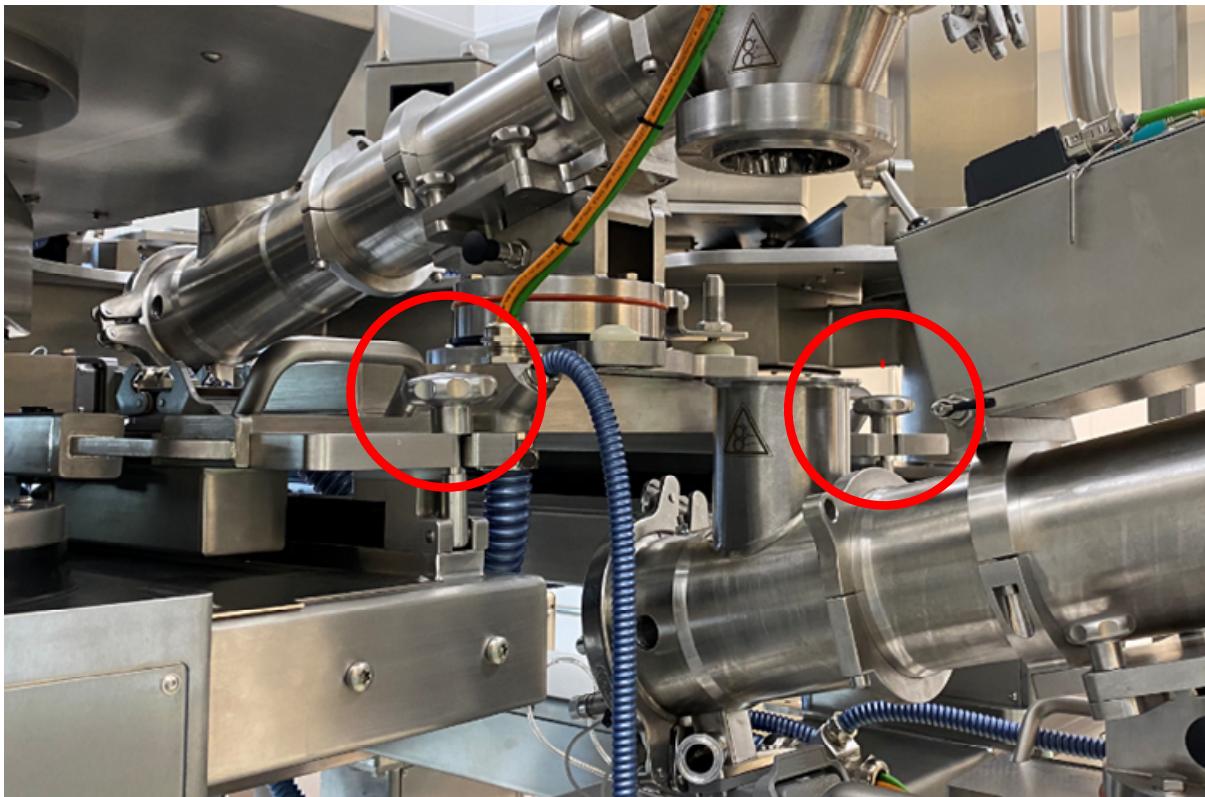


The actuator is connected to the carriage via the handle

The stroke of the actuator is spring compensated to ensure that the actuator is not overloaded

(k) Instructions for use - Getting Ready to Operate

During manufacturing, when the CDB01 and blender 1 are active, the actuator will be unpowered. The blender carriage will be in the retracted position and the carriage locked into position using the two large thumbwheels located at the front of the carriage.



**IT IS VITAL THAT THESE THUMBWHEELS ARE LOOSENED AND DROPPED DOWN PRIOR TO
ANY ATTEMPT TO OPERATE THE ACTUATOR**

Loosen the two thumbwheels and drop them down, so that they will clear the carriage. Visually check that all cables/plugs/connectors associated with blender 1 are disconnected and out of the way of the carriage, prior to attempting to operate the actuator.

The blender carriage is also used for fitting and removing the Quadro U5 Mill using the specifically supplied adapter. It is important to make sure that the compact feeders are retracted when the carriage is being used to move the mill.

(l) information about the residual risks that remain despite the inherent safe design measures, safeguarding and complementary protective measures adopted;

If the blender actuator is powered and the feeders are still in place – then a collision may occur. To prevent this, always perform the visual check below. If the feeders are in place when attempting to use the actuator, remove them – following the procedure described in section 6.2.5 of the CDB01 user instructions.



Visually check that all of the compact feeders are retracted and that nothing will impede the motion of the carriage.

