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Single-use (SU) systems have great potential in antibody-drug conjugate (ADC) manufacturing. The use of organic solvents in the ADC process might, however, raise questions about potential leachables from the plastic and elastomeric materials of single-use components. To address those concerns, extractables studies were performed on a disposable mixer bag assembly, a disposable chromatography column housing, and a disposable flow path provided by GE Healthcare. The extractables studies were performed with two solvents commonly used in the ADC cytotoxin conjugation step: DMA and DMSO. The studies were designed to ensure that conditions were exaggerated compared with existing ADC manufacturing processes. Extractable organic compounds and trace elements from the single-use components were identified and semi-quantitated with a complementary set of analytical techniques. The low levels of extractables found in this study support the use of Xcellerex™ XDM 50 Basic Quad mixer bag assemblies, ReadyToProcess™ columns, and ÄKTA™ ready Flow Kits in ADC processes.

Introduction

ADCs are biotherapeutic molecules consisting of a cytotoxin coupled to a monoclonal antibody (mAb) by a linker. The target specificity of the mAb enables delivery of the toxic drug to cancer cells, while minimizing collateral damage to healthy cells. mAbs used in ADC production are typically manufactured according to traditional processes, including purification via protein A-platform processes (1, 2). Before coupling the linker, the mAb needs to be transferred to a suitable solution. This solvent exchange is normally performed by an ultrafiltration/diafiltration (UF/DF) operation. After the linker coupling reaction, the next step is the conjugation reaction, which couples the cytotoxic drug. Figure 1 provides an example workflow for manufacturing an ADC from a bulk mAb product.

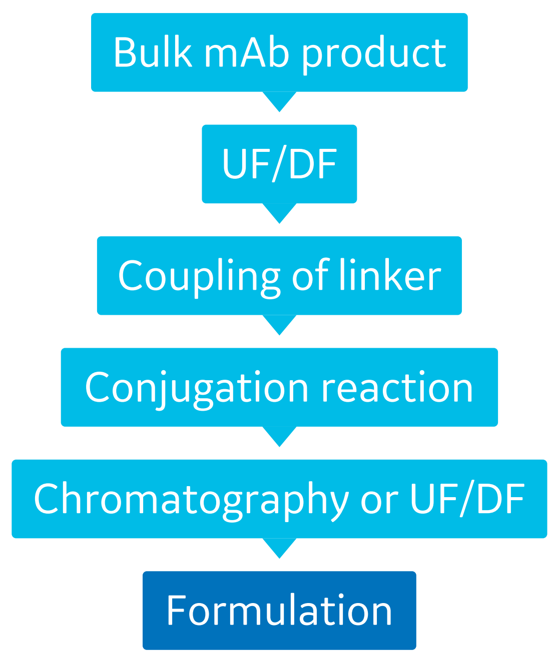

Fig 1. Simple workflow for preparing an ADC from bulk mAb.

Conjugation reactions are typically performed in a solvent containing either N,N-dimethylacetamide (DMA) or dimethyl sulfoxide (DMSO) (3).

Single-use systems are well suited to ADC manufacturing for several reasons. Importantly, SU systems minimize operator exposure to toxins, while also protecting the product from the operator and environment. The high potency of ADCs means that relatively small amounts of products need to be produced per batch. The small batch sizes are well suited for incorporation of single-use technology, which provides a cost-efficient solution for multi-product manufacturing. In addition to the lower upfront capital cost compared with reusable systems, single-use technologies are quicker to start using because they are supplied ready to use. Cleaning and cleaning validation between manufacturing campaigns is unnecessary, and the risk of carryover of cytotoxin from one batch to another is minimized. Because cleaning is not performed, single-use technologies minimize the volume of contaminated waste that must be handled and disposed of.

To support the adoption of single-use technologies in ADC production, relevant extractables information is needed. Therefore, extractables studies were performed on three single-use products from GE: the XDM 50 Basic Quad mixer bag assembly used in the conjugation reaction, and the ReadyToProcess 1 L column housing and the disposable ÄKTA ready Flow kit (Fig 2) used in the chromatography step.

Fig 2. ÄKTA ready system with a 20 L ReadyToProcess column and ÄKTA ready Flow Kit. In this study, 1 L column housings were used.

