

OPUS® Pre-packed Chromatography Columns

Regulatory Support File



OPUS Columns RSF-10

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Abbreviations

ABS	Acrylonitrile Butadiene Styrene
AGS	Associated Global Systems
As	asymmetry
BCMS	Business Continuity Management System
BSA	bovine serum albumin
C	Celsius
CE	Conformite Europeenne
CF	compression factor
CFD	computational fluid dynamics
CFU	colony forming units
cm	centimeter
cm ²	centimeter squared
CMC	Chemistry, Manufacturing & Controls
CoA	Certificate of Analysis
CP	Customer Property
CV	column volume
EMA	European Medicines Agency
EU	endotoxin units
FOS	factor of safety
ft ³	cubic feet
FTIR	Fourier Transform Infrared Spectroscopy
G	acceleration
GMP	Good Manufacturing Practice
HCl	hydrochloric acid
hr	hour
Hz	hertz
ID	internal diameter
in	inches
IPA	isopropyl alcohol
IPPC	International Plant Protection Committee
ISO	International Organization for Standardization
ISPM	International Standards for Phytosanitary Measures

ISTA	International Safe Transit Association
kg	kilogram
L	liter
lb	pound
m	meter
M	molar
m ³	cubic meter
min	minute
mL	milliliter
mm	millimeter
mS	milliSiemens
N	plates
NaCl	sodium chloride
nm	nanometer
NVP	non-viable particulate
OD	optical density
OPUS	Open Platform User Specified
PD	Process Development
PETG	polyethylene terephthalate glycol
PP	polypropylene
ppm	parts per million
PSD	power spectral density
psi	pounds per square inch
QA	Quality Assurance
QC	Quality Control
R&D	Research and Development
RODI	reverse osmosis deionized water
RSF	Regulatory Support File
TNTC	too numerous to count
TOC	total organic carbons
TSA	tryptic soy agar
TSE	transmissible spongiform encephalopathy
w/v	weight/volume
µm	micron
µS	microSiemens

1. Introduction

The Regulatory Support File (RSF) for OPUS® (Open Platform User-Specified) Pre-packed Chromatography Columns is intended to be used as:

- A guide for appropriate application use in process development, clinical, and commercial purification processes
- A guide to validation in manufacturing processes
- A support reference for chemistry, manufacturing, and control (CMC) drug development submissions for regulatory license approval
- A guide for supplier audits
- In place of a Drug Master File submission

This Regulatory Support File covers all column sizes including OPUS Pre-packed Chromatography Columns 2.5, 5, 8, 10, 12.6, 14, 20, 25, 30, 36R, 45, 45R, 60, 60R, and 80R. Unless otherwise specified, all information applicable to OPUS Pre-packed Chromatography Columns 45R and 60R designs is also applicable to OPUS Pre-packed Chromatography Columns 45 and 60 designs.

For more information covering OPUS Gamma Pre-packed Chromatography Columns 2.5, 5, 8, 10, 12.6, 14, 20, 25, and 30, please refer to the specific Regulatory Support File on this portfolio on [repligen.com](https://www.repligen.com).

Repligen is committed to providing all relevant technical, manufacturing, and quality information, however, only non-confidential information is presented in this document. Confidential details may be made available upon request through a formal confidentiality agreement or as part of a supplier audit.

1.1 Repligen Quality Policy

Copies of the Repligen quality policy, quality manual, and ISO certificate can be found on the following website, <https://www.repligen.com>.

1.2 Safety notices

- Follow all local regulations for safe disposal
- For laboratory and manufacturing production only

1.3 Responsible official

The individual designated responsible for quality and regulatory affairs for Repligen, and to whom all correspondence or requests for audits should be addressed.

Senior Director of Quality
Telephone: +1-781.250.0111
Email: quality@repligen.com

2. Product information

2.1 Product overview

OPUS Pre-packed Chromatography Columns are designed to perform chromatographic purification of biological molecules in either Good Manufacturing Practice (GMP) or non-GMP applications. The OPUS 2.5 – 80R Pre-packed Chromatography Column platform offers an easy-to-use alternative to traditional self-packed columns with configurable diameter, bed height, and chromatographic resin. Additional end-user requirements, such as release criteria for plate count, asymmetry, and storage solution, can be specified. All OPUS 2.5 – 80R Pre-packed Chromatography Columns are built-to-order. Repligen does not maintain stock of standard configurations. Please consult with Repligen for specific lead time information.

2.2 Quality standards

OPUS 2.5 – 80R Pre-packed Chromatography Columns are manufactured in the Waltham, MA, USA. or Breda, The Netherlands under the following quality standards for GMP manufacturing:

- Repligen maintains an ISO 9001 compliant Quality Management System. A copy of the current ISO certification can be downloaded from the following web address, <https://www.repligen.com/resources/quality>.
- All materials in direct fluid contact path meet USP Class VI, and USP <88> requirements for In Vivo Biological Reactivity.
- All columns are packed in a controlled, classified clean room that meets ISO Class 7 Non-Viable Particulate (NVP) standards.
- All fluid contact components are free from materials of animal origin or compliant with EMA 410/01 Rev 3.

2.3 OPUS Pre-packed Chromatography Column features overview

Obtaining User Specified Column Inputs

All OPUS Columns are produced based on user specifications, captured from the Repligen internal quote configuration tool.

All specifications are summarized on the OPUS Column Specification Sheet for each column or part number. Available user specified inputs are summarized below:

- Column details (4 parameters): internal diameter, bed height, resin type, and GMP level
- Resin supply (two options): Repligen-supplied or customer supplied
- Acceptance criteria (two options):
- Repligen recommended:
 - Specifications derived based on resin manufacturer recommendations, statistical process control (SPC) OPUS Columns packing data, and inputs from applications development or historical packing experience.
- Customer specified:
 - Chromatographic release criteria: plate count (N/m), asymmetry range, injection volume, injection solution, Mobile phase solution, and linear velocity (cm/hr)

Application specific (if required):

- Pressure vs. flow requirements
- Maximum working flow rate
- Maximum working pressure to inform maximum packing pressure
- Chromatography resin sanitization method (post packing)
- Storage solution

Some column packing parameters cannot be configured as they are unique to the Repligen OPUS Column hardware, customized packing techniques, and Standard Operating Procedures (SOP). Examples include:

- Chromatography resin compression or consolidation factor
- Packing solution
- Packing methods

Repligen will make an effort to understand and accommodate all requests. For example, request for packing with a specific flow rate will initiate a conversation towards understanding the importance of that parameters to the overall process followed by adjustment of the OPUS Column packing method as appropriate. The OPUS Specification Sheet documents all packing adjustments for each column or part number.

OPUS Column hardware components, which includes inlet and outlet connection size, are not adjustable. See [Figure 6](#) through [Figure 12](#) for more information on the OPUS Column hardware design.

The final OPUS Column configuration, generated by either quote request form or internal configuration tool, is submitted for review by the Repligen Process Engineering and Manufacturing teams. Approval triggers issue of a quotation and an OPUS Column Specification Sheet (QA-FM-04-10015), which documents user specified requirements. The Specification Sheet is provided to the end-user for review and approval with the quotation package. Production of an OPUS Column requires receipt of both a Purchase Order and an approved OPUS Column Specification Sheet from the end-user.

2.4 Resin supply

Resin used to pack an OPUS Pre-packed Chromatography Column may be procured by the end-user from the manufacturer followed by drop shipment to Repligen or procured by Repligen directly from the manufacturer. Repligen maintains the following policy on resin expirations dates for Repligen procured resin:

1. Repligen guarantees ≥ 12 months remaining resin shelf-life at the time of shipment.
2. For resins with less than 2 years of total shelf-life as stated from the supplier, Repligen will guarantee 50% of the shelf-life upon column shipment.
3. Packing of resin with shelf-life expiry less than described above to availability requires customer notification and approval prior to column packing.

End-user procured resin requires completion of the Customer Property Declaration Form (QA-FM-02-10035), which confirms health and safety as well as customer procured resin tracking information. The unique Customer Property (CP) number assigned to each OPUS Column Specification Sheet provides traceability of customer procured resin throughout the Repligen facility.

It is the responsibility of our customers to ensure resin delivered to Repligen has the necessary remaining shelf life based on your project requirements. The Customer Property Declaration Form prompts our customers to agreeing for Repligen to release any resin delivered to Repligen for column packing. Opting out of this statement on the form may lead to extended lead time of your OPUS Column(s) based on extended resin lead times for additional resin volumes.

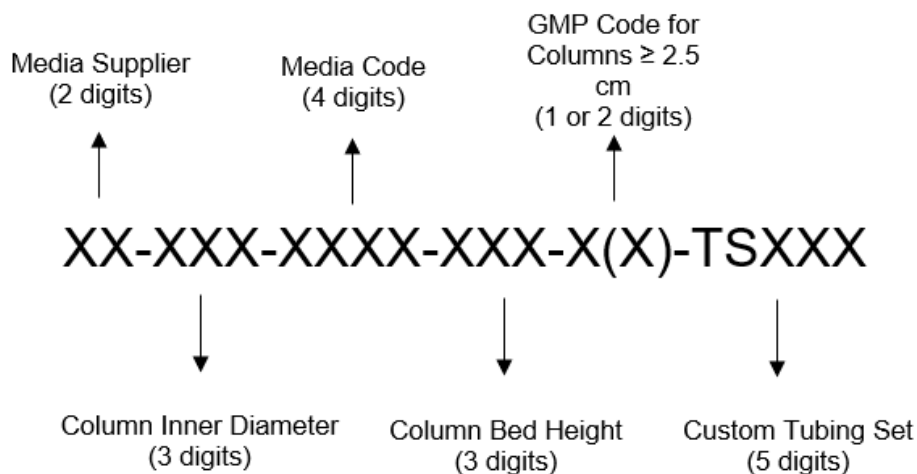
It is Repligen policy to pack no more than three (3) resin vendor lot numbers within a single OPUS Column. Should a customer send greater than 3 resin vendor lot numbers for a column pack, Repligen requires written approval on official letterhead from the end user customer to pack the resin.

2.5 OPUS Pre-packed Chromatography Column part numbers

OPUS Pre-packed Chromatography Column part numbers are structured as smart, embedded with select column configuration information. [Figure 1](#) describes the part number format for OPUS Column larger than 2.5 cm inner diameter.

- Field one (two characters) describes procurement mechanism.
 - CC indicates end-user procured resin.
 - BC indicates Repligen procured resin.
 - CX indicates end-user procured resin and gamma irradiated column.
 - BX indicates Repligen procured resin and gamma irradiated column.
- Field two (three characters) describes nominal column diameter in millimeters.
- Field three (four characters) describes the unique resin code (CPRI).
- Field four (three characters) describes the target/nominal bed height in millimeters.
- Field five (up to two characters) describe GMP level (Pre-GMP or GMP Run Ready) as well as if the column configuration includes an OPUS Resin Recovery port (PR or GR).
- Field six (five characters) describes the optional tubing set for attachment to the OPUS Column prior to release (TSXXX).

Figure 1. OPUS Column part number format



The OPUS Column part number system, governed by QA-FM-10107, does not generate a unique output for all column specifications. The OPUS Column Specification Sheet ([Figure 14](#)), generated upon initiation of column production serves as a unique identifier, even if the same column/part number is re-ordered.

For example, an OPUS 45R Pre-packed Chromatography Column with a 15 cm bed height and packed with Repligen-procured CaptivA® Resin, would be assigned the part number BC-450-CPRI-150-GR. In some cases, customer specific part numbers can be created upon request to reflect specific end-user requirements.

2.6 Summary of OPUS Pre-packed Chromatography Column production processes

Column components: Incoming raw materials and components prioritized by risk assessment are subject to an inspection procedure. Parts that comply with the criteria described in the Raw Materials and Component Specifications documents are released for column assembly and packing.

Resins: Consistent with good documentation practices, Repligen maintains material control of all resins, including assignment of internal lot numbers, to enable full traceability within batch records. The SOP that govern these procedures include SOP-1094 (Control of Incoming Materials), SOP-10042 (Control of Incoming Components) and SOP-10035 (Customer Property).

Manufacturing qualification: Column assembly processes are qualified and documented with SOP and batch records as specified in the Repligen ISO 9001 Quality Management Systems.

Preparation of Column Components: Column parts are washed and cleaned, according to qualified and validated protocols, prior to assembly.

Column packing: All OPUS GMP Run Ready and Pre-GMP Pre-packed Chromatography Column are packed in controlled and classified clean rooms that meet ISO Class 7 standards.

Note: See [Section 3](#) for more detailed information on the OPUS Column production process.

Quality control and Release: Individual OPUS Columns are individually tested according to the corresponding OPUS Column Specification Sheet. The specifications and the results of the release tests are documented on the Certificate of Analysis (CoA).

Packaging: Packed columns are secured in qualified shipping containers using foam protective packaging material. All OPUS Columns ship with tamper evident packaging and all inlets and outlets are secured with tamper evident SaniSure® clamps ([Figure 2](#)).

Figure 2. OPUS Pre-packed Chromatography Column packaging: Tamper evident clamps



OPUS 60R Pre-packed Chromatography Column shipped with tamper evident SaniSure® Clamps on inlet and outlet ports.

Figure 3. OPUS 60R Pre-packed Chromatography Column prepared for shipment



See [Section 5](#) for more information on packaging and shipping qualification.

2.7 Performance

OPUS Pre-packed Chromatography Columns provide chromatographic performance equivalent to or better than traditional self-packed columns. Performance is attained through a semi-automated packing process and a flow distribution system design.

- Optimal flow distribution is achieved through a flow distributor designed with minimal dead volume. Rigorous Computational Fluid Dynamics (CFD) model, which was validated through experimental testing, supports the design elements that meet or exceed traditional column flow distribution uniformity.
- Multi-cycle performance tests document robust and reproducible chromatographic results.

Note: More information on column performance can be found at repligen.com/OPUS.

Ease-of-use

OPUS Pre-packed Chromatography Columns incorporate ease of use features such as lifting handles, casters and industry standard sanitary tri-clamp flow port connections ([Table 1](#)).

Inlet/Outlet port locations

- OPUS Pre-packed Chromatography Columns sized 10 – 80R cm ID: Inlet and outlet ports both are located on the top of the column. Connection to the column inlet and outlet ports is secured with a tri-clamp fitting, designed by SaniSure to be both leak-proof and tamper-evident.
- OPUS Pre-packed Chromatography Columns sized 5 and 8 cm ID: Inlet and outlet ports are located at both ends of the column tube, typical for lab scale self-pack column design.

Table 1. Column handling features

Feature	OPUS Columns											
	5	8	10	12.6	14	20	25	30	36R	45R	60R	80R
Handles	No	No	No	No	Yes	Yes	Yes	Yes	No	No	No	No
Casters	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Manually lift	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No

Lifting handles

Figure 4. Handles and inlet/outlet ports for OPUS 20 - 30 Pre-packed Chromatography Column



OPUS Pre-packed Columns sized 14 – 30 cm ID: Handles are located on adjacent sides on the top of the column ([Figure 4](#)). Please follow all local or regional safety guidelines when lifting columns. See [Table 11](#) for approximate column mass.

Casters

Four twin wheel swivel castors allow movement through a facility. (Figure 5). Each castor is rated to hold ≥ 100 kg of weight. A manually engaged wheel lock can restrict castor movement. The bottom column of the cap is designed with channels to allow lifting of the column with straps. Please contact Repligen Customer Service for more information on how to utilize straps to lift an OPUS Column.

Figure 5. Caster detail on an OPUS 36R-80R Pre-packed Column



2.8 Reference documentation

The following documents can be found at repligen.com.

Quality Documentation: The Repligen ISO 9001 ISO certificate indicating that Repligen follows industry standards for document control.

Technical specifications: External column dimensions are provided in this Regulatory Support File. All other column packing specifications and end user specified criteria are documented on the OPUS Columns Specification Sheet.

User Guide: User guides for all OPUS Columns

Unpacking Guide: Unpacking guides are available for all OPUS Columns.

Technical Documents: A variety of supporting technical documents, presentations, and videos.

CE-Certificate: EG directive 97/23/EG is not applicable to OPUS Pre-packed Chromatography Columns and therefore columns are not CE-marked.