(k) Instructions for use - Powering Up

The power supply to the actuator is 230v and is facilitated by a 2 pin plug. This can be plugged into the adjacent wall behind the pillar lift.

As the actuator will only be used when assembling and disassembling the CDB01, it will only need to be plugged in for a short time, so should not present an access issue around the machine. As soon as the blender is installed/removed, the actuator can be unplugged and the cable stored securely.





Once the carriage is retracted/extended, remove the power cable from the socket and store securely.

(k) Instructions for use - Remote Control

These instructions are to be supplemented with in-person training for operators. This is to further reduce the possibility of entrapment and emphasise the importance of the check below:



Before operating the controller; always perform the following check:

- 1. That all your body parts and clothing are clear of the actuator carriage**
- 2. That no one is stood near the actuator carriage**

- 3. If there is anyone else in the room, state out loud “I am going to operate the blender actuator”. Make sure for entire operation that you and other operators remain clear of the actuator carriage**

The remote control is a simple pushbutton device. The actuator can either be extended or retracted (Carriage out or Carriage in).

The controller is push to hold – the actuator will only move in the desired direction as long as the button is depressed. Once the finger is taken off the button, the movement will stop.

When the carriage has been moved to the desired position, store the remote securely.

Maintenance

The electric linear actuator is a factory sealed unit and as such has no serviceable parts. However, a visual check of mechanical connection points should be undertaken every time the actuator is used.

1. *Rear Mounting Pivot – check M10 bolt is secure and that there is no visual damage to the pivot point hole.*
2. *Front Mount – check the M8 mounting bolts that connect the handle/actuator mount to the blender carriage are tight and visually check spring compensator assembly.*
3. *Visually check power cable for damage.*
4. *Visually check remote control for damage.*

(j) Considerations of noise and vibration ;

The actuator movement is slow, with a maximum linear speed of 7mm/s. It produces no significant noise or vibration.

(m) instructions on the protective measures to be taken by the user, including, where appropriate, the PPE to be provided; No PPE is required that is specific to use of the actuator. Full PPE must be worn in room LF152 regardless, in accordance with “LDMS_001_00061906” - PPE rules for laboratory work and “LDMS_001_00009901” – PPE rules for handling chemicals. There is a minor finger trap hazard but this is mitigated by the same person needing to hold the actuator button. There is a risk if there’s more than 1 person that one may unknowingly run over another’s hand. It is the responsibility of the user with the remote control to ensure that the area around the actuator is clear so this cannot happen. If any other operators are present in the room, state and make clear that you are about to operate the actuator and that they must stand clear. These checks are detailed in section “(k) Instructions for use - Remote Control” in this manual.

(n) the essential characteristics of tools which may be fitted to the machinery;
The actuator is only held on by 3 bolts. A spanner and Allen key can be used to adjust these.

(q) the operating method to be followed in the event of accident or breakdown; if a blockage is to occur, the operating method to be followed so as to enable the equipment to be safely unblocked;

If the actuator is jammed, take your finger off the button and visually examine the blockage. Ensure the CDB01 is locked out before taking further action; see dedicated CDB01 instructions for how to do this. If the thumbwheels are in the way of the actuator – move them. If any other blockage is present – assess and clear it, if it is safe to do so. Otherwise, the actuator may be broken.

(t) the specifications of the spare parts to be used, when these affect the health and safety of operators;

There are no serviceable parts. If the actuator breaks, replace it.

(v) where machinery is likely to emit non-ionising radiation which may cause harm to persons, in particular persons with active or non-active implantable medical devices, information concerning the radiation emitted for the operator and exposed persons.