Materials and methods

The goal of the extraction studies was to characterize extractables profiles with equipment and conditions relevant to current ADC manufacturing processes. The studies were designed and performed with advice from customers who use disposables in their ADC processes.

Extractables study design

The extractables studies were designed with consideration for test conditions representing a worst-case scenario and for appropriate analytical techniques (3). Solvent concentrations used in typical cytotoxin conjugation reactions were exaggerated, as were surface area-to-volume ratios, temperatures, and contact times (Table 1). The experiments were set up to ensure contact with all wetted parts. Control samples of DMSO and DMA solution that had been stored at the same conditions but not in contact with the test article were included as blank references.

Table 1. Study design parameters compared with standard conditions

	Standard process	Study design
Conjugation reaction		
Solvent concentration (DMSO or DMA) (%)	10–15	20
Temperature (°C)	20–25	30
Contact time (h)	12	24
Surface area-to-volume considerations	Surface area-to-volume will depend on fill volume in the bag.	The smallest bag size (50 L) was selected and as much air as possible was removed with the purpose to wet as much of the surface as possible. Mixer speed was set to maximum without vortex.
Chromatography step		
Solvent concentration (DMSO or DMA) (%)	10–15	15
Temperature (°C)	20–25	30
Contact time (h)	6–8	24
Surface area-to-volume considerations	Flow velocity at running conditions will yield large volume in contact with chromatography system.	The smallest column size (1 L) was used to obtain the highest possible area-to-volume ratio. All inlets and outlets of the smallest flow kit size were extracted to obtain the highest possible area-to-volume ratio.

Materials

Extraction solutions

A 20% or 15% (v/v) solution of N, N-dimethylacetamide (DMA) was prepared in ultrapure water at neutral pH. A 20% or 15% dimethyl sulfoxide (DMSO) solution was prepared the same way.

Mixer bag assembly

XDM 50 Basic Quad mixer bag assemblies were used gamma irradiated within the product dose range specification of 27.5–45 kGy. Table 2 lists materials in the wetted parts.

Table 2. Materials in wetted parts of XDM 50 Basic Quad mixer bag assembly

Materials	Sources
Polyamide (PA) Ethylene vinyl alcohol (EVOH) Linear low-density polyethylene (LLDPE)	Outer layer of bag film
Ultra low-density polyethylene (ULDPE)	Inner layer of bag film
Thermoplastic elastomer (TPE)	Tubing
Polyethylene (PE) Stainless steel Zirconium oxide	Impeller
Polyethylene (PE) Silicone gasket	Ports
Polycarbonate Silicone gasket	Swabable valve
Polypropylene (PP) Polycarbonate Silicone gasket	Connectors

ReadyToProcess 1 L column

Column housings, assembled at the manufacturing site, were used. See Table 3 for a list of the materials in the wetted parts. Additional tubing needed for the experimental setup with the column was polytetrafluoroethylene (PTFE).

Table 3. Materials in wetted parts of ReadyToProcess columns

Materials	Sources
Polypropylene (PP)	Tube, lids, TC outlet, TC and hose connections, nets, net rings, support nets, hose
Polytheretherketone (PEEK)	Plug, net holder, nozzle tube
Polyolefin (POE)	Hose
Ethylenepropylenediene monomer (EPDM)	TC gasket
Fluorocarbon rubber (FPM/PKM)	O-rings

ÄKTA ready Low Flow Kit

ÄKTA ready Low Flow Kit (code no 28930182). Complete flow kits, manufactured with the standard method, were used. This method includes gamma irradiation of the parts except for the pump tubing, which is autoclaved. See Table 4 for a list of the materials in the wetted parts. Additional EPDM gaskets and TC clamps were used for the experimental setup with flow kits to connect the column tubings and the six inlets with the outlets.