2.9 Materials of construction:

OPUS Pre-packed Chromatography Columns from 2.5 to 80 cm ID are designed using plastics best suited for downstream processing of biologic molecules. These plastics were chosen for performance characteristics including:

- Suitability for pharmaceutical use with process fluid contact
- USP Class VI compatibility
- Low levels of extractables
- Free from materials of animal origin and/or compliant with EMA 410/01

Table 2. Product contact materials of construction

OPUS Column component	Material	USP <88> Class	CFR 21 177	Animal origin
Column Tube (2.5 – 30 cm ID)	Polypropylene (PP)	Class VI	177.1520	Animal Free
Column Tube (36R – 80R)	70% w/w E-Glass/PP engineered composite structure	Class VI	177.1520	Animal Free
Flow Distributors	Polypropylene	Class VI	177.1520	Animal Free
Inlet and Outlet Ports	Polypropylene	Class VI	177.1520	Animal Free
Bed Support Screens	Polypropylene	Class VI	177.1520	EMA 410/01
Flow Distributor O-Rings	Platinum-cured medical grade silicone	Class VI	177.2600	Animal Free
Return Lines	Platinum-cured medical grade silicone, reinforced with strong polyester fiber	Class VI	177.2600	Animal Free
R Plug and Inside Port	Polypropylene	Class VI	177.1520	Animal Free
R Inner/Outer Gaskets and Plug O-ring	Platinum-cured medical grade silicone	Class VI	177.2600	Animal Free

Note: The 12 µm polypropylene bed support screen is ultrasonically welded to the flow distributor.

Non-product contact materials summary

- Top and bottom caps: acrylonitrile butadiene styrene (ABS) co-polymer or high-density polyethylene (HDPE)
- Side guard: ABS (blue)
- Inlet and outlet port grommets: silicone (blue)
- Handles: polyurethane (blue)
- Castors: Polyamide casing with non-marking grey polyurethane tires
- OPUS R outer nut and washer: ABS
- OPUS R Bio Clamp: glass filled nylon

For a signed copy of the OPUS Pre-packed Chromatography Columns BSE/TSE Free Statement, contact Customer Support at customerserviceUS@repligen.com or customerserviceEU@repligen.com.

2.10 Column design

Figure 6. OPUS 2.5 Pre-packed Chromatography Column design

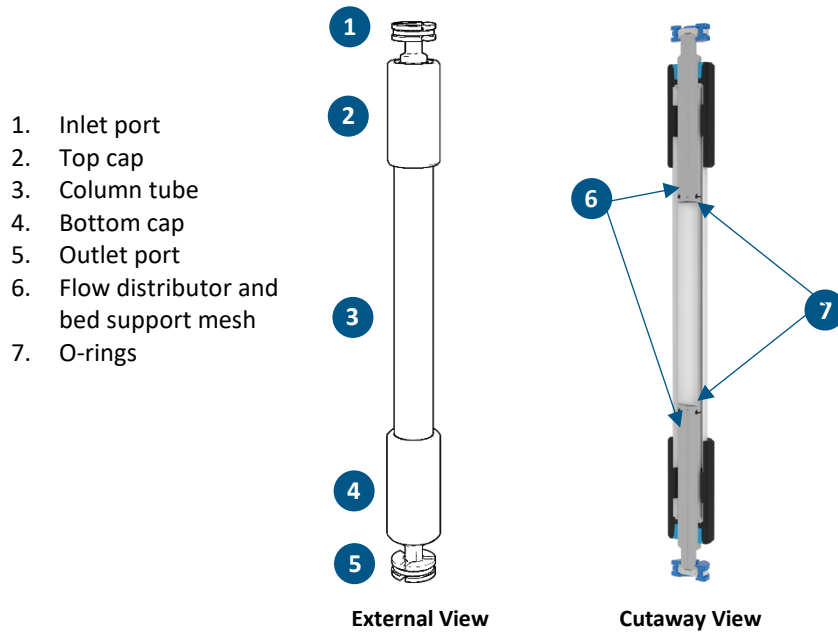


Figure 7. OPUS 5 and 8 Pre-packed Chromatography Column design

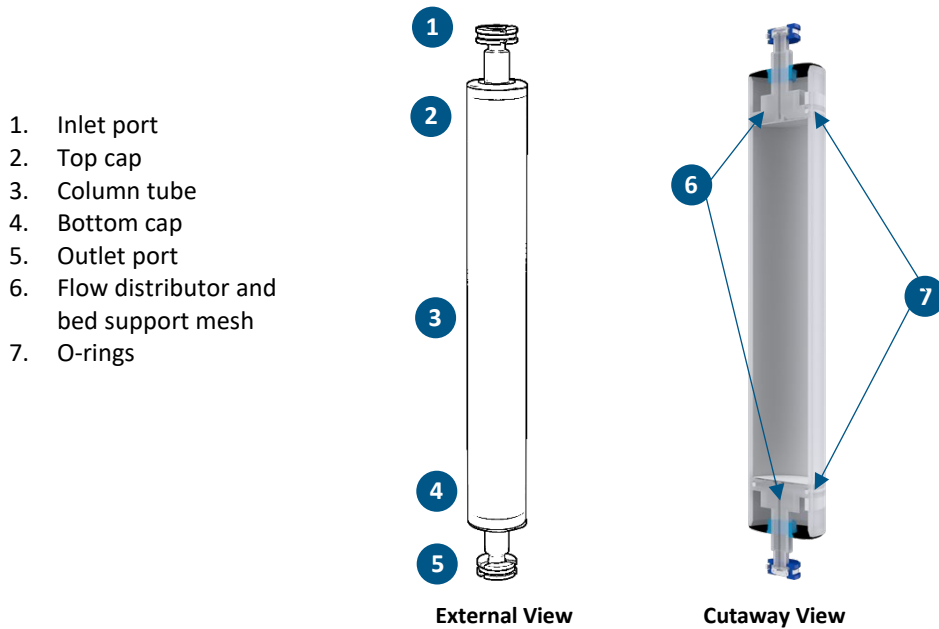
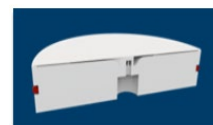
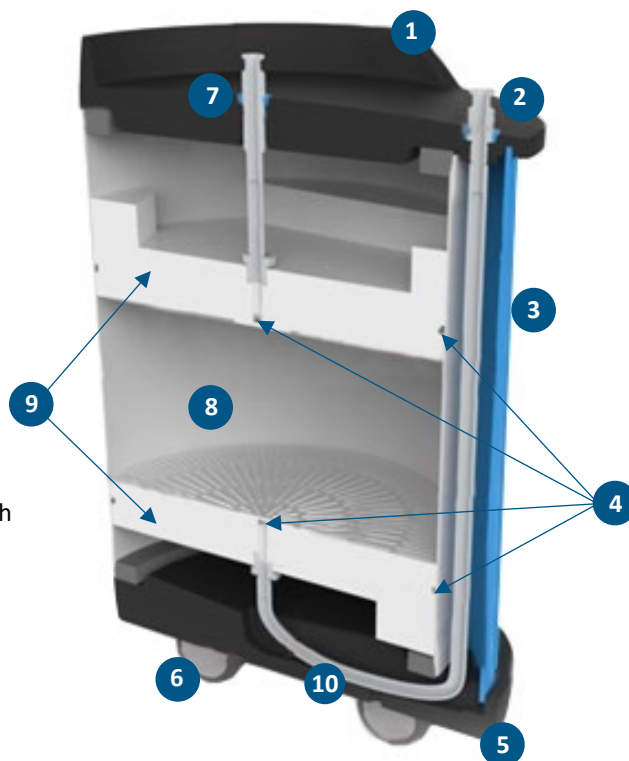


Figure 8. OPUS 10 – 30 Pre-packed Chromatography Column design (OPUS 20 shown)



Figure 9. OPUS 45 – 60 Pre-packed Chromatography Column design (no R port)

1. Top cap
2. Outlet
3. Side-guard
4. O-rings
5. Bottom cap
6. Casters
7. Inlet
8. Tube
9. Flow distributor and 12 µm mesh
10. Return line



Flow Distributor
(12 µm mesh size)

Figure 10. OPUS 36R – 80R Pre-packed Chromatography Column design (OPUS 80R shown)

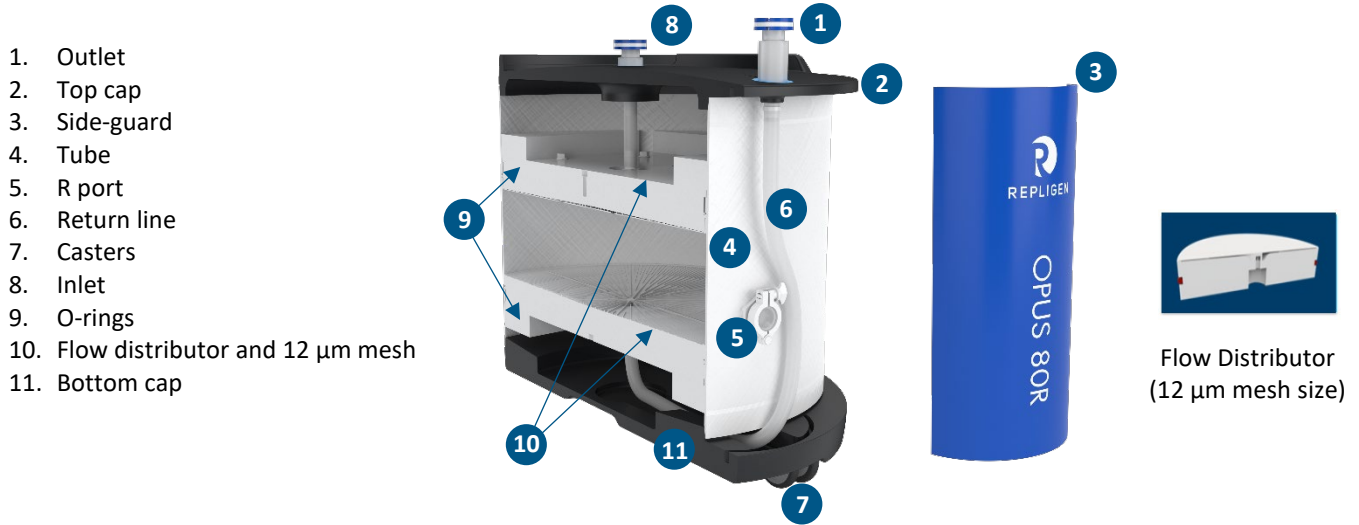
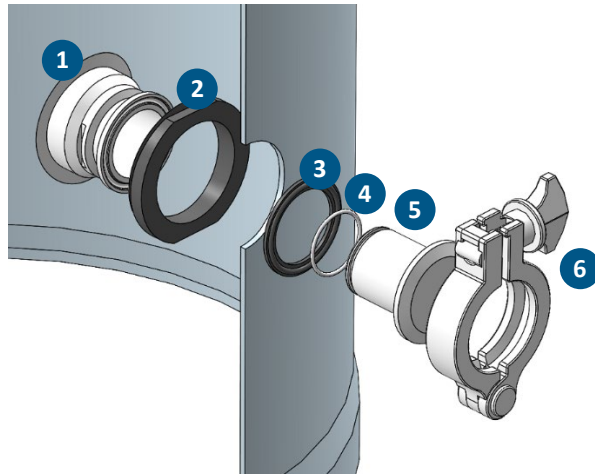


Figure 11. OPUS R Port design

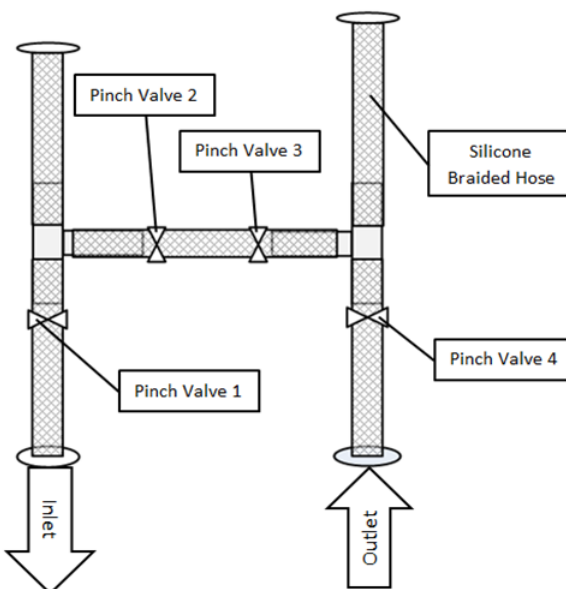
1. Inside port (Polypropylene)
2. Inner gasket (Silicone)
3. Outer gasket (Silicone)
4. Plug O-ring (Silicone)
5. OPUS® R Plug (Polypropylene)
6. 1 inch TC sanitary clamp (Glass Filled Nylon)



2.11 OPUS H-Tubing Sets

The H-tubing set utilizes a column bypass mechanism that enables a flush and sanitization of the flow path, eliminates the need for bulky stainless steel 3- or 4-way valves, and reduces the likelihood of air entering the packed bed.

Figure 12. OPUS H-tubing Set Design



Use Instructions:

- Column is delivered with the tubing filled with storage solution and attached to the inlet and outlet of the column.

Note: All four pinch clamps will be engaged.

- To prime the tubing, connect the inlet line from the pump to the top of the inlet side of the tubing set (above pinch valve 1).
- Open pinch valves 2 and 3 for bypass mode of the tubing set
- Connect the outlet line to the top of the outlet side of the tubing set (pinch valve 4).
- Flush buffer through the tubing set in bypass mode for removal of air and cleaning. Ensure constant flow is exiting the tubing set and there are no visual bubbles in the tubing
- Close pinch valves 2 and 3
- Open pinch valve 1 and 4 to direct flow through the column.

Note: If removing storage solution, start the operation using a linear velocity of 50 cm/hour. Flow rate can be increased slowly as long as backpressure does not exceed 80% of the maximum pressure achieved during column packing.

Materials of construction:

- Braided platinum cured silicone tubing
- Polypropylene T-adapters and end-fittings

Tubing sets are also available with aseptic connectors for the OPUS 2.5 – 30 cm ID columns. See below for available tubing sets based on flow path ID and connector types ([Table 3](#)).

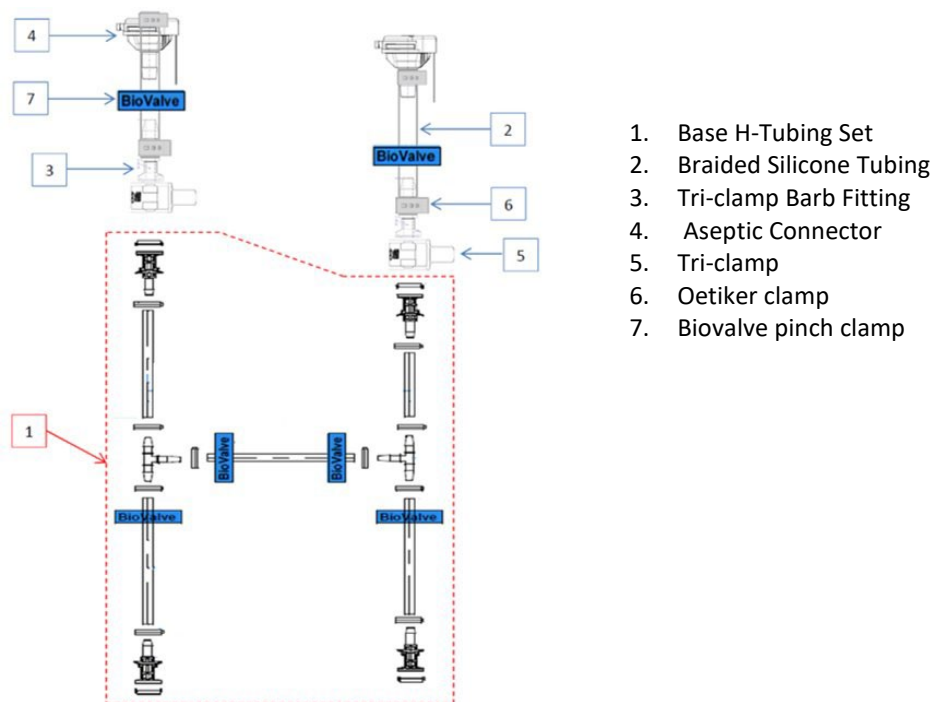
Table 3. OPUS H-Tubing Set Connector and sizing options

ID Range	Tri-Clamp	ReadyMate™	AseptiQuik®	Kleenpak™ Presto
OPUS 2.5	1/8" ID Flow Path (TS024)	N/A	1/8" ID Flow Path AQS (TS025)	N/A
OPUS 5 – 8 ¹	1/8" ID Flow Path (TS033)	1/8" ID Flow Path (TS019)	1/8" ID Flow Path AQS (TS023)	1/8" ID Flow Path (TS020)
OPUS 10 – 12.6	1/4" ID Flow Path (TS006)	1/4" ID Flow Path (TS018)	1/4" ID Flow Path AQG (TS007)	1/4" ID Flow Path (TS010)
OPUS 14 – 20	1/4" ID Flow Path (TS001)	1/4" ID Flow Path (TS009)	1/4" ID Flow Path AQG (TS012)	1/4" ID Flow Path (TS011)
OPUS 25 – 30	3/8" ID Flow Path (TS002)	3/8" ID Flow Path (TS016)	3/8" ID Flow Path AQG (TS015)	3/8" ID Flow Path (TS017)
OPUS 36R	1/2" ID Flow Path (TS031)	N/A	N/A	N/A
OPUS 45R	1/2" ID Flow Path (TS003)	N/A	N/A	N/A
OPUS 60R	3/4" ID Flow Path (TS004)	N/A	N/A	N/A
OPUS 80R	3/4" ID Flow Path (TS013)	N/A	N/A	N/A

¹ 1/4" ID flow path (TS032) with AseptiQuik G also available.