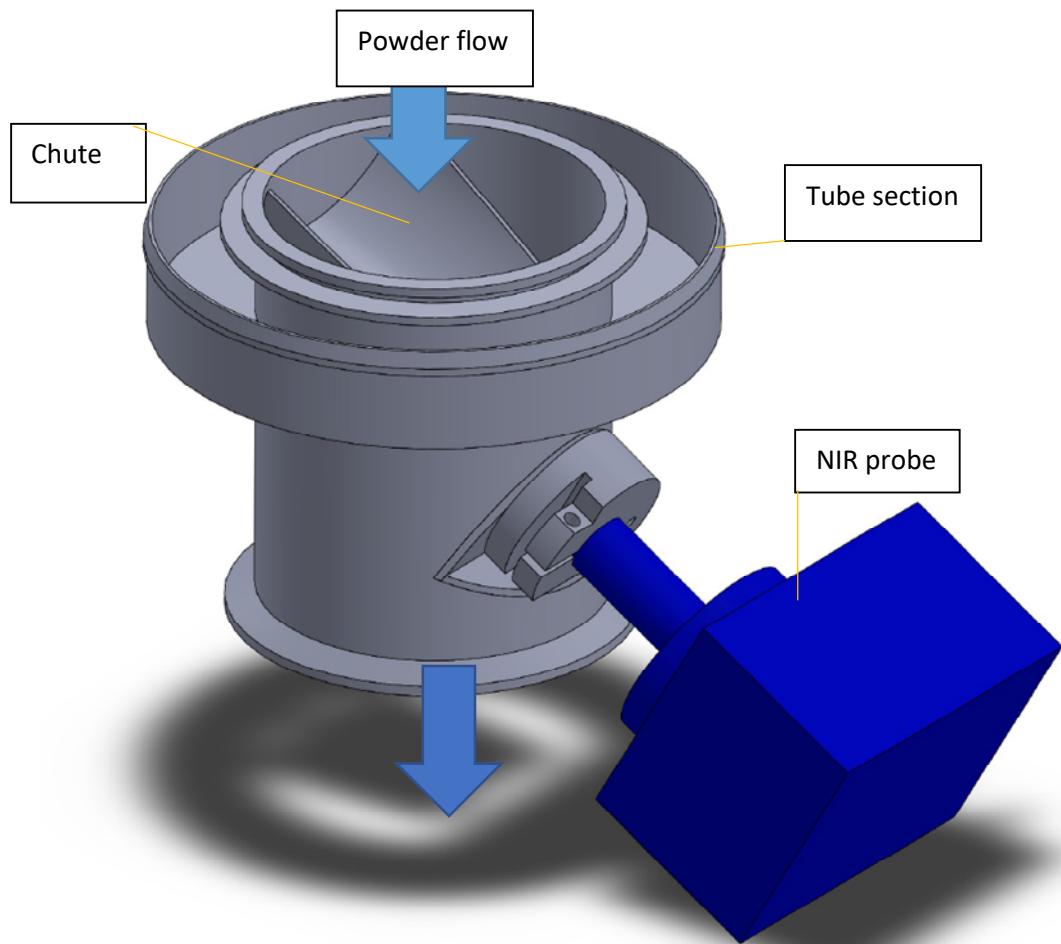
The actuator does not emit non-ionising radiation to any level that may cause harm to an operator or any associated medical devices.

(d), (g) General Description

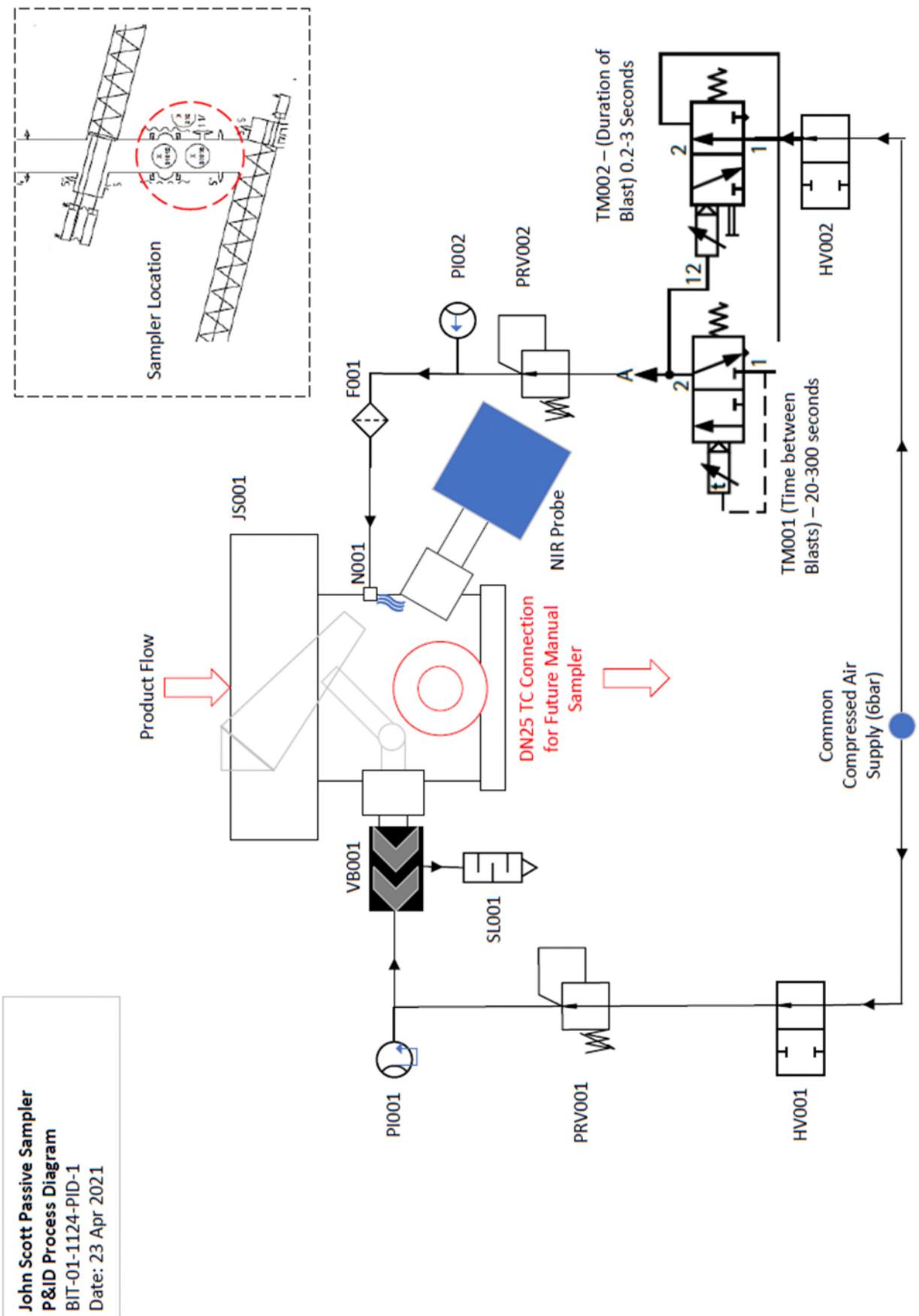
This part of the manual sets out the instructions for a Passive NIR Powder Sampler, in accordance with Appendix 1.7.4 of the Machinery Directive. Each section of this manual corresponds to the specified list of contents in 1.7.4.2 and the same descriptions and lettered bullets are used as in 1.7.4.2.