Table 4. Materials in wetted parts of ÄKTA ready Flow Kit

Materials	Sources
Polypropylene (PP)	Connections, housings, and other parts
Polyetheretherketone (PEEK)	Plug, T- and Y-connections
Ethylenepropylenediene monomer (EPDM)	TC gasket, pressure membranes, O-rings
Polyamide (PA)	Airtrap housing
Thermoplastic elastomer (TPE)	UV cell, double mould
Polymethylpentene (PMP)	Flowmeter parts
Silicone (Si)	Hose
Titanium (Ti)	Conductivity cell
Polytetrafluoroethylene/silicone (PTFE/Si)	Pump hose

Process setup for mixer bag

The test articles were two 50 L Basic Quad disposable mixing bag assemblies (Fig 3). The wetted materials of construction are listed in Table 2. Mixing bag was installed into an Xcellerex XDM Mixing System and the temperature was set to 30°C. The required weights of water (water for injection) and DMSO or DMA were added to obtain a volume of 25 L in the bag and mixed. As much air as possible was removed to ensure the maximum wetted surface area. When temperature was stabilized at 30°C, the inlet tubing was sealed, the powder addition port was capped off and lids were installed on the XDM Mixing System. Mixer speed was set to maximum without vortex and extraction was performed at stabilized temperature for 24 h. Thereafter, sample was collected from the sample port of the bag into clean containers made of glass and inert plastic (PP), suitable for the different analytical methods. Control samples were prepared by filling extraction solution in separate containers for the different analytical methods. The containers were agitated at the highest rotational speed without vortex for 24 h at 30°C.

The extracted bags were rinsed and tested for chemical resistance after exposure to 20% DMSO or 20% DMA. Bag films were examined by visual inspection for evidence of loss of gloss, development of texture, decomposition, discoloration, swelling, cloudiness, tackiness, rubberiness, crazing, bubbling, cracking, and solubility per the ASTM D543-14 standard practices for evaluating the resistance to chemical reagents. Mechanical properties were tested by measuring ultimate strength, break energy, modulus, and seal strength of the perimeter seals (n = 30). The results were compared with untreated control film.

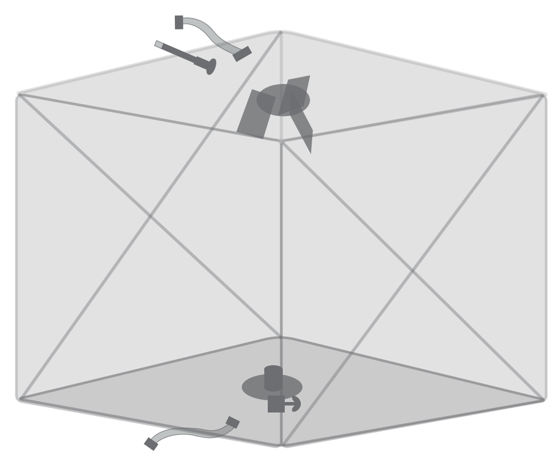

Fig 3. XDM 50 Basic Quad mixer bag assembly used in this study.

Process setup for column housings

The test articles were two 1 L ReadyToProcess column housings (Fig 4). Because of the wide variety of resins that could be used, this study was limited to the column hardware. The smallest size ReadyToProcess column was selected to ensure the highest possible surface area-to-volume ratio, representing a worst case. The wetted materials of construction are listed in Table 3. Tubing was connected to the inlet of each column. The other end of each piece of tubing was placed into a volumetric cylinder containing 1 L of either 15% DMA or 15% DMSO. The extraction solutions were pumped into the columns using a peristaltic pump. After filling, the tubing was removed, and the inlet and outlet tubes of the columns were clamped.

Fig 4. ReadyToProcess 1 L column. Column housings without chromatography resin were used for this study.

The filled columns were placed upright on an orbital shaker (19 mm orbit diameter) and incubated at 100 rpm for 24 h at 30°C. After incubation, the clamps from the inlet and outlet tubes were removed. The extracts were transferred to separate bottles by applying nitrogen pressure.

The control samples were prepared by pumping 1 L of each solution through two pieces of tubing from a volumetric cylinder into a glass bottle, using a peristaltic pump. The bottles were placed on an orbital shaker alongside the filled columns and agitated at 100 rpm for 24 h at 30°C.

After incubation, extraction solutions from the test articles and control samples were collected for analysis, divided into separate containers for the different analytical techniques, and stored at 5°C.

Process setup for disposable flow paths

The test articles were two ÄKTA ready Low Flow Kits. The smallest size flow kit was selected to ensure the highest possible surface area-to-volume ratio, representing a worst case. The wetted materials of construction are listed in Table 4. The open ends of the tubings of a Low Flow Kit (Fig 5) were connected to each other using EPDM gaskets and TC 25 clamps. The pump tubing of each flow kit was connected to a peristaltic pump, and the pump was used to fill the flow kit with 700 mL of either 15% DMA or 15% DMSO. During filling, the air trap of the flow kit was mounted at the highest position to let the air escape from the flow kit and to make sure that all surfaces were wetted with extraction solvent. Subsequently, the solution was circulated through the flow kit for 24 h at 30°C in an incubator (Fig 5).