For OPUS H-tubing sets with aseptic connectors, two additional pinch valves are engaged on both the inlet and outlet tubing below the aseptic connectors. Operation of the tubing set in bypass or flow-through mode be performed with both pinch clamps disengaged.

Figure 13. Example OPUS H-Tubing Set with Aseptic Connectors



2.12 OPUS Pre-packed Chromatography Column physical specifications

2.12.1 Mechanical strength: Column hardware pressure rating

All columns were designed and qualified with a factor of safety (FOS) of >2X the maximum operating pressure. Pressure integrity was established with pressure hold studies on empty columns filled with water. To pass a pressure hold integrity test a column must hold a designated pressure with minimum decay (e.g., ≤5 psi) over a defined period of time. Ambient, 4°C, and 40°C have been evaluated with passing results. See below for representative tests and results.

Table 4. OPUS Column 2.5 cm ID pressure integrity testing

Pressure Test	Verification Method	Acceptance Criteria	Results
Temperature: Ambient	Pressure hold test at >1.5x the recommended operating pressure (4 bar).	≥6 bar (87 psi) pressure hold for 2 hours in water. After 30 minutes stabilization column must have ≤5 psi decay over 90 min, with no visible water leaking.	Pass
Temperature: 4°C	Incubate water-filled column (no resin) overnight in 4°C chamber, and test column integrity at maximum recommended operating pressure.	Pressure test at ≥6 bar, must be less than 5 psi decay over 90 min after 30 min stabilization.	Pass
Temperature: 40°C	Incubate water-filled column (no resin) overnight in 40°C chamber, and test column integrity at maximum recommended operating pressure.	Pressure test at ≥6 bar, must be less than 5 psi decay over 90 min after 30 min stabilization.	Pass
Burst pressure	Destructive test on assembled column.	Record burst pressure for assembled column (no resin)	Pass Failure at >200 psi (>13 bar).

Table 5. OPUS Column 8 cm ID pressure integrity testing*

Pressure Test	Verification Method	Acceptance Criteria	Results
Temperature: Ambient	Pressure hold test at >1.5x the recommended operating pressure (4 bar).	100 psi pressure hold for 2 hours in water. After 60 minutes stabilization column must have ≤5 psi decay over 60 min, with no visible water leaking.	Pass
Temperature: 4°C	Run cooled water through system (no resin) until equilibrium, and test column integrity at maximum recommended operating pressure.	Pressure test at 4 bar, must be less than 5 psi decay over 30 min after 30 min stabilization.	Pass
Temperature: 40°C	Run heated water through system (no resin) until equilibrium, and test column integrity at maximum recommended operating pressure.	Pressure test at 4 bar, must be less than 5 psi decay over 30 min after 30 min stabilization.	Pass
Burst pressure	Destructive test on assembled column.	Record burst pressure for assembled column (no resin)	Pass Failure at >500 psi (>34 bar).

*Representative of 5 and 8 cm ID columns.

Table 6. OPUS Column 12.6 cm ID pressure integrity testing*

Pressure Test	Verification Method	Acceptance Criteria	Results
Temperature: Ambient	Pressure hold test at >1.5x the recommended operating pressure (4 bar).	100 psi pressure hold for 2 hours in water. After 60 minutes stabilization column must have ≤5 psi decay over 60 min, with no visible water leaking.	Pass
Temperature: 4°C	Run cooled water through system (no resin) until equilibrium, and test column integrity at maximum recommended operating pressure	Pressure test at 4 bar must be less than 5 psi decay over 30 min after 30 min stabilization.	Pass
Temperature: 40°C	Run heated water through system (no resin) until equilibrium, and test column integrity at maximum recommended operating pressure.	Pressure test at 4 bar must be less than 5 psi decay over 30 min after 30 min stabilization.	Pass
Burst pressure	Destructive test on assembled column.	Record burst pressure for assembled column (no resin).	Pass Failure at >400 psi (>27 bar).

*Representative of 10 – 30 cm ID columns.

Table 7. OPUS 80R Pre-packed Chromatography Column pressure integrity testing*

Pressure Test	Method	Acceptance Criteria	Results
Temperature: Ambient	Pressure hold test at 2x the recommended operating pressure (3 bar).	Pressurize column assembly to 6 bar for 2 hours with water at 22°C ± 3°C. 30 minutes pressure stabilization, 1.5 hr hold ≤5 psi decay, no visible water leaking w/ 3 assemblies	Pass
Temperature: 4°C	Fill column with water; Store column in 2 – 8°C overnight (to equilibrate). Pressurize assembly to maximum recommended operating pressure.	Pressurize column assembly to 3 bar for 2 hours with water. 30 minutes pressure stabilization, 1.5 hr hold ≤5 psi decay, no visible water leaking.	Pass
Temperature: 40°C	Circulate 40 ±3°C water through system for 1 hour @ 100 cm/hr. Pressurize assembly maximum recommended operating pressure for 2 hours with water.	Pressurize column assembly to 3 bar for 2 hours with water. 30 minutes pressure stabilization, 1.5 hr hold ≤5 psi decay, no visible water leaking.	Pass
Burst pressure	Due to large size of the column, a suitably safe environment was not available to evaluate for burst pressure.		

*Representative of 36R – 80R Columns.

Note: Exceeding the maximum column hardware pressure rating will void the Repligen warranty statement ([Section 2.16](#)).

Table 8. OPUS Column Hardware pressure ratings

Column ID	OPUS 5	OPUS 8	OPUS 10	OPUS 12.6	OPUS 14	OPUS 20	OPUS 25	OPUS 30	OPUS 36R	OPUS 45R	OPUS 60R	OPUS 80R
Pressure Rating (bar)	4	4	4	4	4	4	4	4	3	3	3	3

Note: The pressures reported above are the pressure limits of the hardware to prevent leaks, cracks, breaks, and damage to components. The suggested operating pressure will be based on the packing pressure of the resin, and will be less than the above pressure limits. Refer to column label and CoA for the column-specific packing pressure.

2.12.2 Packed bed integrity: packed column pressure rating

OPUS Pre-packed Chromatography Columns are packed according to Repligen SOP and end-user specifications. Maximum pressure achieved during packing is noted on either the column label and/or Certificate of Analysis. Exceeding the maximum packing pressure stated on the Certificate of Analysis and column label will likely compromise the packed bed integrity and void the Repligen warranty statement ([Section 2.16](#)). Therefore, Repligen recommends establishing an appropriate margin of safety to the maximum packing pressure achieved when assigning a maximum operating pressure.

Table 9. Physical specifications summary: OPUS Columns 2.5 – 30

Physical Attributes	OPUS 5	OPUS 8	OPUS 10	OPUS 12.6	OPUS 14	OPUS 20	OPUS 25	OPUS 30	
Diameter	5.1 cm	8.1 cm	10 cm	12.6 cm	14 cm	20 cm	25 cm	30 cm	
Internal cross section	20.4 cm ²	51.5 cm ²	78.5 cm ²	125 cm ²	154 cm ²	314 cm ²	491 cm ²	707 cm ²	
Column body pressure rating	4 bar	4 bar	4 bar	4 bar	4 bar	4 bar	4 bar	4 bar	
Bed height range	5 – 30 cm	5 – 30 cm	5 – 30 cm	5 – 30 cm	5 – 30 cm	5 – 30 cm	5 – 30 cm	5 – 30 cm	
Column volumes	10 cm bed height	0.2 L	0.5 L	0.8 L	1.3 L	1.5 L	3.1 L	4.9 L	7.1 L
	20 cm bed height	0.4 L	1 L	1.6 L	2.5 L	3.1 L	6.3 L	9.8 L	14.1 L
	30 cm bed height	0.6 L	1.5 L	2.4 L	3.8 L	4.6 L	9.4 L	14.7 L	21.2 L
Assembled column height (plus column bed height)	~20 cm	~20 cm	~20 cm	~28 cm	~30 cm	~30 cm	~33 cm	~35 cm	
Outer diameter (cm, including caps)	7 cm	10 cm	16 cm	20 cm	21 cm	27 cm	33 cm	38 cm	
Inlet/outlet flow path internal diameter	3.45 mm (5/32 in)	4.57 mm (3/16 in)	6.35 mm (1/4 in)	6.35 mm (1/4 in)	6.35 mm (1/4 in)	6.35 mm (1/4 in)	9.53 mm (3/8 in)	9.53 mm (3/8 in)	
Inlet/outlet port connectors	3/4 in mini tri-clamps	3/4 in mini tri-clamps	3/4 in mini tri-clamps	3/4 in mini tri-clamps	3/4 in mini tri-clamps	3/4 in mini tri-clamps	3/4 in mini tri-clamps	3/4 in mini tri-clamps	

Table 10. Physical specifications summary: OPUS 36R – 80R Pre-packed Chromatography Columns

Physical Attributes		OPUS 36R	OPUS 45R	OPUS 60R	OPUS 80R
Diameter		36 cm	45.7 cm	59.9 cm	79.9 cm
Internal cross-section		1020 cm ²	1640 cm ²	2818 cm ²	5014 cm ²
Column body pressure rating		3 bar	3 bar	3 bar	3 bar
Bed height range ¹		10 – 30 cm	10 – 30 cm	10 – 30 cm	10 – 30 cm
Column volumes	10 cm bed height	10 L	16 L	28 L	50 L
	20 cm bed height	20 L	33 L	56 L	100 L
	30 cm bed height	31 L	49 L	84 L	150 L
Assembled column height ¹	≤22 cm bed height	~87 cm	~90 cm	~93 cm	~97 cm
	>22 cm bed height	~113 cm	~116 cm	~120 cm	~123 cm
Outer diameter (including caps)	10 cm bed height	45 cm	54 cm	68 cm	91 cm
Inlet/outlet flow path internal diameter		12.7 mm (1/2 in)	12.7 mm (1/2 in)	19.1 mm (3/4 in)	19.1 mm (3/4 in)
Inlet/outlet port connectors		¾" mini tri-clamps	¾" mini tri-clamps	1" tri-clamps	1" tri-clamps

¹Estimates based on the target bed height.

Note: OPUS 36R – 80R Pre-packed Chromatography Columns have a minimum bed height of 10 cm, OPUS 45 and 60 Pre-packed Chromatography Columns without an R port have a minimum bed height of 5 cm.

Table 11. Column mass (approximate weight of packed columns in kilograms)

Bed height	OPUS 5	OPUS 8	OPUS 10	OPUS 12.6	OPUS 14	OPUS 20	OPUS 25	OPUS 30	OPUS 36R	OPUS 45R	OPUS 60R	OPUS 80R
5 cm	0.5	1.0	2.0	4.0	4.0	6.0	10	14	43	69	117	235
10 cm	0.5	1.5	2.5	4.5	5.0	8.0	13	18	48	77	131	260
15 cm	1.0	1.5	3.0	5.5	6.0	10	16	22	54	86	145	285
20 cm	1.0	2.0	3.5	6.0	7.0	12	19	26	59	94	159	310
30 cm	1.5	2.5	4.0	8.0	9.0	16	24	34	69	110	187	335

2.1.3 Thermal stability

Column construction can support a working temperature range of 2°C to 40°C based on the general properties of polypropylene as well as OPUS Pre-packed Chromatography Column ISTA shipping tests ([Section 5.3](#)).

2.13 Column shelf-life

Repligen conducted four studies to assess shelf-life stability for OPUS Pre-packed Chromatography Columns when stored according to instructions in the user guide. The rationale for the multi-study approach was to group columns based on their cylindrical tube design and minimize potential variables during evaluation. The first study evaluated OPUS 10 – 30 Pre-packed Chromatography Columns over an 18 month period. The second study evaluated OPUS 36R – 80R Pre-packed Chromatography Columns family over a longer period in response to end-user requests for time points up to 5 years. In this study, the OPUS 80R Pre-packed Chromatography Column was deemed the worst-case condition for column stability given the high volume of resin and lack of column wall support for the packed resin beads. The third study qualifies the shelf life of OPUS 5-30 Pre-packed Chromatography

Columns for at least 24 months based on mechanical stability testing within an on-going study. The fourth study qualifies the shelf life of OPUS 5 – 8 Pre-packed Chromatography Columns for 5 years based on single point retrospective data.

Table 12. Column shelf-life summary

Study Number	Column Family	Column IDs Tested	Tube Materials	Time Period	Status
1	OPUS 10 –30 Columns	OPUS 10, 20, 30	Polypropylene	18 months	Complete
2	OPUS 36R – 80R Columns	OPUS 80R	70% w/w E-Glass/Polypropylene engineered composite structure	60 months	Complete
3	OPUS 5 - 30	OPUS 5, 30	Polypropylene	24 months	On-going
4	OPUS 5- 8	OPUS 5, 8	Polypropylene	60 months	Complete

For column performance testing, Study 1 –3 used agarose resin type for the packed column aspect of the study. Study 4 used styrene based resin type for the packed column aspect of the study. Therefore, this study can serve as general guidance for the >250 types of resins which can be packed into OPUS Columns. All columns were stored cold at 2 – 8°C, which represents most challenging temperature for the integrity of plastic components, and then allowed to equilibrate to room temperature (25°C) before experiments were performed.

Note: An additional study has been completed for gamma irradiated OPUS 2.5 – 30 Columns. Details of this study are found within the OPUS Gamma Regulatory Support File.

2.13.1 Mechanical stability

The mechanical stability assessment looked at column structural integrity at pre-determined time points post-assembly. Columns were filled with 18.5% ethanol (Study 1) or RODI water (Study 2, 3, and 4) and then were pressurized. Pressure decay was monitored over a set period. During this pressure hold period, the column was visually inspected for gross failure such as leakage from ports and/or threads, and general structural integrity. See [Table 13](#) for the mechanical stability test schedule and acceptance criteria and [Table 14](#) for results.

Note: The OPUS 80R Pre-packed Column exhibited increased pressure drop in the initial 30 minutes of the hold because of the higher surface area subject to plastic stretching. To confirm the column was not leaking, the OPUS 80R Pre-Packed Chromatography Column hold time was increased to 120 minutes. Based on the reported pressure trend data for the OPUS 80R Pre-Packed Chromatography Column, the same conclusion of an integral column design and assembly could be achieved at the 60 minute data point.

2.13.2 Chromatographic performance

Chromatographic performance was assessed over multiple time points by demonstrating that no significant performance degradation occurs during time in storage. For Study 1, one column was re-tested at each of the time intervals and compared to the performance of that specific column at time zero. For Study 2, a single OPUS 80 Pre-Packed Chromatography Column was retested at each of the time intervals and compared to the performance at time zero. For Study 4, only one testing of columns at 5 year timepoint is used for comparison against performance at time zero. See [Table 13](#) for acceptance criteria and [Table 15](#) for results.