The “John Scott” passive sampler is a device used to examine the near-infrared (NIR) spectra of a vertical flow of powder for tablet manufacture. These spectra are used to verify the concentrations of active pharmaceutical ingredients within the powder flow. The device is positioned between two powder blenders, as part of the CDB01 assembly. Powder flows, from blender 1, through the sampler which consists of a tube section, internal chute and port for a Sentronic NIR probe. The powder continues to flow out of the sampler and is then transported to blender 2 of the CDB01.

The sampler has no moving machine parts but can be fitted with a pneumatic vibrator to assist with powder flow and an air blaster to keep the probe face clean. The vibrator can be adjusted for frequency and intensity (amplitude) by adjusting the air pressure and air flow. The air blast can be adjusted for air pressure. The duration of the air blast and the time between blasts is also adjustable using pneumatic timers. Both can be switched off if not required. These components operate under a compressed air supply that is detailed in a dedicated P&I diagram. The only electrical component is a low-power removable NIR probe; a Sentronic “SentroPAT FO analyzer”.



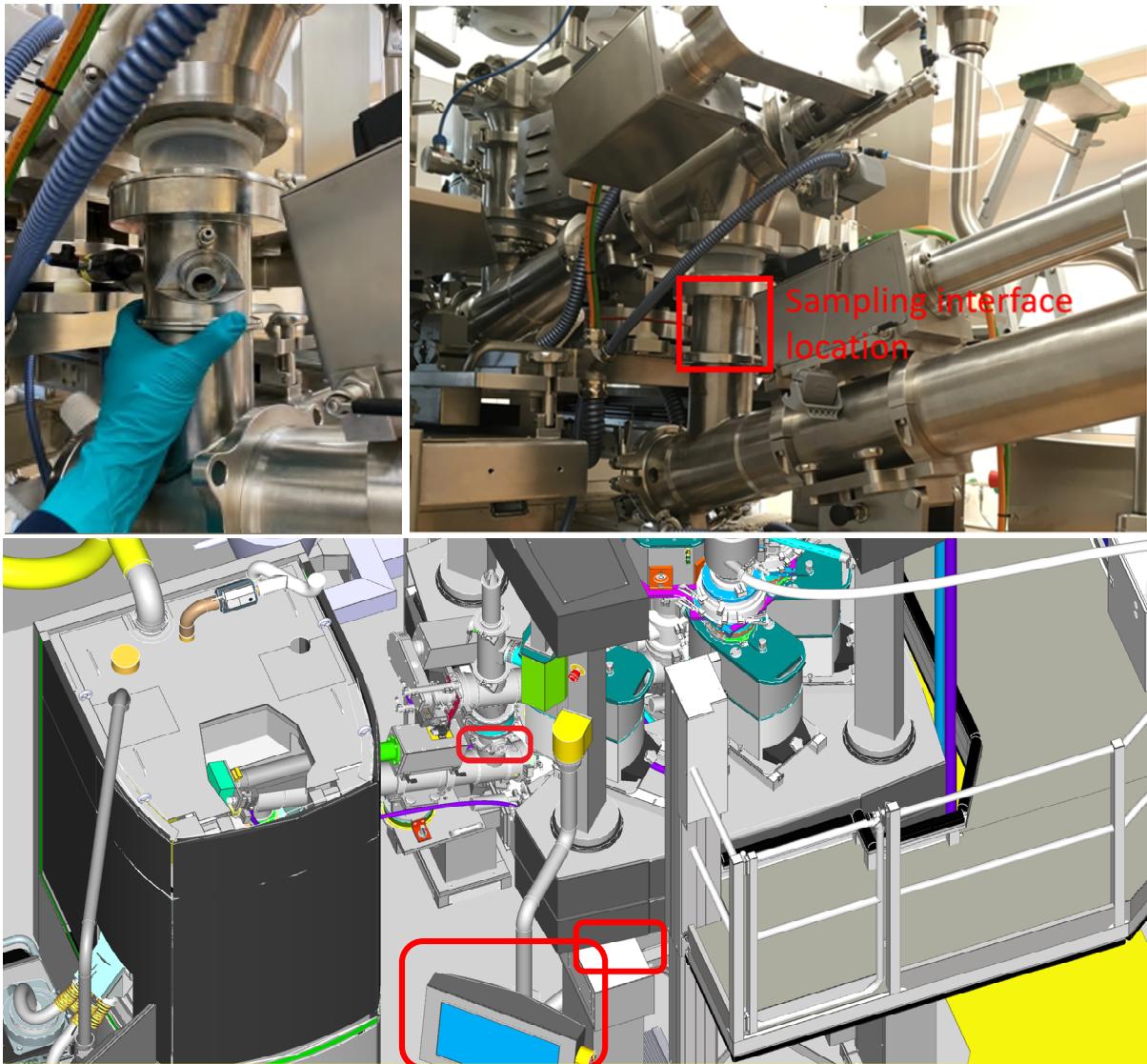
(e) Piping and Instrumentation Diagram



(f) Workstation

The sampler is part of a manufacturing line located in an ISO grade 8 clean room and will only be handled by trained operators. The sampler is intended for technical development and laboratory trials so would be removed (and replaced with a straight pipe section) during full GMP manufacture.

The sampler has two associated control interfaces; one for the NIR probe and one for the pneumatic systems. The NIR probe readings are displayed on the HMI control panel for the CDB01. The pneumatic systems have a dedicated control box next to the HMI.



Snapshot of 3D model with marked (higher) sampler location and (lower) control interfaces. The pneumatics control box is installed on the step to the right of the HMI screen.

(h), (i), (k) Instructions for assembly, installation and use

The sampler is fitted manually via standard tri-clamp connections, between blenders 1 and 2 of the CDB01. Improper assembly is unlikely to cause harm though the rotational alignment of the pipe is important. Proper alignment allows the NIR probe to fit in the surrounding space without clashing with adjacent machinery. To ensure this, there are markings on the pipe section and the flanges of the CDB01. If the markings on both are aligned, the sampler is oriented correctly, and the probe can be fitted without risk of collision.

(j) Considerations of noise and vibration

The sampler can only produce noise and vibration if the pneumatic components are active and in use. See the data sheets and manual for the Netter vibrator for further information. The vibration produced by the pneumatic components is meant to displace small quantities of powder and occurs in short, controlled bursts. It is therefore unlikely to cause harm or discomfort to operators, who will be stood 1m away and will not contact the device in operation.

Importantly, the sampler will typically be used along with the CDB01 which can produce sustained noise at 80 dB or above. Row 45 of the risk assessment for the CDB01 should be referred to for further detail on the risk of noise. Ear protection needs to be worn in the room, especially when the CDB01 is running – this is in the immediate vicinity of the sampler. See section 4.8 of document “LDMS_001_00061906” - PPE rules for laboratory work, for specific guidelines covering ear protection.

(l) Information about the residual risks that remain despite the inherent safe design measures, safeguarding and complementary protective measures adopted;

The sampler has few moving parts and no high-powered electronics. The only energised aspect is the compressed air supply, as detailed in the P&I diagram. The risk of uncontrolled escape of powder is minimised by containment within the pipe section and further mitigated by the full PPE required for handling the CDB01. A pressure and relief review is available for the CDB01 in document “AZDoc0203462”. The powder flow through the sampler is introduced at ambient air pressure and contributions from the pneumatic components are mitigated by the presence of regulators and vents, further detailed in the P&I diagram.