Fig 5. Filling and circulation procedure of ÄKTA ready Low Flow Kit in an incubator. The peristaltic pump is placed behind and connected to the pump tubing. The bottle with the control sample is seen to the right.

Control samples were prepared by filling a glass bottle with 500 mL of either extraction solution and placed in the incubator at 30°C for 24 h.

After incubation, extraction solutions from the test articles and control samples were collected for analysis, divided, and stored in the same manner as the solutions from the column housing study.

Analytical methods

Two classes of extractable compounds were analyzed: organic compounds and a spectrum of elements. Organic compounds were identified and semi-quantitative results obtained with liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS) methods. Test methods for volatile (VOC), semi-volatile (SVOC), nonvolatile compounds (NVOC), and elements are listed in Table 5. Analyses of organic compounds were performed by Toxikon Europe NV in Leuven, Belgium. Elemental analysis was performed by ALS Scandinavia AB in Luleå, Sweden by inductively coupled plasma/sector field mass spectrometry (ICP-SFMS).

Table 5. Overview of chemical analyses performed on liquid from test and control articles incubated with 20% or 15% DMSO or 20% or 15% DMA

Analysis*	Target compounds	Typical compounds that could be detected if present	Explanation
HS-GC-MS	Volatile organic compounds (VOC)	Residual monomers and solvents, small polymer degradation products	Combination of headspace (HS) sampling and GC-MS analysis allows identification of a volatile compound.
GC-MS	Semi-volatile organic compounds (SVOC)	Process lubricants, plasticizers, antioxidants, polymer degradation products, high boiling solvents	For detection of organic compounds that are not sufficiently volatile for detection using HS-GC-MS but are volatile enough for GC-MS detection.
LC-MS APCI, pos and neg mode	Nonvolatile organic compounds (NVOC)	Anti-oxidants, fillers, plasticizers, polymerization or hydrogenation catalysts, polymer additives, and nonvolatile degradation products of those compounds	A rapid and sensitive UPLC method in combination with high resolution accurate mass (HRAM) mass spectrometry. APCI mode chosen as most appropriate, because most extractables from a polymer are relatively small molecules with medium to low polarity.
ICP-SFMS	Elements	Metals in fillers, pigments, catalyst residues	Method allows determination of multiple elements by scanning for them simultaneously.

* MS = mass spectrometry; GC = gas chromatography; HS = headspace; APCI = atmospheric pressure chemical ionization; ICP-SFMS = inductively coupled plasma/sector field mass spectrometry; UPLC = ultra performance liquid chromatography

Sample preparation

Prior to GC-MS and LC-MS, liquid/liquid extraction was performed on samples of the test and control solutions to transfer organic compounds to a low boiling point organic solvent. Dichloromethane (DCM) was used as extraction solvent for the 20% or 15% DMSO samples, while hexane was used as extraction solvent for the 20% or 15% DMA samples because of the solubility of DMA in DCM. Liquid/liquid extractions were performed at three different pH's. The combined extracts of different pH were concentrated under nitrogen flow with a concentration factor of 10.

VOC analysis using HS-GC-MS

Samples (13 mL) from EPA vials for test articles and blanks were transferred to 20 mL headspace vials containing anhydrous Na_2SO_4. After adding an internal standard solution (Toluene-d_8) at known concentration for concentration calculations for semi-quantitation of detected compounds, vials were tightly capped and heated to 75°C for 20 min. One mL of the headspace in each vial was injected for GC-MS analysis. Separation was performed on a 60 m DB-624 column with temperature program from 45°C to 220°C. Detection was performed in scan mode (35–300 amu) of the quadrupole MS.

Chromatograms of the test article and blank solutions were compared and screened for differential peaks. Compounds in differential peaks were identified through their chromatographic data and mass spectra matched to reference databases. One of the following identification levels was assigned: identified compound; most probable compound; tentatively identified compound; or unidentified. The concentrations of detected volatile compounds were estimated by a semi-quantitative internal calibration method. The reporting limit was set at 5 µg/L.