Note: Study 1 is the only study to sample bioburden and endotoxin data because only a single column was tested at each time point; the potential for artifact bioburden and endotoxin results due to reuse was probable based on experimental design for Study 2, 3, and 4.

Table 13. Stability study schedule and acceptance criteria

Study Number	Time Interval	Mechanical Stability Criteria (Empty Columns)	Performance Stability Criteria (Packed Columns)
Study 1	T = 0	Testing: Time at Pressure: 60 minutes Pressure: 4 bar Acceptance: Pressure decay: ≤5 psi Visual: No gross defects or leaks	Acceptance: Asymmetry: 0.8 – 1.6 Plate count: >1500 N/m (100 cm/hr) Endotoxin: ≤1.0 EU/mL Bioburden: ≤100 CFU/mL
Study 1	T = X months	Acceptance: Pressure decay: ≤5 psi Visual: No gross defects or leaks	Acceptance: Endotoxin: ≤1.0 EU/mL Bioburden: ≤100 CFU/mL <i>Comparison to T = 0 time point:</i> N/m Δ = <15% A _s Δ = <15%
Study 2	T = 0	Testing: Time at Pressure: 120 minutes Pressure: 3 bar Acceptance: Pressure decay: ≤5 psi Visual: No gross defects or leaks	Acceptance: Asymmetry: 0.8 – 1.8 Plate count: >2000 N/m (100 cm/hr)
Study 2	T = X months	Acceptance: Pressure decay: ≤5 psi Visual: No gross defects or leaks	Acceptance: <i>Comparison to T = 0 time point:</i> N/m Δ = <20% A _s Δ = <20%
Study 3	T = 0	Testing: Time at Pressure: 60 minutes Pressure: 4 bar Acceptance: Pressure decay: ≤5 psi Visual: No gross defects or leaks	N/A
Study 3	T = X months	Acceptance: Pressure decay: ≤5 psi Visual: No gross defects or leaks	N/A
Study 4	T = 0	Testing: Time at Pressure: 60 minutes Pressure: 4 bar Acceptance: Pressure decay: ≤5 psi Visual: No gross defects or leaks	Acceptance: Asymmetry: 0.8 – 1.8 Plate count: >4000 N/m (100 cm/hr)
Study 4	T = X months	Acceptance: Pressure decay: ≤5 psi Visual: No gross defects or leaks	Acceptance: <i>Comparison to T = 0 time point:</i> N/m Δ = <20% A _s Δ = <20%

All columns passed acceptance criteria at each interim time point, as well as at the final time point.

Note: At the completion of Study 1 (18 months), bioburden and endotoxin for all columns (serial numbers 0001 – 0004) was 0 CFU/mL and <0.1 EU/mL, respectively.

Table 14. Mechanical stability test results

OPUS Pre-packed Column Size	Months											
	3	6	9	12	18	19	24	30	36	48	60	61
5 x 20 cm	Pass	Pass	Pass	Pass	Pass	N/A	Pass	N/A	N/A	N/A	N/A	Pass
10 x 20 cm	Pass	Pass	N/A	Pass	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20 x 20 cm	Pass	Pass	N/A	Pass	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A
30 x 20 cm	Pass	Pass	Pass	Pass	Pass	N/A	Pass	N/A	N/A	N/A	N/A	N/A
80 x 20 cm	Pass											

Table 15. Performance stability study results

OPUS Pre-packed Column Info	Months											
	3	6	9	12	18	19	24	30	36	48	60	61
5 x 20 cm	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Pass
8 x 20 cm	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Pass
20 x 15 cm Serial number 0001	Pass	N/A	N/A	N/A	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20 x 15 cm Serial number 0002	N/A	Pass	N/A	N/A	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20 x 15 cm Serial number 0003	N/A	N/A	N/A	Pass	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20 x 15 cm Serial number 0004	N/A	N/A	N/A	N/A	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A
80 x 20 cm	Pass ¹											

¹80 cm column Serial number 0001 N/m increased by 23% from t = 0 to t = 3 month testing. Results were deemed satisfactory because 1) no degradation in column performance was observed relative to t = 0, and 2) the column performance was stable throughout all subsequent tests after the t = 3 month result.

2.13.3 Conclusion and Interpretation of OPUS Pre-packed Chromatography Column shelf-life data

OPUS Pre-packed Chromatography Columns are designed to enable multi-campaign use over a period of months or years. The data presented for Study 2 demonstrates OPUS 36R, 45R, 60R, and 80R Pre-packed Chromatography Columns maintain mechanical and chromatographic performance characteristics over a 61-month period. Therefore, this study confirms a 61-month shelf life for OPUS 36R, 45R, 60R, and 80R Pre-Packed Chromatography Columns, but does not consider the potential impact of process design (e.g., flow rates, pressure) or process fluids.

In conjunction with the data from the shelf-life studies, we provide guidance below for the justification of column operation over-time in a downstream chromatography process: An end user may justify extending OPUS Column hardware and packed bed shelf-life by assessing plate count and asymmetry data combined with pressure flow tests (e.g., pressure flow curve). Trending asymmetry, plate count, and pressure flow data over time allows an end user to confirm the integrity of the column hardware as well as the integrity of the packed bed. This data can then be used to justify the extension of pre-packed column shelf life. In addition, resin expiration dates and process qualification data (i.e. cycle stability of the resin), should also be considered when assessing pre-packed column shelf-life.

Data trending over time of asymmetry, plate count, and pressure flow for pre-packed columns should be similar to how self-packed column lifetime and hardware integrity is assessed. For example, self-packed columns are tested against specifications prior to use in purification processes to assess hardware integrity as well as packed bed integrity. A similar approach can be used for OPUS Columns.

2.14 Solvent compatibility

The solvents listed had no detected effect on the integrity of the plastic. This is equivalent to an A = Excellent rating for chemical compatibility.

- 20% Acetic acid
- 10% Acetone
- Benzyl alcohol
- Citric acid
- 2% (w/v) Detergents
- 20% Ethanol
- 6 M guanidine HCl
- HCl (< 20%)
- Isopropyl alcohol (IPA)
- Methanol
- Phosphoric acid
- Potassium hydroxide
- 2 M sodium hydroxide
- Sulfuric acid (< 50%)
- 8 M Urea
- Water

2.15 Cleaning

OPUS Pre-packed Chromatography Columns are used for purification of biological products which have specific regulatory requirements for bioburden and endotoxin levels. Therefore, a quantitative cleaning investigation was performed to demonstrate the effectiveness of sanitization using sodium hydroxide as a cleaning agent.

Method

Several different OPUS Columns were packed with agarose resin in 20 cm bed heights. Each column was loaded with 1 column volume of E. coli bacteria at a concentration of 0.1 OD (optical density) at 600 nm. The columns were left to incubate at ambient temperature overnight, and then flushed with reverse osmosis deionized (RODI) water for 2 – 3 column volumes in downflow. Samples were collected to measure bioburden and endotoxin.

A sanitization procedure was subsequently used as followed:

- Flush with 1 M sodium hydroxide in upflow at 100 cm/hr for 30 minutes
- Flush with 1 M sodium hydroxide in downflow at 100 cm/hr for 30 minutes
- Recirculation of 1 M sodium hydroxide for 2 hours in upflow at 100 cm/hr
- Incubation of the column in 1 M sodium hydroxide for 1 – 5 hours (static sanitization for complete removal of endotoxins)
- Flush with RODI water at 100 cm/hr until neutral pH is achieved

Each column was then left to incubate at ambient temperature overnight prior to pulling samples for bioburden and endotoxin testing.

Results

Results for bioburden and endotoxin levels from the microbial challenge are outlined in the table below, which shows the sanitization procedure completely removed bioburden from millions of CFU to zero CFU in the post-sanitization water rinse. In addition, endotoxin levels were brought below the limit of detection (0.25 EU/mL) for the assay.

Table 16. Results of bioburden and endotoxin testing

Cleaning Method	Column Diameter								
	2.5	8	12.6	20	30	36R	45R	60R	80R
0.1 M NaCl effluent after overnight <i>E. coli</i> incubation	TNTC ¹ CFU/mL >0.25 EU/mL								
0.1 M NaCl post sanitization effluent	0 CFU/mL <0.25 EU/mL								

¹Too numerous to count.

Conclusions

In order to test effectiveness of sanitization on an OPUS Column, a worst-case scenario was devised where the column was loaded with an excess of *E. coli* culture (a gram-negative, endotoxin producing bacteria). The results of the sanitization protocol demonstrate the effective removal of bioburden and endotoxin contamination.

2.16 Warranty

2.16.1 General warranty

Repligen aspires to complete customer satisfaction and has implemented the following warranty policy for OPUS Pre-packed Chromatography Columns.

- If the column arrives at the customer site in damaged condition, Repligen will accept the damage risk and issue a replacement at no charge
- If the column fails passing specifications as agreed to on the OPUS Column Specification Sheet, Repligen will conduct troubleshooting efforts and if unsuccessful, will ask for the column to be returned for further evaluation. If the root cause of the failed test is determined to be a compromised packed bed, Repligen will pack a replacement at no charge
- If the packed bed is compromised (e.g., a channel develops) and the root cause is packing, then Repligen will replace the column at no charge

Note: *If an end-user exceeds the maximum packed bed pressure and/or the maximum hardware pressure as stated on the column label and/or Certificate of Analysis, warranty is void.*

2.17 Use of TempTale® Multi-alarm Temperature Monitors

The addition of a TempTale Multi-Alarm Temperature Monitor is an add-on service Repligen offers at the request of our customers.

- Temperature monitoring data extracted from the monitor is for customer informational purposes only
- Customer cannot reject a shipment based on temperature monitoring data extracted from the monitor
- Customer cannot submit a warranty claim based on temperature monitoring data extracted from the monitor. Repligen will require column qualification results post-delivery in order to compare a column performance post-delivery with the chromatographic performance results indicated on the Certificate of Analysis
- Repligen accepts no liability for any claims that losses or damages are based on temperature monitoring data extracted from the monitor

If customer requires guaranteed temperature control during transit from the Repligen manufacturing location to the delivery destination, customer shall be invoiced for such service separately.

2.18 OPUS Gamma Pre-packed Chromatography Column Service Liability Statement

Repligen offers OPUS Pre-packed Columns that are gamma irradiated at the request of the customer. This customer-requested service is subcontracted by Repligen to a third-party vendor for gamma processing.

Note: *Repligen will not guarantee resin chromatographic performance post-gamma irradiation (e.g., capacity, selectivity). It is the burden of the customer to investigate gamma irradiated resin compatibility and chromatographic performance for the customer process. OPUS MiniChrom Columns are available to evaluate the impact of gamma irradiation on resin functionality.*

This service is only offered for the OPUS 2.5 – 30 column ID size range. Customers must choose this option at the quoting stage. The option is not available for previously packed OPUS Columns. For more information, please refer to the OPUS Gamma Regulatory Support File on repligen.com.

2.19 Safety Data Sheet (SDS)

OPUS Pre-packed Chromatography Columns are made from plastic components only and therefore no Safety Data Sheet (SDS) is needed. An SDS for the chromatography resin packed into an OPUS Column may be obtained from the resin manufacturer.

3. Manufacturing information

3.1 Introduction

All OPUS 2.5 – 80R Pre-packed Chromatography Columns are manufactured in both the Repligen corporate headquarters, located at 41 Seyon Street, Waltham, Massachusetts 02453, USA and Repligen Europe B.V., Hoeksteen 13, 4815 PR BREDA, The Netherlands. The Quality Assurance (QA) and Quality Control (QC) operations are also based in the same locations. Neither the facility nor products manufactured require registration or market approval. Therefore, the Repligen column packing facility and products manufactured herein are not subject to regulatory review or audit by organizations such as the US Food and Drug Administration or European Medicines Agency.

3.2 Manufacturing Quality Assurance Standards and Policy

Repligen recognizes the need for high quality standards and has therefore established an ISO 9001 Quality Management System. Refer to [Section 1.1](#) for the Repligen Quality Policy.

3.2.1 Manufacturing Controls and SOP

Training [SOP-1498]: Manufacturing is performed by qualified and trained operators. Training documentation is maintained by Quality Assurance.

Process documentation [SOP-1302, SOP-1098]: Repligen manufacturing processes are governed by an ISO 9001 compliant Quality Management System. All manufacturing work instructions are contained in controlled documents, issued in advance of each manufacturing batch. Batches and process intermediates are fully traceable through an internal lot numbering system. All manufacturing data are recorded by operators at the time of manufacturing. Batch records are archived for 3 years on site, and then stored off site for a minimum of 10 years.

Raw materials [SOP-1094]: Raw materials are controlled with pre-approved specifications. Receipt of material is verified and released by QA prior to use in manufacturing.

Customer property [SOP-10035]: All customer property, including user supplied resin, is documented, tracked, and released prior to the start of packing. Customer property is stored in segregated areas within the Repligen warehouse.

Supplier management [SOP-1496]: Repligen assesses critical suppliers of raw materials and components based on the impact to the quality of the product they are used to manufacture. Critical suppliers are subject to a qualification process, monitored and routinely audited according to a pre-determined schedule. The supplier audit schedule is established based on a critical supplier audit cycle, supplier performance, past audit results, and business requirements.

Components [SOP-10042]: Components are controlled with pre-approved specifications. Receipt of material is verified and released by QA prior to use in manufacturing. In addition, each OPUS Column component has a pre-approved engineering drawing, and is subject to incoming QC inspection, which includes review of materials certificates, and verification of critical dimensions.

Process change management [SOP-1447]: Manufacturing process changes are governed by change management procedures that include provisions for customer notification of major changes.

Product storage control [SOP-1263]: Product is stored either at ambient temperature, or in temperature-controlled units as dictated by the packed resin. All temperature-controlled storage units have backup power supplies, 24/7 electronic monitoring, and alarms that are monitored.

Preventive maintenance [SOP-1501] and calibration [SOP-1181]: Equipment and monitoring devices are controlled through the Repligen Equipment Control process [SOP-1171]. Individual equipment components are uniquely identified and have a preventive maintenance and/or calibration schedule as necessary.

High purity water [SOP-MFG-1209]: Purified water is supplied to all manufacturing areas from a Reverse Osmosis/Deionization (RODI) system. The RODI system is fully automated and provides high quality water in a continuously circulating loop. The water system design performance specifications are ASTM Type I Reagent Grade Water, with the addition of low endotoxin and bioburden specifications ([Table 15](#), [Table16](#)).

Water quality is monitored continuously using an on-line total organic carbon (TOC) device and is routinely sampled and tested by Repligen Quality Control.

Business continuity policy [CAP-1006]: The Repligen Corporation Business Continuity Management System (BCMS) is designed to maintain the continuity of critical business activities in the case of an emergency situation and/or an event that severely impacts business operations and ultimately the ability to supply product. Such events may include operational incidents, un-forecasted product demand, man-made or environmental incidents or threats, and natural disasters. Proper maintenance and application of BCMS processes will allow for the control and restoration of business practices in an acceptable amount of time to maintain product reliability and mitigate the possibility of a product shortage. For OPUS 2.5 - 80R Pre-packed Chromatography Columns, recovery of production is assumed to be 24 weeks within the United States.

3.2.2 Manufacturing facilities

An OPUS Pre-packed Chromatography Column packing suite consists of multiple ISO Class 7 column packing rooms and a central ISO Class 8 prep area. Two airlock entry ways are maintained, one for people and one for materials and equipment. In general, product contact column parts enter the suite through a validated parts washer and are cleaned with sodium hydroxide-based solutions followed by a rinse with reverse osmosis deionized (RODI) water. The OPUS Column suite is completely segregated from all other product manufacturing at Repligen and is a restricted-access area.

The clean-room environment is controlled and monitored as follows:

- Air quality is maintained by 100% HEPA filtered air
- Environmental monitoring is performed to check for viable contamination
- Preparation room air quality is tested to ISO Class 8 standards for non-viable particulates
- Column packing room air quality is tested to ISO Class 7 standards for non-viable particulates
- Room pressure differentials are maintained and monitored according to SOP
- All rooms are on a routine cleaning and disinfection schedule
- Access is restricted to authorized personnel only
- Gowning is required for entry into controlled areas including a secondary gowning procedure for entry into the ISO Class 7 packing rooms

4. OPUS Pre-packed Chromatography Column packing and manufacturing

4.1 Packing environment and environmental controls

All OPUS 2.5 - 80R Pre-packed Chromatography Columns are packed in ISO Class 7 classified clean rooms and buffers prepared in an ISO 8 classified clean room. The rooms are monitored on a weekly basis for viable contaminants using TSA settle plates. Microbial contaminants (bacteria) are counted and reported. Counts which exceed an alert or action limit are investigated according to SOP-MFG-1207.