(m) Instructions on the protective measures to be taken by the user, including, where appropriate, the PPE to be provided. (q) the operating method to be followed in the event of accident or breakdown; if a blockage is to occur, the operating method to be followed so as to enable the equipment to be safely unblocked;

Under normal operation of the CDB01, ear protection should be worn along with full PPE as specified in section 4.10.1 of document “LDMS_001_00009901” – PPE rules for handling chemicals. This standard mitigates against the risk of exposure to airborne powders of high potency (active pharmaceutical ingredients). In any instance of accident or blockage where the fixing of this blockage may release contained powder – PPE must be worn and the CDB01, all pneumatic components and the NIR probe switched off before any attempt at disassembly. This should only also occur once the powder risk has been thoroughly assessed.

(n) the essential characteristics of tools which may be fitted to the machinery;

No tools are required for regular operation of the sampler. It is installed manually via standard tri-clamp connections.

(o) the conditions in which the machinery meets the requirement of stability during use, transportation, assembly, dismantling when out of service, testing or foreseeable breakdowns and (p) instructions to ensure that transport, handling and storage operations can be made safely, giving the mass of the machinery and its parts where these are to be transported separately.

Disassembly of the sampler would only be undertaken by a dedicated service engineer, not an operator. To disassemble the sampler, first remove the two pneumatic hoses that run from the control box to the outside of the sampler (one for the vibrator, one for the air blaster). These have quick release fittings which can be manually removed. There is no need to isolate the compressed air supply as the fittings are self-locking.

The main tube section weighs less than 10kg and is easily handled and transported. It is simply removed manually via tri-clamp connections. The control box will remain fixed to the CDB01.

(t) the specifications of the spare parts to be used (r) the description of the adjustment and maintenance operations that should be carried out by the user and the preventive maintenance measures that should be observed; and (s) instructions designed to enable adjustment and maintenance to be carried out safely, including the protective measures that should be taken during these operations;

Few spare parts are required as there are no wear parts apart from the pneumatic components. Further maintenance instructions for these are available in the supplier documentation folder in the digital technical file. If components are broken beyond the scope of these manuals, they should be replaced. The NIR probe has no specified maintenance apart from that the bulbs should be replaced if broken, typically after 14,000 hrs. The replacement of these components should be performed by the local service engineer.

(u) Information on airborne noise emissions:

The sampler itself does not produce noise emissions at 70dB(A) or at a sound pressure of more than 63 Pa under normal operation. It is, however, typically used along with the CDB01 which can produce sustained noise emissions at these levels. Further details are given in row 45 of the CDB01 risk assessment. Ear protection needs to be worn in the room due to noise hazards from other machines in the CDC line, especially when the CDB01 is running. See section 4.8 of document "LDMS_001_00061906" - PPE rules for laboratory work, for specific guidelines covering ear protection.

(v) where machinery is likely to emit non-ionising radiation which may cause harm to persons, in particular persons with active or non-active implantable medical devices, information concerning the radiation emitted for the operator and exposed persons:

The sampler (optionally) contains a removable NIR probe for chemical analysis of powder. The wavelengths of the NIR radiation emitted by the probe are 1100-2500nm at no more than 10W. This poses no risk to medical devices and minimal risk to the operator otherwise. The risk is further minimised as, by design, the sampling interface and probe emissions are wholly contained within the outer tube of the device. The risk of harm can be lowered even further if the probe is never activated until it is inserted into the sampler, where all emissions are contained by the device.

List of components

1. Netter NTS-120 HF Vibrator
2. 2x Festo Timers (air blast separation, air blast duration)
3. Festo Regulator
4. Festo Flow Control Valve
5. Sentronic "SentroPAT FO analyzer"

(d) General Description

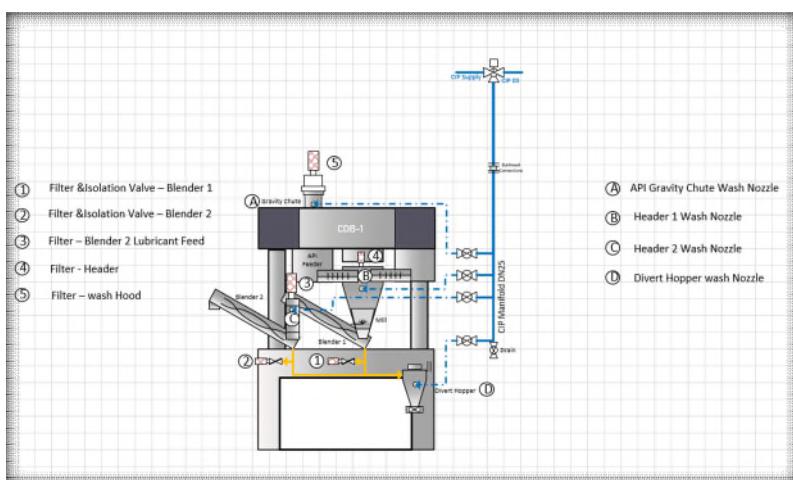
This part of the manual sets out the instructions for ancillaries relating to a Wet-in-Place (WIP) cleaning system, in accordance with Appendix 1.7.4 of the Machinery Directive. Each section of this manual corresponds to the specified list of contents in 1.7.4.2 and the same descriptions and lettered bullets are used as in 1.7.4.2.