SVOC analysis using GC-MS

An internal standard solution (2-fluorobiphenyl) was added to a sample of each test or control solution to enable semi-quantitation of detected compounds. Separation was performed on a 30 m HP-5MS column with temperature program from 50°C to 300°C. Detection was performed in full scan mode (35–700 amu) of the quadrupole MS.

Differential peaks were determined and identified as for VOC analysis. The concentration of detected SVOC was estimated as for VOC, except that a different internal standard was used for calculations. The reporting limit was set at 50 µg/L.

NVOC analysis using LC-MS APCI, positive and negative modes

The liquid/liquid extraction sample prep described for GC-MS was used also for LC-MS. An internal standard (Tinuvin™ 327) was added to a sample of each test or control solution.

Separation was performed on a 3 × 100 mm 1.7 µm C18 column with a water:methanol gradient from 20% to 100% methanol. MS detection was performed in alternating full scan polarity-switching mode (positive and negative APCI, 100–1500 amu).

Differential analysis was performed with a software to find differences between the extract and control sample. For each differential peak, retention time, accurate mass of the molecular ion, and mass spectrum were matched against a database to allow identification. Identification level was assigned as: identified compound; most probable compound; tentatively identified compound; or unidentified.

The quantitation of a detected NVOC assigned as identified compound was performed with the compound-specific relative response factor (RRF) available for identified compounds. For other compounds, the response was compared with the response of the internal standard. The reporting limit was set at 50 µg/L.

Elemental analysis

The analysis with ICP-SFMS targeted 25 elements (aluminum, arsenic, barium, cadmium, calcium, chromium, cobalt, copper, iron, lead, lithium, magnesium, manganese, molybdenum, nickel, palladium, potassium, silicon, silver, strontium, sulfur, titanium, vanadium, zinc, and zirconium). Detection limit was in the range of 0.1 to 10 µg/L for all elements except for iron (20 µg/L), magnesium (30 µg/L), potassium (100 µg/L), silicon (500 µg/L), and sulfur (10 mg/L).

Results and discussion

XDM 50 Basic Quad mixer bag assemblies

Two organic extractables were found above reporting limit in the extraction samples with 20% DMSO or 20% DMA using HS-GC-MS, GC-MS, and LC-MS. The extractable compounds were assigned confirmed identity level as identified compounds related to an antioxidant that is used in the bag film. The concentrations were estimated at or below 70 µg/L (ppb) in both extraction solvents (i.e., at or below 1750 µg/bag, because the extraction volume was 25 L). Analysis with ICP-SFMS showed no extractable elements.

The film met acceptance criteria for visual and mechanical properties upon exposure to 20% DMSO or 20% DMA for 24 h at 30°C. No change was observed by visual examination compared with an untreated control film. The results for tensile strength, elongation at break, modulus, and seal strength fulfilled the acceptance criterion of ≤ 10% difference between test article and control.

ReadyToProcess column housings

No organic extractable compounds were found above reporting limit with HS-GC-MS or GC-MS in the extraction samples with 15% DMA or 15% DMSO. The results with LC-MS showed one organic compound that was present in both 15% DMA and 15% DMSO. The extractable compound was assigned a confirmed identity level as an identified compound related to a curing agent used with elastomeric material. The concentration was estimated below 200 µg/L (ppb) in both extraction solvents (i.e., less than 200 µg/ReadyToProcess column).

Analysis with ICP-SFMS showed low levels of a few extractable elements. The most abundant were calcium (< 100 µg/L) and magnesium (< 25 µg/L), followed by zinc (< 10 µg/L) and barium (< 2 µg/L). The extractable elements were found at a similar level in both 15% DMA and 15% DMSO.

ÄKTA ready Low Flow Kit

The results showed five organic extractable compounds above reporting limit with HS-GC-MS, GC-MS, and LC-MS. Two of the compounds were found in 15% DMA, and three compounds were found in 15% DMSO. All five extractable compounds were assigned a confirmed identity level as identified compounds related to polyamide and silicone materials and one solvent. The highest abundant extractable compound was present at a concentration below 600 µg/L (i.e., 410 µg/Low Flow Kit, because the extraction volume was 700 mL).