Viable contamination limits have been set for the ISO 8 rooms as follows:

- Alert Limit: > 20 CFU/plate
- Action Limit: > 35 CFU/plate

Viable contamination limits have been set for the ISO 7 rooms as follows:

- Alert Limit: > 10 CFU/plate
- Action Limit: > 25 CFU/plate

The OPUS manufacturing suite is monitored on a weekly basis for Non-Viable Particles ($\geq 0.5 \mu\text{m}$). Each room is monitored in predetermined locations, measuring 1 cubic foot of air over the course of 1 minute. NVP limits have been set for the ISO Class 8 clean room spaces as follows:

- Alert Limit: $\geq 25,000$ particles per ft^3 (880,000 particles per m^3)
- Action Limit: $\geq 50,000$ particles per ft^3 (1,760,000 particles per m^3)
- ISO 8 Specification: $\leq 100,000$ particles per ft^3 (3,520,000 particles per m^3)
- NVP limits have been set for the ISO Class 7 clean room spaces as follows:
 - Alert Limit: $\geq 2,500$ particles per ft^3 (88,000 particles per m^3)
 - Action Limit: $\geq 5,000$ particles per ft^3 (176,000 particles per m^3)
 - ISO 7 Specification: $\leq 10,000$ particles per ft^3 (352,000 particles per m^3)

Table 17. Water specifications compared with ASTM, USP purified water and water for injection

Parameter	ASTM Type I	USP Purified Water	WFI	Repligen Specification
Conductivity	0.05 $\mu\text{S}/\text{cm}$	1.3 $\mu\text{S}/\text{cm}$	1.3 $\mu\text{S}/\text{cm}$	<0.01 mS/cm
Endotoxin	N/A	N/A	<0.25 EU/mL	<0.5 EU/mL
Bioburden	N/A	100 CFU/mL	0.1 CFU/mL	≤ 10 CFU/mL
pH	N/A	N/A	5 – 7	5 – 7
TOC	0.1 ppm	0.5 ppm	0.5 ppm	0.1 ppm

4.2 OPUS Column Specification Sheet and User Specified Inputs

The OPUS Column Specification Sheet compiles column information from the proposal package such as pricing and configuration details, as well as user specified inputs.

Note: OPUS 5 PD Columns are packed in an uncontrolled lab environment. The OPUS 2.5 and OPUS 5 GMP Run Ready and all OPUS 8 – 80R Pre-GMP and GMP Run Ready Columns are packed in the clean room environment as stated above.

Note: All OPUS Columns are built to order and each configuration ordered must have a unique Specification Sheet which outlines critical user specified inputs. In addition, each OPUS Specification Sheet is assigned a unique Specification Sheet Detail Number which corresponds to a Repligen Quote Number.

The OPUS Specification Sheet captures a variety of information, including, but not limited to, the following:


- Quote number and column part number
- Column size, type, and resin

- GMP level (Pre-GMP or GMP Run Ready)
- Solutions used and storage conditions
- Column performance release method and specifications (i.e., asymmetry and plate count)

Repligen sends the OPUS Column Specification Sheet to the appropriate customer contact for review as part of the formal quote proposal package. If all the details in the document are satisfactory, the customer signs with current date and returns the form to Repligen. Once a purchase order has been placed and the signed Specification Sheet has been received, Repligen schedules the column(s) for production.

Note: Column packing cannot begin without a customer approved Specification Sheet ([Figure 14](#)).

Figure 14. OPUS Column Specification Sheet example

				
OPUS® Specification Sheet Information				
Repligen Quote Number:	OPUS-00001234			
Spec Sheet Detail Num.	WD-005678			
Company Name:	Test Account			
Issue Date:	30-Dec-22			
Quality Form:	QA-FM-04-10015-03			
Repligen Lot Number				
OPUS Pre-Packed Column Details				
OPUS® Catalog Number	Internal Diameter	Bed Height	GMP Level	
CC-100-APV9-127-G	10 cm	12.7 cm	GMP Run Ready	
Resin Part Number	Resin Description		Resin Supplier	Column Storage Condition
100AAV9-XXXX	AVIPure® – AAV9		Customer	2-8C
Manufacturing Details				
Bed Height Tolerance		Storage Solution	QC Resin Sample for Customer	
± 0.5 cm		20% Ethanol	Required	
Quality Control Specifications				
Mobile Phase	Injection Solution	Injection Volume	Test Flow Rate	
0.4M NaCl	0.8M NaCl	1% CV	60 cm/hr	
Efficiency (N/m)	Asymmetry (Min)	Asymmetry (Max)	Bioburden	Endotoxin
≥ 3,000	0.80	1.60	< 10 CFU / mL	< 0.25 EU / mL
Additional Instructions				

4.3 Chromatography resin control

The SOP governing chromatography resin control procedures are SOP-1094 (Control of Incoming Materials), SOP-10042 (Control of Incoming Components) and SOP-10035 (Customer Property).

It is Repligen policy to pack no more than three (3) resin vendor lot numbers within a single OPUS Column. Should a customer send greater than 3 resin vendor lot numbers for a column pack, Repligen requires written approval on official letterhead from the end user customer to pack the resin.

Repligen procured resins

Resins procured by Repligen for column packing are controlled as a raw material according to SOP-1094 (Control of Incoming Materials). Upon arrival, each resin is placed into quarantine pending disposition by Repligen Quality Assurance. Upon release, each batch of resin is given a unique internal lot number and expiration date to ensure full traceability throughout the manufacturing process.

Customer procured resins

The Repligen customer property procedures (SOP-10035) are designed to end user financial and intellectual property interests as well as to prevent unauthorized use, disclosure, or disposal. Resins shipped to Repligen for column packing must be unused. User procured resin is assigned a unique customer property number which is typically linked to a specific Specification Sheet, purchase order and part number.

The user property number is noted on the form entitled, Customer Property Declaration Form (QA-FM-02-10035), which must be filled out by an end user prior to shipping resin to Repligen. Upon arrival, the resin is managed according to SOP-10035, which dictates the resin must be labeled, segregated, and then stored according to the resin vendor's recommendation. Unused resin is either returned or discarded according to the customer's instructions.

Repligen understands in some instances customers may have a requirement to sample and test a small aliquot of the resin for identity (ex. FTIR). Unused resin in containers, which have been sampled for QC testing, is compatible with the Repligen quality requirements; therefore, they can be accepted for column packing.

Resin preparation

Once the appropriate resin has been released, parts cleaned, and column packing batch record documentation has been issued, the following steps occur:

1. Manufacturing operators move sealed resin containers into one of the OPUS ISO 7 clean rooms.

Note: Only the released resin is allowed in the packing room, and only one resin type at a time can be present.

2. Manufacturing operators verify the appropriate resin by checking against the OPUS Column Specification Sheet.
3. After verifying the resin, containers are opened for resin preparation (decantation of storage solution, fines removal, etc.).
4. For OPUS GMP Run Ready Columns only, prior to beginning resin prep an operator removes ~30 mL of resin per resin lot from the original container. This operation is performed using a sterile pipette and the operator dispenses the resin aliquot into a 60 mL gamma irradiated, tamper evident PETG (polyethylene terephthalate) bottle. The bottle is then sealed and labeled with resin name, lot number, part number, date, and operator initials. In the event multiple resin lots are packed into a single column, a single side sample of each resin lot will be taken. Therefore, multiple side samples will be delivered with a GMP Run Ready Column if multiple resin lots are packed.

Note: in some cases, the volume and/or number of resin sides samples can be changed. Please contact Repligen for more information.

5. Slurry preparation and percent solids determination:
 - a. Decant off storage solution.
 - b. Perform de-fining of resin as necessary or as specified by resin supplier.
 - c. Suspend resin in packing buffer to target the desired percent solids.
 - d. Combine resin from multiple resin supplier bottles in a holding tank (if required).
 - e. Pipette two 9 – 11 mL samples of the complete resin slurry .
 - f. Record mass and volume added for density calculations.
 - g. Spin samples in a centrifuge.
 - h. Read spin down solids volume of resin.
 - i. Determine average percent solids (solids vol./total vol.).
 - j. Use target compression factor (CF = target column vol./uncompressed resin vol.) as derived by Resin manufacturer recommendations, historical manufacturing empirical data, and Repligen R&D recommendations.
 - k. Calculate the required target solids volume to add (target bed volume/CF).

- I. Apply percent solids (Step i) and density (Step f) to target solids calculations to determine mass of slurry required:

$$mass\ slurry = \frac{Target\ solids\ volume}{\% solids} \times density$$

Assembly, packing, and performance testing

OPUS Pre-packed Chromatography Columns are assembled from qualified and controlled components. Inspected and released component parts are taken from inventory and brought into the ISO 8 classified cleanroom through an automated parts washer. Parts that do not enter through the parts washer are chemically cleaned with sodium hydroxide, followed by RODI water rinse to depyrogenate and reduce bioburden. Both processes have been qualified and validated ([Table 18](#)).

Table 18. Parts cleaning specification

Parts Cleaning Specifications					
Method	Bioburden	Endotoxin	Total Organic Carbon	Conductivity	pH
Parts washer	≤10 CFU/mL	≤0.5 EU/mL	<10 ppm	<10 µS/cm	5.0 – 7.0
Sodium hydroxide soak	≤10 CFU/mL	≤0.25 EU/mL	N/A	≤50 µS/cm	5.0 – 7.0

The following points summarize the major steps which occur during OPUS Column packing:

1. Prepare solutions and buffers in the ISO 8 area of the OPUS clean rooms. All buffers and solutions are filtered with a 0.2 µm filter.
2. Bring packing solutions/buffers and allocated parts, which have been cleaned, into the designated ISO 7 packing room. All subsequent steps are performed in the designated ISO 7 clean room.
3. Insert bottom flow distributor with the ultrasonically welded mesh into the bottom end of the tube to form a water-tight seal.
4. Secure flow distributor assembly in place with a polypropylene weld or epoxy adhesive bond. Both the polypropylene weld and the epoxy adhesive are only applied to non-product contact areas.
5. Add chromatography resin to the open-ended column by dosing directly into the column or using a peristaltic pump.
6. Insert top flow distributor into the column tube and initiate packing to establish a uniform bed.

Note: OPUS Columns utilize flow packing, axial compression, and/or a combination of both methods to achieve a well packed bed. In general, packing protocols are developed in the Repligen R&D department and subsequently transferred to the production team.

7. Position the top flow distributor, following the prescribed packing procedure, to create the correct resin compression.
8. Test bed performance according to the procedure and specifications as documented on the OPUS Column Specification Sheet.

Note: A column may be tested, and flow distributor adjusted during the packing process to ensure optimal performance.

9. The packing process concludes when the final top flow distributor position is set, and the column has met the performance specifications (theoretical plate count/efficiency and asymmetry) as documented on the OPUS Column Specification Sheet.
10. Sanitize the column using a procedure recommended by the resin manufacturer and/or as documented on the OPUS Column Specification Sheet
11. Neutralize column (typically with RODI water or low conductivity solution).
12. Take bioburden and Endotoxin samples and deliver Repligen QC laboratory for testing. (OPUS GMP Run Ready Columns only).
13. Exchange buffer into a final storage solution as documented on the OPUS Column Specification Sheet.
14. Secure the top flow distributors in place using a polypropylene weld or epoxy adhesive bond.
15. Secure the top cap, bottom cap, and side-guard in place.

Note: The top cap, bottom cap, and side guard serve cosmetic and ergonomic functions, and therefore do not impact the performance of the column.

16. Cap and seal inlet and outlet ports using a tamper evident SaniSure clamp.
17. Seal column (sizes 2.5 – 30 cm) column in a polyethylene bag before being removed from the OPUS cleanroom suite.

Note: OPUS 36R, 45R, 60R, 80R Pre-packed Chromatography Columns are not bagged since they are on wheels.

18. Store column according to storage conditions (ambient or 2 – 8 degrees Celsius) as noted on the OPUS Column Specification Sheet. Resin retain sample/s are stored with the finished OPUS GMP Run Ready Column for shipment.

Resin verification upon arrival

A copy of the OPUS Column Certificate of Analysis (CoA), which documents the resin description, resin supplier part number, and resin supplier lot number, is shipped with every column. In addition, OPUS GMP Run Ready Columns are delivered with a resin retain sample (one per resin lot packed into the column) intended for incoming quality control identity testing. If Repligen has procured the resin for packing, the resin supplier CoA will also be included. Finally, the OPUS Column label can also be referenced by OPUS part number, lot number, and serial number to match with the applicable CoA.

Equipment used in the manufacturing of OPUS Columns

Wherever possible, supplies used to pack OPUS Columns are disposable and dedicated to the production lot:

- Slurry tanks and carboys
- Single-use liners for buffer tanks
- Single-use platinum cured tubing

Where reusable components are used in the manufacturing process which might come into contact with the resin or the inside of the column, Repligen employs validated cleaning protocols to ensure the risk of cross resin contamination is mitigated.

Note: A copy of the resin vendor CoA will be included with the OPUS CoA for all columns with Repligen-supplied resin. If the resin is customer-supplied, a copy of the resin CoA can be obtained on most resin vendor websites.

Columns are tested according to the specifications detailed in the OPUS Column Specification Sheet. Bioburden and endotoxin testing are performed on OPUS GMP Run Ready Columns. Retain sample are taken in RODI water post sanitization and just prior to introducing the storage solution. Release specifications are as follows:

- Bioburden: < 10 CFU/mL
- Endotoxin: < 0.25 EU/mL

Repligen performs endotoxin and bioburden testing in-house using the following two methods:

Bioburden assay method

Bioburden is analyzed by a vacuum filtration method.

1. The sample is applied to a sterile filter under vacuum and then rinsed with peptone water.
2. The filter is collected aseptically and placed onto TSA media.
3. The plate is placed into an incubator at 32°C +/- 2°C for 5 days.
4. An analyst reads the plates at day 3 and day 5 and documents the results.
5. A negative control of the peptone water is also plated and incubated to demonstrate the reagents used during the analysis were not contaminated.

Endotoxin assay method

Endotoxin levels are analyzed using a validated Charles River Endosafe® MCS™ system.

1. 25 µL of the column effluent is loaded onto a 0.5 EU/mL cartridge (purchased from Charles River Lab) and inserted into the Endosafe instrument for analysis. Each cartridge has 4 wells: sample, spike, sample, spike.
2. Once the test is complete, a report will be generated, and all results are documented as part of the OPUS Column batch record.

Bioburden and endotoxin test results are documented on the Certificate of Analysis as a pass/fail result for each GMP Run Ready column. See the next section ([Section 4.4](#)) for sample CoA documents.

Note: OPUS Pre-GMP Columns are not tested for bioburden or endotoxin.

4.4 OPUS Pre-packed Chromatography Columns Certificate of Analysis (CoA)

Each OPUS Pre-packed Chromatography Column is delivered with a Certificate of Analysis with the content noted in [Table 19](#).

Note: Please visit repligen.com for the most up-to-date information on OPUS Column Certificate of Analysis details, including templates.

Table 19. OPUS Pre-GMP and GMP applications

Certificate of Analysis Component	Pre-GMP 8 – 80R cm ID	GMP Run Ready 2.5 – 80R cm ID
GMP level	X	X
Catalog number	X	X
Lot number	X	X
Serial number	X	X
Column diameter	X	X
Final/Achieved bed height	X	X
Chromatography resin type	X	X
Chromatography resin lot number	X	X
Shipping/Storage solution	X	X
Date of manufacture	X	X
Customer property number (if applicable)	X	X
Asymmetry specification and result	X	X
Theoretical plate count (N/m) specification and result	X	X
Chromatography release test chromatogram	X	X
ISO 9001 Compliance Statement	X	X
Product Contact Materials Compliance Statement (animal free, EMA 410/01, USP Class VI)	X	X
Packing Environment Statement	X	X
Copy of resin Certificate of Analysis (applies to Repligen supplied resins)	X	X
Chromatography Resin Control Statement	X	X
Endotoxin specification and test result (pass/fail)		X
Bioburden specification test result (pass/fail)		X

Note: OPUS 5 Columns are available in a process development (PD) format which comes with a CoQ. Please contact Repligen or visit repligen.com/OPUS for more information.