The WIP system ancillaries are a combination of pipes and nozzles that direct cleaning media onto the CDB01 assembly. This is done prior to dismantling of the CDB01 for further manual cleaning and prevents the dispersal of airborne dust that may pose a risk to operators. The system is also able to direct cleaning media to a tablet press (TaP06/ModulQ) for the cleaning of its removable tablet ECM (Exchangeable Compression Module). The WIP ancillaries are not a standalone system ; they are extensions to the existing WIP system to further the reach of cleaning media from a dedicated WIP ring main.

Lechler "Pop Up" nozzles are fitted into the WIP ports provided on the CDB01. These nozzles terminate in DN40/1.5" TC connections.



The WIP ports are marked on the following diagram for the CDB01:



To supply WIP media to these nozzles, a new feed system was installed and piped in 316L stainless steel tube, terminating in DN25/1" BS4825-3 TC connectors. DN40 and DN25 connections share the same size flange, so direct connection is possible.

(g) Further System Description

The WIP pipework consists of a split feed from the main CIP03 ring main. See P&ID below.

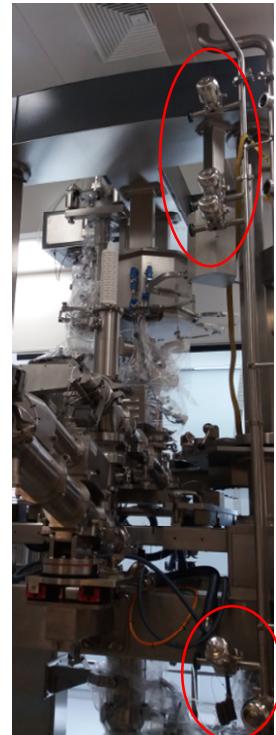
One supply goes to the CDB01 and is further split by a manifold so that the WIP media can be diverted to different parts of the CDB01 as defined by the recipe.

This is done by actuated diaphragm valves mounted on the individual manifold outlets.

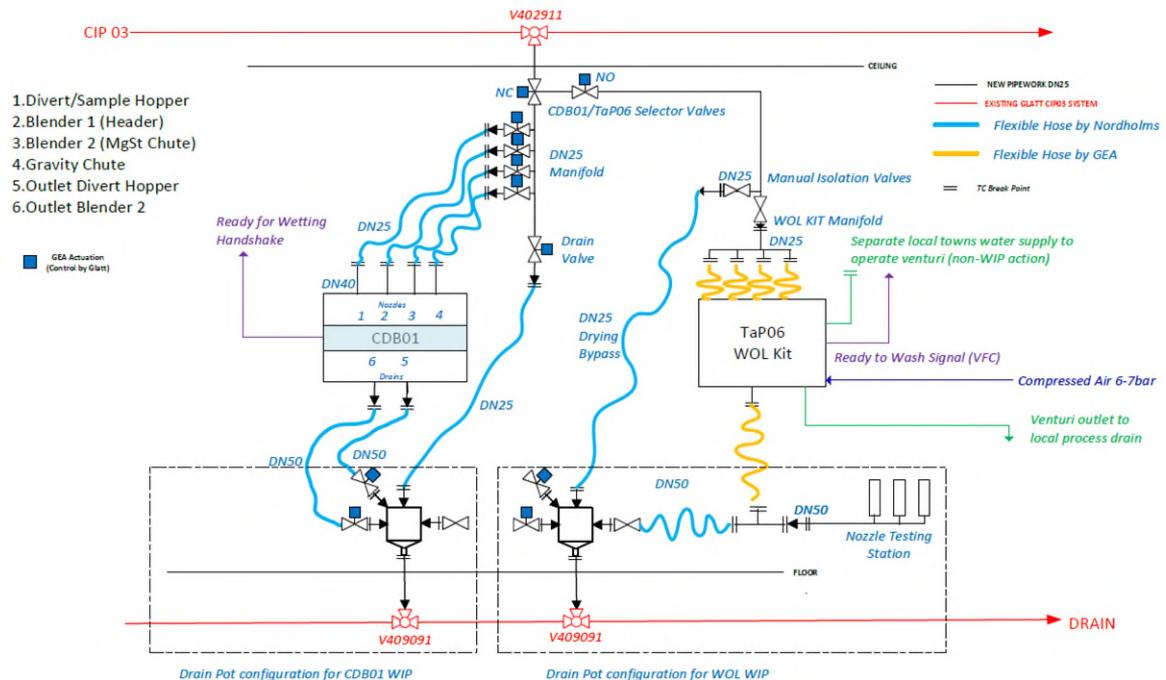
The nozzles are connected to the outlets of the valves by flexible hoses.