Analysis with ICP-SFMS showed that the most abundant extractable element was silicon, which was present below 9 mg/L (ppm). Additionally, calcium, barium, zinc, and copper were found at lower levels. The extractable elements were found at a similar level in both 15% DMA and 15% DMSO.

Assessment of results

A general toxicity and safety evaluation of extractable compounds as a worst case was conducted. The evaluation can only be general, because the specific details regarding the route of administration, dosage level, or toxicity of the proposed drug compounds will differ between different ADCs.

Toxicological information and a derived risk index (RI) for seven out of the eight identified extractable compounds were listed in a reference containing compiled safety impact information (4). In that reference, risk indices were obtained by subjecting toxicological safety data such as no observed effect levels (NOELs), no observed adverse effect levels (NOAELs), lowest published toxic dose (TDLOs), and others to a systematic evaluation process using appropriate uncertainty factors. An RI value represents a daily intake value for life-long intravenous administration. An additional RI value was derived for the final identified extractable compound from a reported NOAEL value and appropriate uncertainty factors.

Assumptions for the assessment were:

- Single-use equipment included in this assessment comprise the mixer bag assembly, the column housing, and the flow kit. All extractables from these disposables end up as impurity in the ADC product.
- Batch size is 5 g, considered a small batch, representing a worst case.
- Dosage is 3.6 mg/kg given every three weeks (21-day cycle), i.e., 3.6 mg/kg x 70 kg bw / 21 days = 12 mg/person/day.

Potential exposure to extractables was calculated from the highest result on extractables divided with the batch size of ADC multiplied with the daily dosage of ADC (Table 6).

Table 6. Calculations for the safety assessment of the eight extractable compounds found from the XDM Basic Quad mixer bag assembly[1], ReadyToProcess column[2], and ÄKTA ready Flow Kit[3]

Extractable compound	Highest results on extractables (µg/system)	Batch size ADC (g)	Daily dosage ADC (mg/d)	Potential exposure to extractables (µg/d)	RI exposure limit (µg/d) (4)
Related to antioxidant[1]	1750	5	12	4.20	175
Related to antioxidant[1]	148	5	12	0.40	21 300
Related to polyamide[3]	410	5	12	0.98	21 000
Related to curing agent[2]	190	5	12	0.46	560
Related to silicone[3]	150	5	12	0.36	1750
Solvent[3]	25	5	12	0.06	50 000
Related to silicone[3]	8	5	12	0.02	700
Related to silicone[3]	7	5	12	0.02	11 200

Assessment of the results according to the listed assumptions shows that the potential exposure to extractables is well below the RI for each extractable compound. Therefore, extractables from the XDM mixer bag assembly, ReadyToProcess column housing, and ÄKTA ready Flow Kit should pose no safety concern for use in ADC manufacturing within the conditions of this study.

Conclusions

The low levels of extractables found in this study demonstrate chemical compatibility of XDM 50 Basic Quad mixer bag assemblies, ReadyToProcess columns, and ÄKTA ready Flow Kits with two organic solvents typically employed in ADC manufacturing processes: DMSO and DMA. Detailed results of these studies are added to the validation guides for these single-use components to supplement existing data generated with aqueous solvents and ethanol. Along with other single-use components and systems, the XDM 50 Basic Quad mixer bag assemblies, ReadyToProcess columns, and ÄKTA ready Flow Kits offer a solution to some of the main challenges in ADC manufacturing. Single-use technologies provide a closed system to protect both operator and product and reduce the risk of cross-contamination between batches. Components are supplied ready to use without cleaning, and cleaning between batches is unnecessary, saving time, handling, and water. In addition, single-use systems offer lower upfront capital expenditures, greater flexibility, and a smaller footprint compared with traditional technologies.

Contact your regional GE Healthcare sales office for access to the validation guides for these studies.

Fast Trak Services for E&L studies

GE's Fast Trak Services for extractable and leachable (E&L) studies are designed to help biomanufacturers assess and manage their risk for E&L related drug impurities. Our team of E&L scientists have wide experience in analytical techniques and support GE's commitment to meet the standard user requirements defined by the BioPhorum Operations Group (BPOG). In addition, a toxicological risk assessment based on your process conditions can be performed and used to guide you to a decision about whether you need to perform custom E&L studies to meet regulatory submission needs.

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