Note: The OPUS 2.5 Pre-packed Chromatography Column configuration is not available in the Pre-GMP format.

4.5 OPUS Columns Certificate of Analysis examples


Figure 15. Pre-GMP OPUS CoA: OPUS 8 – 80R Pre-packed Chromatography Columns

Product Identification		Quality Control Release Data		
Criteria	Description	Criteria	Specification	Result
GMP Level:	Pre GMP	Column Efficiency: (Plates/meter)	≥ XXXX	XXXX
Catalog Number:	XX-XXX-XXXX-XXX-P	Column Asymmetry:	X.XX – X.XX	X.XX
Lot Number:	XXXXXXXX	Max. Column Hardware Pressure	X bar (3 bar ≥45cm or 4 bar ≤30cm)	
Serial Number:	XXXXXXXX-XXX	Max. Packing Pressure (bar):	Report	X.X
Column Diameter:	XX cm	Max. Packing Flow Rate (cm/hr):	Report	XXXX
Bed Height:	XX.X cm			
Resin Type:	<insert resin name>			
Resin Lot Number:	<insert resin lot #>			
Shipping Solution:	<insert shipping solution>			
Storage Temperature:	XXXXXX (Ambient or 2-8°C)			
Date of Manufacture:	DD MMM YYYY			
Customer Property #:	CPXXXXXX (if applicable)			

Reviewed and approved for accuracy and completeness

QA Representative Signature _____ Date _____

Document Number: QA-FM-10162-16 <Insert Resin Name> is a <registered> trademark of <Insert Company name>

1 41 Seyon Street, Bldg 1, Suite 100, Waltham, MA 02453 | www.repligen.com 

Each Pre-GMP Column produced is issued a Certificates of Analysis. Content is derived from the template information as well as customer required specifications as detailed on the OPUS Column Specification Sheet. For columns containing Repligen procured resin, a copy of the resin supplier CoA is also included.

Note: Please visit repligen.com for the most up-to-date information on OPUS Column Certificate of Analysis details, including templates.

Figure 16. GMP Run Ready OPUS Column CoA: OPUS Columns 2.5 – 80R

OPUS® Column Certificate of Analysis

Product Identification		Quality Control Release Data		
Criteria	Description	Criteria	Specification	Result
GMP Level:	GMP Run Ready	Column Efficiency: (Plates/meter)	≥ XXXX	XXXX
Catalog Number:	XX-XXX-XXXX-XXX-G	Column Asymmetry:	X.XX – X.XX	X.XX
Lot Number:	XXXXXXXX	Microbial Bioburden: (CFU/mL)	<10	pass/fail
Serial Number:	XXXXXXXX-XXX	Endotoxin Level: (EU/mL)	<0.25	pass/fail
Column Diameter:	XX cm	Max. Column Hardware Pressure	X bar (3 bar ≥45cm or 4 bar ≤30cm)	
Bed Height:	XX.X cm	Max. Packing Pressure (bar):	Report	X.X
Resin Type:	<insert resin name>	Max. Packing Flow Rate (cm/hr):	Report	XXXX
Resin Lot Number:	<insert resin lot #>			
Shipping Solution:	<insert shipping solution>			
Storage Temperature:	XXXXXX (Ambient or 2-8°C)			
Date of Manufacture:	DD MMM YYYY			
Customer Property #:	CPXXXXXX (if applicable)			

Reviewed and approved for accuracy and completeness

QA Representative Signature

Document Number: QA-FM-10164-18

Date

<Insert Resin Name> is a <registered> trademark of <Insert Company name>

1
41 Seyon Street, Bldg 1, Suite 100, Waltham, MA 02453 | www.repligen.com

Each OPUS GMP Run Ready Column is issued a Certificate of Analysis. Content is derived from the template information as well as user required specifications detailed on the OPUS Column Specification Sheet. For columns containing Repligen procured resin, a copy of the resin supplier CoA is also included.

Note: Please visit repligen.com for the most up-to-date information on OPUS Column Certificate of Analysis details, including templates.

Figure 17. OPUS CoA: Testing conditions and chromatograms

OPUS® Column Certificate of Analysis

<p>Column Information: Catalog Number: XX-XXX-XXXX-XXX-G Lot Number: XXXXXXXX Serial Number: XXXXXXXX-XXX</p>	<p>Test Conditions: Injection Solution: <insert injection solution description> Injection Volume (mL): XXX Mobile Phase: <insert mobile phase description> Flow Rate (cm/hr): XXX</p>
---	--

[Insert Chromatogram here – Shape Height = 4.5]

Reviewed and approved for accuracy and completeness

QA Representative Signature	Date
Document Number: QA-FM-10164-18	<Insert Resin Name> is a <registered> trademark of <Insert Company name>

2
41 Seyon Street, Bldg 1, Suite 100, Waltham, MA 02453 | www.repligen.com

For both OPUS Pre-GMP, and GMP Run Ready Columns, the Certificate of Analysis comes with a second page detailing the testing conditions and chromatogram. See [Figure 16](#) and [Figure 17](#) for the OPUS GMP Run Ready CoA.

Note: Please visit repligen.com for the most up-to-date information on OPUS Column Certificate of Analysis details, including templates.

Figure 18. CoA: Quality Assurance Statements

OPUS® Column Certificate of Analysis

Quality Assurance Statements

Quality Standard
Manufactured in the U.S.A under an ISO 9001 Quality Management System

Material Compatibility
All materials in direct fluid contact meet USP class VI <88> requirements for In Vivo B Biological Reactivity

Animal Origin Free
All materials in direct fluid contact comply to EMA/410/01 Rev.3

Environment
Columns are packed in a controlled, classified clean room that meets ISO Class 7 NVP standards

Chromatography Resin Control
All resins are subject to incoming material controls including resin identity testing. Traceability is achieved using controlled documents and records according to good documentation practices.

Reviewed and approved for accuracy and completeness

QA Representative Signature	Date
Document Number: QA-FM-10164-18	<Insert Resin Name> is a <registered> trademark of <Insert Company name>

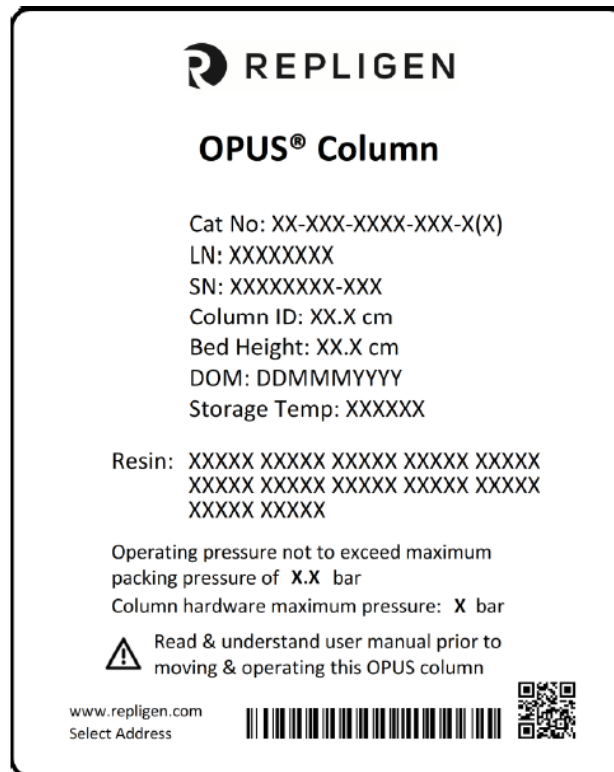
3
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For both OPUS Pre-GMP, and GMP Run Ready Columns, the Certificate of Analysis comes with a third page detailing the applicable quality standards and statements. See [Figure 18](#) for an example of the third page of the OPUS GMP Run Ready CoA.

Note: Please visit repligen.com for the most up-to-date information on OPUS Column Certificate of Analysis details, including templates.

4.6 OPUS Column labeling

Figure 19. OPUS 10 – 80R cm ID Column label



Each individual OPUS 10 – 80R cm ID Pre-packed Chromatography Column is labeled with the following information:

1. Catalog number
2. Lot number
3. Serial number
4. Column Internal Diameter
5. Column Bed Height
6. Date of Manufacture
7. Storage Temperature (Ambient or 2 – 8°C)
8. Resin type
9. Pressure rating

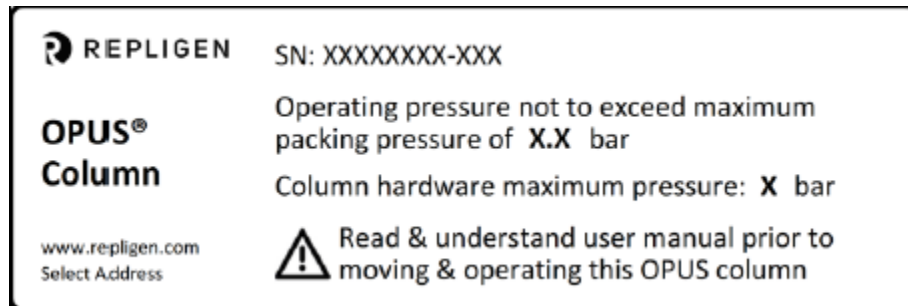
Figure 20. OPUS Small Scale (2.5 – 8 cm) Pre-packed Chromatography Column label



Each individual OPUS 2.5 – 8 cm Pre-packed Chromatography Column is labeled with the following information:

1. Catalog number
2. Lot number
3. Serial number
4. Column Internal Diameter
5. Column Bed Height
6. Date of Manufacture
7. Storage Temperature (Ambient or 2 - 8 °C)
8. Resin type

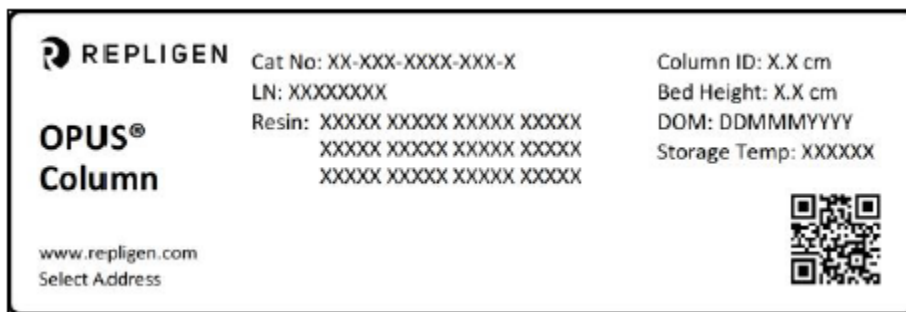
Figure 21. OPUS 2.5 cm Pre-packed Chromatography Column supplementary label



Each individual OPUS 2.5 cm Pre-packed Chromatography Column has a supplementary label with the following information:

1. Serial number
2. Pressure rating

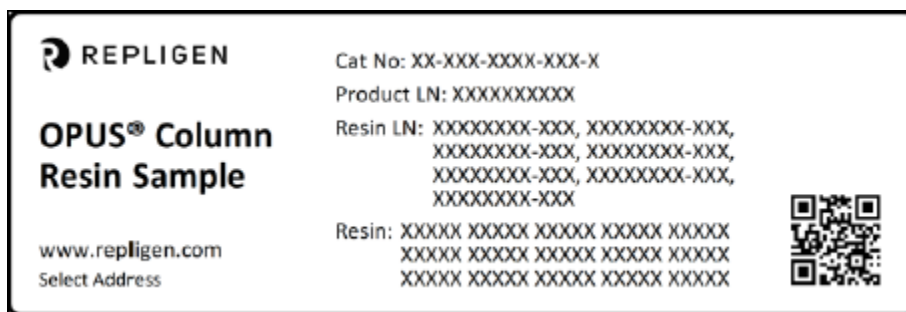
Figure 22. OPUS 2.5 – 8 cm Pre-packed Chromatography Columns box label



OPUS 2.5 – 8 cm Pre-packed Chromatography Columns are packaged in a box. Each box is labeled as follows:

1. Catalog number
2. Lot number
3. Column Internal Diameter
4. Column Bed Height
5. Date of Manufacture
6. Storage Temperature (Ambient or 2 - 8 °C)
7. Resin type

Figure 23. OPUS Column Resin sample label



OPUS Column Resin side sample is labeled with the following:

1. Catalog number
2. Product lot number
3. Resin lot number
4. Resin type

5. Shipping packaging qualification

5.1 Introduction

To certify packaging, column components, and column performance remain within quality parameters after shipping, International Safe Transit Association (ISTA) transport simulation performance test protocols were conducted on a variety of OPUS Column sizes. Third-party ISTA-certified laboratories performed the simulations to represent typical damage-inducing motions, forces, conditions, and sequences of transport environments. Repligen tested chromatographic performance pre- and post-simulation. Results from the studies show the packaging withstands the expected stressors typical of commercial shipping, and chromatographic performance is maintained.

The objective of the simulated shipping performance studies is to demonstrate the custom-made packaging ([Figure 24](#) through [Figure 30](#)) and pre-packed columns of multiple diameters arrive intact after rigorous transport simulations. See [Section 6](#) for engineering drawings of packaging used for various internal diameter columns.

OPUS Pre-packed Chromatography Columns employ custom packaging based on size and weight. To cover the range of different column dimensions and packaging methods/materials the following column sizes were evaluated.

- OPUS 2.5 Pre-packed Chromatography Column (uses similar design as the OPUS 5 Pre-packed Chromatography Column)
- OPUS 5 Pre-packed Chromatography Column (uses similar design as the OPUS 8 Pre-packed Chromatography Column)
- OPUS 8 Pre-packed Chromatography Column (uses similar design as the OPUS 5 Pre-packed Chromatography Column)
- OPUS 10 Pre-packed Chromatography Column (uses identical packaging as the OPUS 12.6 and 14 Pre-packed Chromatography Column)
- OPUS 12.6 Pre-packed Chromatography Column (uses identical packaging as the OPUS 10 and 14 Pre-packed Chromatography Column)
- OPUS 20 Pre-packed Chromatography Column (uses identical packaging as the OPUS 25 and 30 Pre-packed Chromatography Column)
- OPUS 36R Pre-packed Chromatography Column (uses similar packaging as the OPUS 45R Pre-packed Chromatography Column)
 - Both heat-treated wood and corrugated fiberboard packaging
- OPUS 45 Pre-packed Chromatography Column (uses identical packaging as the OPUS 45R Pre-packed Chromatography Column)
 - Both heat-treated wood and corrugated fiberboard packaging
- OPUS 60R Pre-packed Chromatography Column (uses identical packaging as the OPUS 60 Pre-packed Chromatography Column)
- OPUS 80R Pre-packed Chromatography Column (uses unique packaging, but similar to the 45/R and 60/R Pre-packed Chromatography Column design)

5.2 Materials of packaging construction

The largest OPUS Columns, 36, 45, 60, and 80 cm sizes, are packed in traditional heat-treated wooden crate structures with interior foam cushioning, an integrated ramp for column loading and unloading, and metal fasteners for stability. Wood construction materials all comply with International Standards for Phytosanitary Measures (ISPM-15) and carry the International Plant Protection Committee (IPPC) stamp to verify conformance.

The OPUS 36 and 45 cm Pre-packed Chromatography Column is also packed in a non-wood crate design constructed primarily of multi-wall corrugated fiberboard. It, too, carries an integrated non-wood ramp for column unloading. These materials are manufactured with glue, heat, and pressure. Thus, they are exempt from the provisions of the ISPM standard and do not require the IPPC stamp. Metal and plastic fasteners are used for stability where required.

OPUS 2.5 – 30 Pre-packed Chromatography Columns packaging utilizes corrugated fiberboard as the main material of construction with internal foam cushioning as required for added protection. Repligen non-wood OPUS Column packaging designs can be easily disassembled into their different base materials of construction for recycling.