The other supply is for the WIP media feed for TaP06 required for wetting/washing the ECM down.

In the system's default state, the feed will always go to TaP06. The feed will only be directed to the CDB01 when the CDB01 control system calls for WIP media.



(e) Piping and Instrumentation Diagram



(f) a description of the workstation likely to be occupied by operators;

The WIP system is operated remotely using an HMI control panel in the corridor outside LF152. This is to eliminate the risk of any operator exposure to cleaning media.

(j), (u) considerations of noise and vibration;

No significant vibration or noise is emitted by the pipes, valves, nozzles or cleaning media.

Furthermore, the operator can only activate the system remotely (from the HMI in the adjacent corridor). The WIP cleaning operations are set up to occur in an empty room to eliminate the risk that pressurised media can escape and harm operators. There is therefore minimal risk that noise and vibration can also cause harm.

(k) instructions for the putting into service and use of the machinery and, if necessary, instructions for the training of operators;

These ancillaries are additions to the wider WIP cleaning system which has its own training package and operating procedure. See “CDB1_ModQ Cleaning Strategy Document v02” and “AZDoc0168719 - CDB1 wetting overview” for further information on the training scope of the WIP system. The ancillaries detailed in this manual (nozzles, hoses, pipes) merely add destinations for WIP media and do not constitute a standalone system. They have no training requirements beyond this manual and the changing of the diaphragm of the Gemu valves (in the wider technical file).

(m) instructions on the protective measures to be taken by the user, including, where appropriate, the PPE to be provided;

The WIP system is controlled and used remotely from the HMI in the corridor outside LF152. Operators are still subject to the PPE guidelines in “LDMS_001_00061906” - PPE rules for laboratory work and “LDMS_001_00009901” – PPE rules for handling chemicals.

(o) the conditions in which the machinery meets the requirement of stability during use, transportation, assembly, dismantling when out of service, testing or foreseeable breakdowns and (p) instructions to ensure that transport, handling and storage operations can be made safely, giving the mass of the machinery and its parts where these are to be transported separately.

The steel pipes, nozzles and valves are fixed in place. The only removable parts are flexible hoses; arrangements for their use and transportation are given in “CDB1_ModQ Cleaning Strategy Document v02”.

(q) the operating method to be followed in the event of accident or breakdown; if a blockage is to occur, the operating method to be followed so as to enable the equipment to be safely unblocked;

The CIP03 main supplies water at 2 Bar with a flow rate of 11L/min. In case of blockage, the operator must stop and lock off the WIP system using the control panel and de-pressurise the system via the drain valve. The drainage procedure is outlined in section 3.4 of “AZDoc0168719” -the CDB1 wetting overview. The operator may then proceed to disassemble the pipes, to find the blockage, but only after a specific assessment has been made of the risks of any residual powders or cleaning media – with appropriate PPE worn.

(r) the description of the adjustment and maintenance operations that should be carried out by the user and the preventive maintenance measures that should be observed, and (s) instructions designed to enable adjustment and maintenance to be carried out safely, including the protective measures that should be taken during these operations;

Before each use, the operator should visually check the conditions of the hoses, valves and nozzles. This check should ensure that no cracks are present and that all fittings are secure. No further maintenance is required, other than that detailed for the Gemu valves (instructions in technical file). All the other components are passive parts with no risk of wear and are proofed against corrosion, being constructed from 316L stainless steel. All maintenance should be performed whilst the system is stopped.

(v) where machinery is likely to emit non-ionising radiation which may cause harm to persons, in particular persons with active or non-active implantable medical devices, information concerning the radiation emitted for the operator and exposed persons; The WIP ancillaries do not emit any optical non-ionising radiation. The only risk present is from the IR emissions that result from the heat of the cleaning media; these are covered separately by the WIP/CIP risk assessment.

List of components

1. GEMU 650 Biostar Diaphragm Valve
2. Position Indicator
3. Lechler Nozzles