Figure 24. OPUS 8 Pre-packed Chromatography Column shipping container design



Figure 25. OPUS 10, 12.6, 14, 20, 25, 30 Pre-packed Chromatography Column shipping container



Note: *Tamper evident straps around the shipping boxes.*

Figure 26. OPUS 36R – 45R Pre-packed Chromatography Column non-wood shipping container



Figure 27. OPUS 45R and 60R Pre-packed Chromatography Column shipping container design



Figure 28. OPUS 60R Pre-packed Chromatography Column crate tamper evident banded straps**Figure 29. OPUS 80R Pre-packed Chromatography Column shipping container design**

5.3 Method: ISTA Protocols 2A, 2B and 3A

- ISTA Protocol 2A is a transport simulation performance test for individual packaged products weighing 150 lb (68 kg) or less.
 - Applicable column sizes: 2.5 – 8
 - In some cases, Repligen applied a modified version of the standard protocol
- ISTA Protocol 2B is a transport simulation performance test for individual packaged products weighing more than 150 lb (68 kg). It can also be used for individual packaged products on a visible skid or pallet and that weigh more than 100 lb (45 kg).
 - Applicable column sizes: 10 – 80R
 - In some cases, Repligen applied a modified version of the standard protocol
- ISTA Protocol 3A is a transport simulation performance test for packaged products weighing 150 lb (68 kg) or less and intended for shipments made through a parcel delivery system.
 - Applicable column sizes: 2.5 – 8
 - In some cases, Repligen applied a modified version of the standard protocol

These tests are used to evaluate the performance of individually packaged products and compare relative performance of package design and product design alternatives.

During the simulation performance tests, the package and product are analyzed together as one bundle; therefore, results refer to packaged product.

Transport simulation tests and conditions

ISTA-certified testing laboratories performed the transport simulation performance tests. The specific test conditions applied are described further in [Table 20](#). All OPUS Pre-packed Chromatography Columns are manufactured by Repligen, packaged into their respective shipping containers, delivered to the ISTA-certified test facility, and tested according to the applicable simulation protocol. ISTA-tested shipping containers were returned to Repligen for post-testing analysis.

Repligen acceptance criteria

The shipping simulation performance tests documented in this Regulatory Support File have two different acceptance criteria categories as detailed below.

Visual appearance and structural integrity pass/fail assessments are made by Repligen and are based on a visual inspection of the packaged product. Results are documented in a separate summary report.

Functional chromatographic performance: Repligen assesses chromatographic performance by measuring plate count and asymmetry to compare pre-shipment simulation performance with post-shipment simulation performance. To pass the chromatographic portion of the assessment, asymmetry must be between 0.8 – 1.8 and theoretical plate count measurements must be within ±25% of pre-shipping results

Table 20. ISTA 2A, 2B, and 3B Testing (OPUS 2.5 – 80R Pre-packed Chromatography Columns)

Test Name	Test Details										
Atmospheric conditioning	Ambient Conditions for 36 hours										
Controlled temperature and humidity conditioning	<ul style="list-style-type: none"> • 38°C ±2°C; Relative Humidity 85% ±5% for 36 hours • 4°C ±2°C; Relative Humidity uncontrolled for 36 hours 										
Random vibration testing	60 minutes of random vibration <table border="1" data-bbox="656 1255 1117 1453"> <thead> <tr> <th>Frequency (Hz)</th> <th>PSD Level, G²/Hz</th> </tr> </thead> <tbody> <tr> <td>1.0</td> <td>0.0001</td> </tr> <tr> <td>4.0</td> <td>0.01</td> </tr> <tr> <td>100.0</td> <td>0.01</td> </tr> <tr> <td>200.0</td> <td>0.001</td> </tr> </tbody> </table>	Frequency (Hz)	PSD Level, G ² /Hz	1.0	0.0001	4.0	0.01	100.0	0.01	200.0	0.001
Frequency (Hz)	PSD Level, G ² /Hz										
1.0	0.0001										
4.0	0.01										
100.0	0.01										
200.0	0.001										
Incline impact (2B and 3B only)	Slide crate down ramp and into a wall (4X – once on each face) with 1.7 meter per second velocity change										
Drop testing	<ul style="list-style-type: none"> • Crate dropped 8 inches to the ground (2B and 3B) • Crate bottom edges dropped 8 inches to the ground (2B and 3B) • Box dropped 38 inches to the ground (2A) 										

Figure 30. OPUS 60R Pre-packed Chromatography Column vibrational, incline impact, drop testing

5.4 Column efficiency test methods

Overview: Column efficiency testing was designed to assess and uncover any discernible differences in chromatographic performance pre-shipping simulation and post-shipping simulation. Repligen conducted all chromatographic performance tests on OPUS Columns packed with agarose based resin with nominal particle size of 90 μm . The one exception is the 20 – 30 Study supported by an OPUS 20 Pre-packed Chromatography Column packed with silica based resin.

- 2.5 Study:
 - 2.5 cm x 5.2 cm column
 - 2.5 cm x 29.5 cm column
- 5 and 8 cm Study:
 - 8 cm x 4.8 cm column
 - 8 cm x 30 cm column
- 10 – 14 cm Studies:
 - 10 cm x 15.3 cm column
 - 12.6 cm x 4.7 cm column
 - 12.6 cm x 30 cm column
- 20 - 30 cm Study:
 - 20 cm x 19 cm column
 - Packed with a silica based resin (~60 μm particle size)
- 36R Study:
 - 36 cm x 21 cm column
- 45R Study:
 - 45 cm x 21 cm column
- 60R Study:
 - 60 cm x 20.5 cm column
- 80R Study:
 - 80 cm x 19 cm column

Each column was tested at 100 cm/hr with pulse injection of 1% column volume (CV) using either salt or acetone as the injection solution.

5.5 Results: Package performance and column efficiency tests

Results: Visual inspection

ISTA test facility:

- After shipping simulation performance tests were completed, Repligen visually inspected the packaged product for signs of damage. Results are documented in test reports issued by the ISTA-certified testing laboratory to Repligen. For all tests, the custom designed OPUS Column packaging passed the visual inspection without any significant signs of damage.

Repligen:

- Upon receipt from the ISTA-certified testing laboratory, all packaged-product shipments were inspected and found to be undamaged and intact.

5.6 Chromatographic performance test results

The data show that the efficiency of all OPUS Pre-packed Chromatography Columns remain stable following the applicable shipping simulation ([Table 21](#)). Stability is exhibited by a negligible change in asymmetry (A_s) and efficiency, while meeting the acceptance criteria.

Table 21. OPUS Pre-packed Chromatography Column chromatographic performance data

Column	Packaged Product Transport Simulation Performance Testing	Efficiency (N/m)	A _s	Pass/Fail
OPUS 2.5 Pre-packed Chromatography Column (5.2 cm Bed Height)	Pre-shipment simulation	3114	1.4	PASS
	Post-shipment simulation	3223	1.4	
OPUS 2.5 Pre-packed Chromatography Column (29.5 cm Bed Height)	Pre-shipment simulation	2849	1.2	PASS
	Post-shipment simulation	2734	1.3	
OPUS 8 Pre-packed Chromatography Column (4.8 cm Bed Height)	Pre-shipment simulation	3570	1.4	PASS
	Post-shipment simulation	3767	1.3	
OPUS 8 Pre-packed Chromatography Column (30 cm Bed Height)	Pre-shipment simulation	3583	1.2	PASS
	Post-shipment simulation	3463	1.4	
OPUS 10 Pre-packed Chromatography Column	Pre-shipment simulation	2936	1.2	PASS
	Post-shipment simulation	2889	1.2	
OPUS 12.6 Pre-packed Chromatography Column (4.7 cm Bed Height)	Pre-shipment simulation	3068	1.3	PASS
	Post-shipment simulation	3033	1.3	
OPUS 12.6 Pre-packed Chromatography Column (30 cm Bed Height)	Pre-shipment simulation	3184	1.3	PASS
	Post-shipment simulation	3279	1.2	
OPUS 20 Pre-packed Chromatography Column	Pre-shipment simulation	4121	1.1	PASS ¹
	Post-shipment simulation	5526	1.1	
OPUS 36R Pre-packed Chromatography Column	Pre-shipment simulation	3175	1.0	PASS
	Post-shipment simulation	2870	1.0	
OPUS 45 Pre-packed Chromatography Column	Pre-shipment simulation	2886	1.2	PASS
	Post-shipment simulation	2800	1.1	
OPUS 60R Pre-packed Chromatography Column	Pre-shipment simulation	3367	1.0	PASS
	Post-shipment simulation	3373	1.0	
OPUS 80R Pre-packed Chromatography Column	Pre-shipment simulation	3570	1.2	PASS
	Post-shipment simulation	3266	1.2	

¹Result for OPUS 20 Pre-packed Chromatography Column post-shipment simulation shows an increase of >25% on efficiency. This result is deemed acceptable for the study given an increase in efficiency denotes improvement to the packed column performance.

5.7 Conclusion

In summary, the following was observed post-shipping simulation performance testing:

- No significant damage to the packaged product
- No damage to the hardware integrity
- No discernable damage to the packed resin beds
- No significant differences in chromatographic performance

Therefore, OPUS Columns designed and tested by Repligen for chromatographic performance, and the shipping containers designed and tested in accordance with ISTA guidelines,, demonstrate suitable robustness for surviving the harsh environments of commercial shipping.

6. OPUS Pre-packed Chromatography Column packaging design

Figure 31. OPUS 5 Pre-packed Chromatography Column packaging (Box Design)

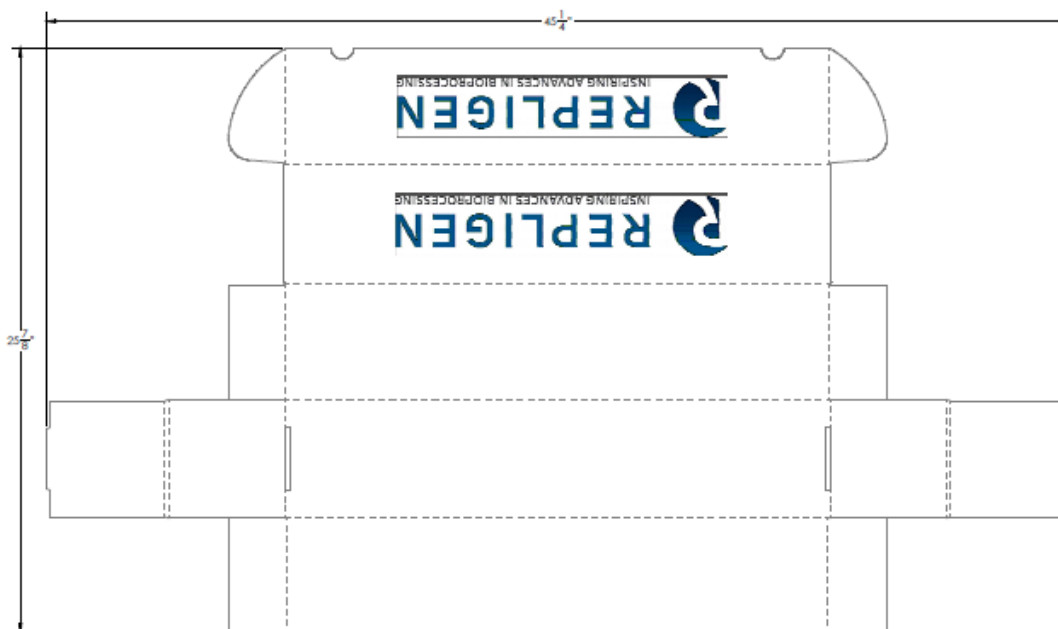


Figure 32. OPUS 5 Pre-packed Chromatography Column packaging (Packing inserts)

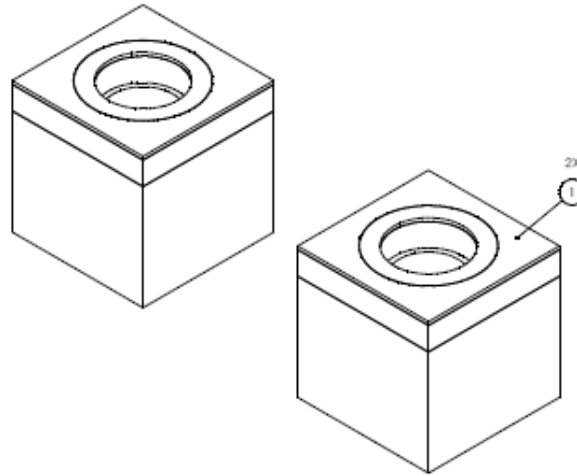


Figure 33. OPUS 8 Pre-packed Chromatography Column packaging

REV	DESCRIPTION	ADDP	ABCD	ZONE	DATE	BY	APP
0	INITIAL DRAFT	12/17			1/9/2018	JR	
1	REVISED	12/17			1/19/2018	JR	
2	REVISED TBM 3	12/17			2/6/2018	JR	
3	MISC DEPTH WAS 1/4 1/16	12/17			3/22/2018	NS	
-	UPDATED FIN & TRF - RELEASE TO PRODUCTION	12/17			6/28/2018	NS	TR
A	ADDED PRINTING	12/17			7/27/2018	JR	BJ

NOTES:
1. SHIPS KDF.

REV. NO.	QTY.	MATERIAL	DESCRIPTION	PAGE
1	1	275# C GRFT	BOTTOM MISC	2
2	1	275# C GRFT	TOP MISC	3
3	2	CORRUGATED P	INSERT	4

TYPE: PACK	VIRI: BOM	TOLERANCE FOR FABR UNLESS OTHERWISE SPECIFIED *SEE ALSO TOLERANCE MATRIX*	CUSTOMER: REPLUGEN CORPORATION
SIZE: --	CLOSURE: --	PROPRIETARY AND CONFIDENTIAL	Customer P/N: M-1184
MATERIAL: --	DR: EDP	DO NOT SCALE DRAWING	TITLE: BOM OPUS COLUMN BOX
DES: --	INCHES OF FILE: --		DRAWN BY: Jason Richard DATE: 07 Jun 2018
			CHECKED BY: Tom Eganoff DATE: 29 Jun 2018
			DOCUMENT NUMBER: 048770
			CLAS. REV: --
			PAGE: 1 OF 4

Figure 34. OPUS 10 – 14 Pre-packed Chromatography Column packaging

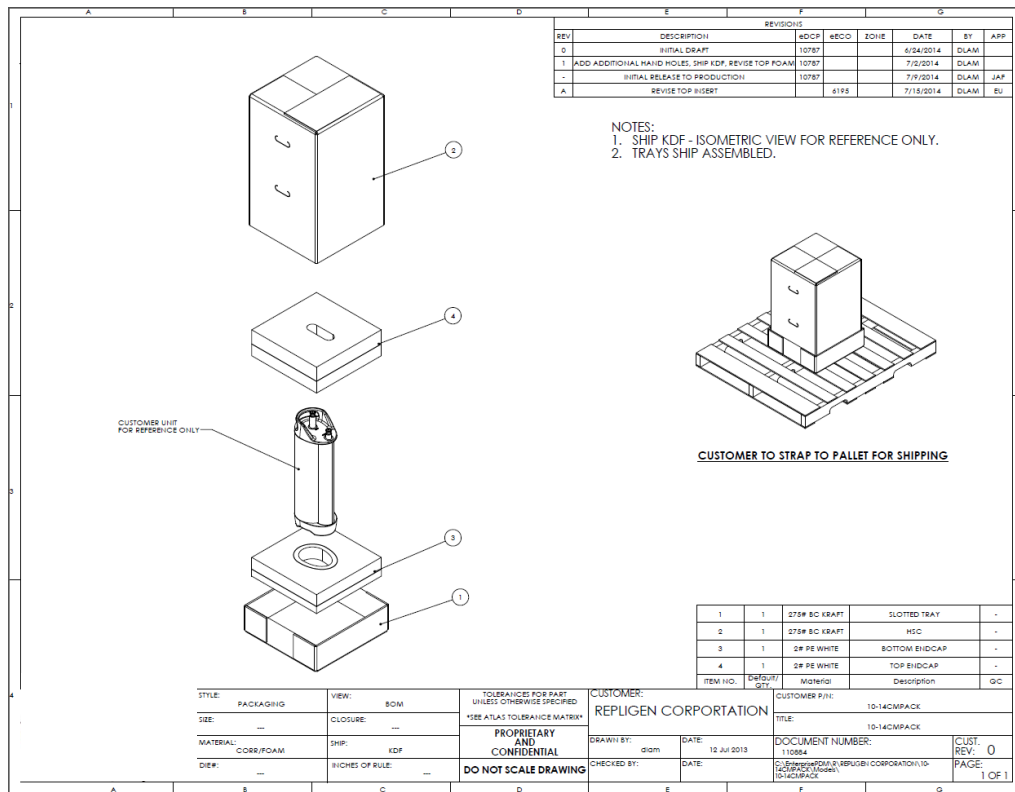


Figure 36. OPUS 36R and 45R Corrugated Pre-packed Chromatography Column packaging

Component Label	Component Description
A	Top Cap
B	Top Plate
C	Sidewall
D	Base Support Block
E	Bottom Plate
F	Bottom Tray
G	Bottom Cap
H	Base Deck
I	Pallet Feet
J	Bottom Support Blocks
K	Connection Port Brace Collar

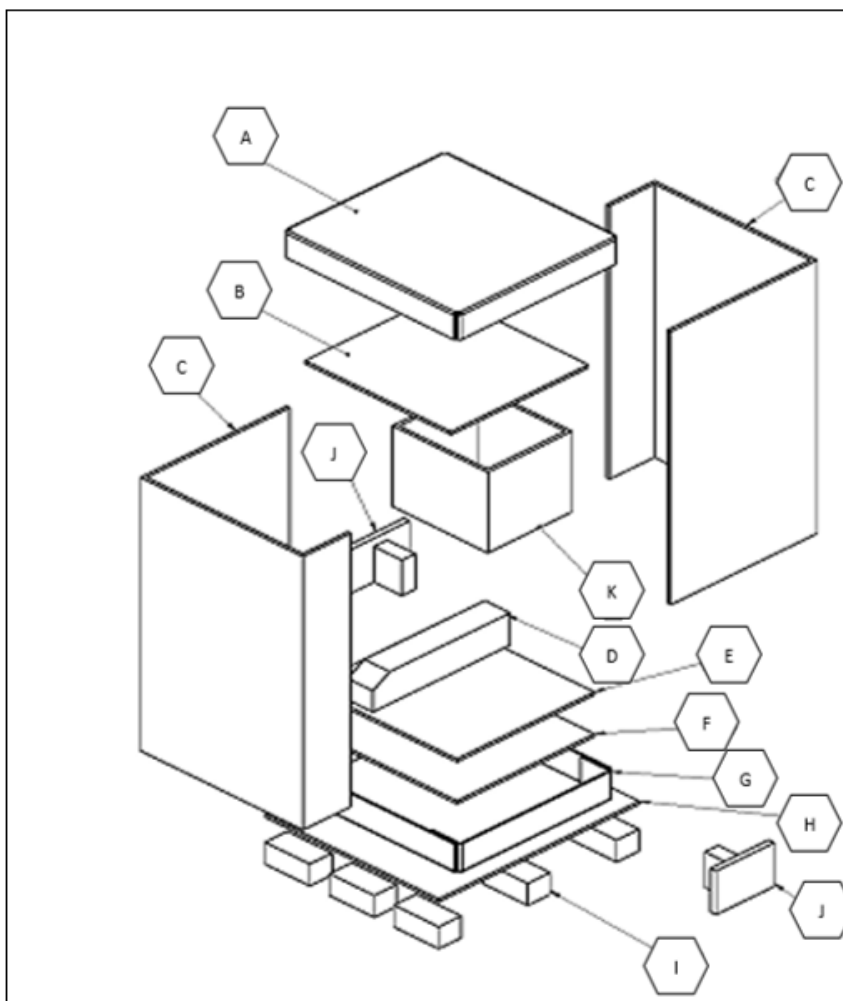


Figure 37. OPUS 45 and 45R Pre-packed Chromatography Column packaging

NOTES:
 1. ITEM 6 (WIDTH BRACE-X2), ITEM 15 (SIDE SUPPORT-X2), ITEMS 12,14, & 18 SHIPS LOOSE INSIDE CRATE
 2. USE HARDWARE SPECIFIED TO SECURE RAMP. (MATCH-DRILL RAMP TO SIDE PANEL HOLES)
 3. SECURE ITEMS 11 & 20 (BAG OF SCREWS) TO SKID FOR DELIVERY.
 4. O.D. SHIPPING ENVELOPE: 39 X 37 X 58.
 5. MATCH MARK TOP AND SIDE AS SHOWN

REVISIONS

REV	DESCRIPTION	WDCP	RECD	ZONE	DATE	BY	APP
D	INITIAL DRAFT	498			10/11/2015	DLAM	
-	INITIAL RELEASE TO PRODUCTION	498			10/22/2015	PS	EU
A	ADD SCREW NOTE		304		10/30/16	TRD	EU
B	REVISED CRATE PER REVIEW		406		12/01/2015	MV	EU
C	REVISED PER REVIEW		780		1/26/2016	MV	EU
D	REVISED CRATE PER CUSTOMER REVIEW, ADDED STECHOLS		960		2/25/2016	MV	EU

NOTE:
 6. WHEN MOUNTING TWIST LOCK PROTECTORS (X4), DO NOT COVER U-CHANNELS ON INSIDE OF PANELS. CUSTOMER WILL NEED TO SCREW BRACE FROM OUTSIDE

ITEM LIST

ITEM NO.	QTY.	Material	Description	PAGE
20	1	MISC.	BAG OF 8 DRYWALL SCREWS (NOT SHOWN)	11
19	4	ZINC PLATED STEEL	SURFACE MOUNT TWIST LATCH PROTECTOR	11
18	1	1.7# PE WHITE	DC FOAM	10
17	4	MISC.	DRAWLATCH CATCH	11
16	4	MISC.	DRAWLATCH	11
15	2	WOOD/FOAM	SIDE SUPPORTS	9
14	1	WOOD/FOAM	FRONT SUPPORT	10
13	1	WOOD	TOP	6
12	1	1.7# PE WHITE	TOP FRAME ASSEMBLY	9
11	1	MISC.	BAG OF 20 DRYWALL SCREWS (NOT SHOWN)	11
10	2	STEEL	HING HILT	11
9	2	HARDWARE	1/4"-50 X 3-1/2" HEX HEAD BOLT	11
8	4	HARDWARE	1/4" FLAT WASHER	11
7	2	ZINC PLATED STEEL	6-INCH HINGE ASSEMBLY	11
6	2	WOOD/FOAM	WIDTH BRACE	8
5	1	WOOD	RAMP	7
4	1	WOOD/HARDWARE/FOAM	BACK	5
3	1	WOOD	RIGHT SIDE	4
2	1	WOOD	LEFT SIDE	3
1	1	WOOD/FOAM	SKID	2

US-09509 HT
 NEMA 6

STYLE:	VIEW:	TOLERANCES FOR PART UNLESS OTHERWISE SPECIFIED *SEE ATLAS TOLERANCE MATRIX*	CUSTOMER:	CUSTOMER P/N:
CRATE	SOM		REPLIGEN CORPORATION	RM-10741
SIZE:	CLOSURE:			
---	---			
MATERIAL:	SHIP:	PROPRIETARY AND CONFIDENTIAL	DRAWN BY:	DATE:
WOOD/FOAM/MISC.	SET UP	DO NOT SCALE DRAWING	ntremer	19 Sep 2013
DIE:	INCHES OF TOLERANCE:		CHECKED BY:	DATE:
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DOCUMENT INFORMATION

DOCUMENT NUMBER:	CUSTOMER REV:	PAGE:
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Figure 38. OPUS 60 and 60R Pre-packed Chromatography Column packaging

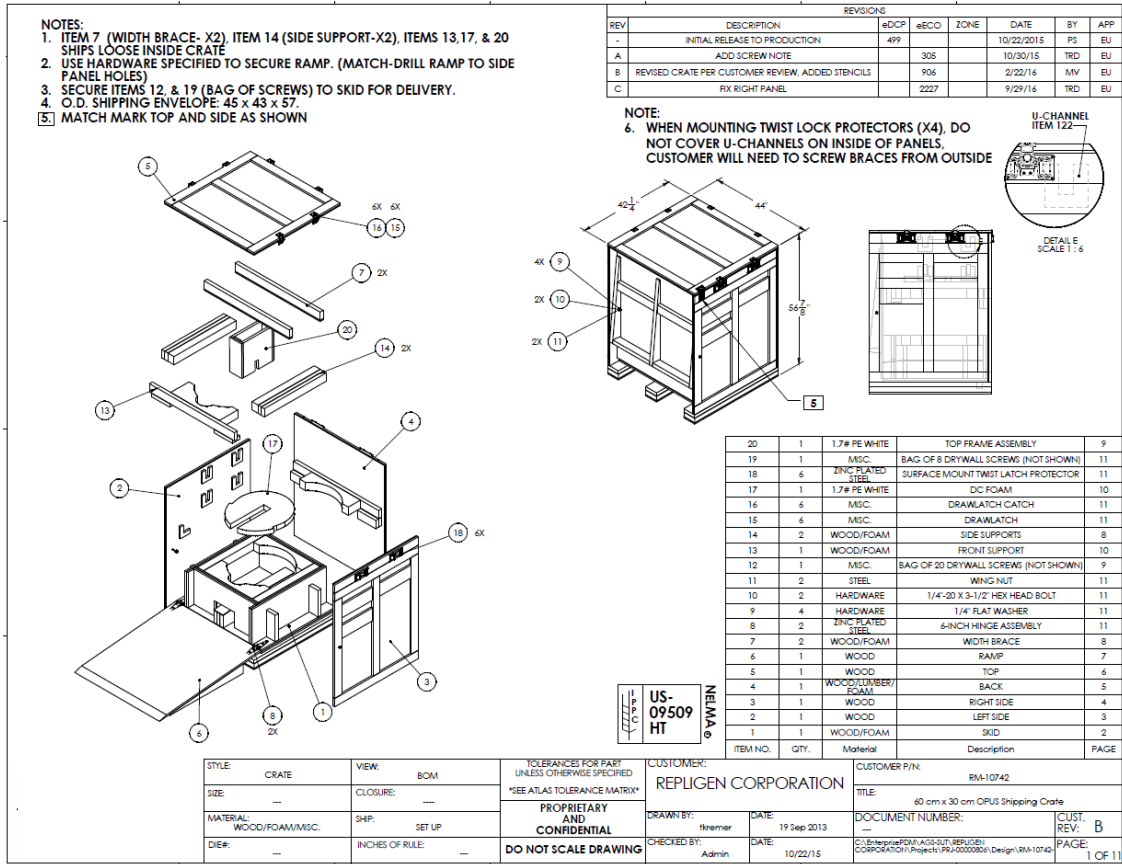
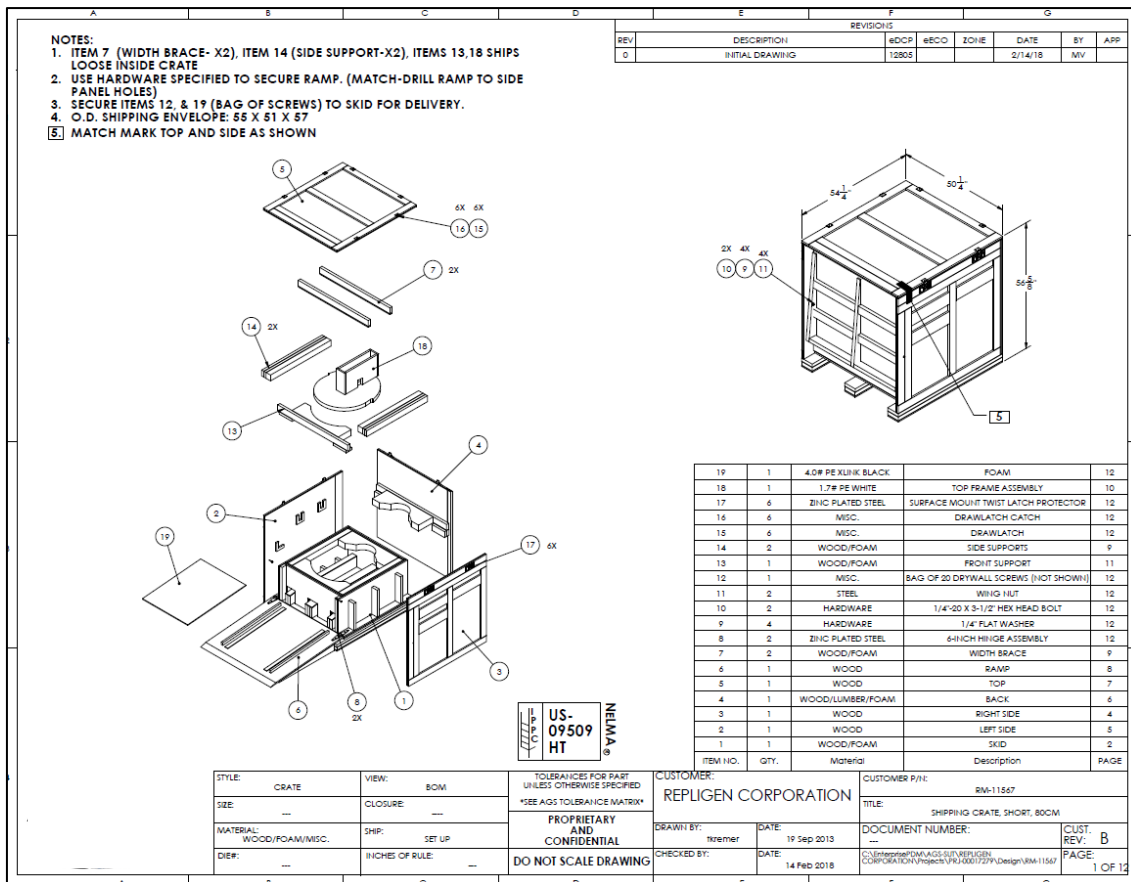


Figure 39. OPUS 80R Pre-packed Chromatography Column packaging



7. List of significant changes contained in this document revision (10.0)

Revision 10.0

- Update for new OPUS 36R size (updates throughout document)
 - Physical Attributes
 - Shipping studies
 - Images
 - Packaging design
- Reference to OPUS Gamma RSF
- Removal of Compression Testing from ISTA table as ISTA 3B does not include this test.
- Adjustment to FTIR policy for customers to opt into testing before column packing
- Addition of tubing set options as attached accessories to OPUS Columns
- Revised template for OPUS Specification Sheet (Figure 14)

Revision 9.0

- Update for new OPUS 2.5 size (updates throughout document)
 - Detail on materials of construction and applicable certifications
 - Physical attributes
 - Labels
 - Shipping studies
- Addition of Gamma Irradiation Section (Section 2.18)
- Addition of Temperature Monitoring Section (Section 2.17)
- Removal of Extractables and Leachables as a supplemental document
- Removal of OPUS Column Engineering drawings as a supplemental document

- Consolidated CoA sample designs
 - OPUS 8 aligned to OPUS 2.5 – 80R for GMP Run Ready CoA design
 - OPUS 8 aligned to OPUS 8 – 80R for Pre-GMP CoA design

Revision 8.0

- Improvement to column renderings
- Addition of references to Breda, NL as an OPUS Column Manufacturing site

Revision 7.0

- Updated for new sizes, OPUS 8, 12.6 and 80R Pre-packed Chromatography Columns (updates throughout document)
 - Detail on materials of construction and applicable certifications
 - Physical attributes
 - Labels, CoAs
 - Cleaning data
 - Shipping studies
 - Engineering drawings (column and shipping crate)
- Added column hardware pressure integrity test summaries for representative column sizes ([Section 2.12.1](#))
- Added packed bed pressure rating - different from column hardware pressure rating. ([2.12.1](#))
- Added detail on OPUS column chromatography resin. ([Section 2.4](#))
- Added detail on automated quoting process ([Section 2.3](#) and [Section 3](#))
 - Change from the OPUS Work Order to the OPUS Column Specification Sheet
- Updated for use of tamper evident packaging ([Section 2.6](#) and [Section 5.2](#))
- Updated endotoxin testing method. As of July 2018, change from previous gel clot method to the Charles River Endosafe MCS system ([Table 16](#))
- Updated the OPUS business continuity policy ([Section 3.2](#))
- Added acid and base extractables data added for all column hardware product contact surfaces ([Section 4](#))

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OPUS Columns RSF-10