GE Healthcare

Single-use extractables and leachables: GE's alignment with the BPOG protocol

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- **Biophorum Operations Group (BPOG) is proposing a standard approach to doing extractables and leachables (E&L) testing on single-use manufacturing components and systems.**
- **After review of the BPOG proposal, we updated our E&L packages.**
- **Our current E&L protocol aligns with the core elements of the BPOG E&L protocol.**

Despite years of discussion and experience, E&L testing approaches for single-use equipment have not yet fully matured into a consensus industry practice. Copious amounts of data have been generated by the industry, but most of it is held under confidentiality. Trade organizations, such as the Bio-Process Systems Alliance (BPSA), of which GE is a member, and suppliers have derived their own approaches to testing. For end users who are adopting single-use (SU) equipment as a manufacturing strategy, this situation becomes unwieldy. The need for a standard approach both to the generation and to the reporting structure of extractables data becomes obvious.

In this environment, BPOG has published a proposal for such a standard approach (1). ASTM is attempting to use the BPOG output as starting material for a true consensus standard on extractables testing of SU manufacturing equipment. On a completely separate track, USP is developing a standard on extractables testing of SU equipment. As data are released to the public domain and are scrutinized by subject matter experts, and as the USP direction becomes clearer, both the industry approach and GE's approach to E&L testing will evolve.

The BPOG proposal has undergone extensive discussion in the industry, which has revealed philosophical fissures on several main aspects of E&L study design. GE has been involved in many of these discussions through both direct interaction with BPOG representatives and through BPSA-BPOG negotiations. These negotiations have been aimed at deriving a proposal that both BPSA and BPOG could accept and support. To date, these efforts have been met with some success, but not enough for BPSA to sign on to the BPOG proposal.

BPSA's position is that E&L testing is still in a state of flux and that until the industry has reached true consensus, it is at best a business decision to spend money on a proposal that might not elevate to the level of a standard. BPSA's position was written by four authors, two of which are from GE. The BPSA position was unanimously endorsed by member organizations for publication.

Nevertheless, GE has listened to the BPOG stated needs and to the rationale that they use to support their proposal. Technical differences aside, GE understands and respects that end users are making this proposal to facilitate and enable high-quality and accurate patient safety assessments. In the absence of an industry standard, BPOG member companies have taken the BPOG protocol and transformed it into a Standard User Requirement (SUR) Pack that is sent out to suppliers. On this basis, we have refined our policy for E&L testing to align with the BPOG protocol.

Philosophically, our policy has been guided by the following:

1. The main objective of an E&L study is to develop a library of compounds that may be released from a test article under physical and chemical conditions that are more conducive to extraction than conditions associated with normal use of the test article. This data is useful in three main ways:
   a. GE assessment of suitability of materials for intended use
   b. GE management of change to product formulation or process conditions
   c. End user initial safety assessment of candidate SU equipment
2. In alignment with principles of ICH Q9 Quality Risk Management, GE will focus greater effort and resources on articles that we perceive to represent relatively greater product risk, based on physical and chemical attributes, and on product claims related to intended use.
3. Recognizing that achieving a study design that incorporates more aggressive extraction conditions than the aggregate product-use conditions of all end users is not practical. The test boundaries applied are thus derived from the BPOG paper in combination with GE's judgment and knowledge of how products are typically used.
4. A policy must be a blend of prescriptive requirements and requirements that require subject matter experts to make situation-based judgment calls according to set guidelines. Thus, our policy sets out default requirements and requires a qualified person to document rationales for alternative approaches.

Table 1 compares our former and current E&L protocols to BPOG's. After a thorough review, we expect that both our former and current approaches will, in the vast majority of cases, be applicable to customer-use conditions. The data can be used by customers in E&L risk assessments. The GE approach was revised in 2013 in response to the publication of BPOG's initial proposal (2).

It was further aligned with the BPOG proposal in 2015 in response to receiving SUR Pack compliance requirement letters from BPOG member companies. The current policy was created with the benefit of having visibility to the full BPOG protocol (1) and thus is much more closely aligned. Deviations from the BPOG protocol are primarily in the area of analytical methodology.

Table 1. Comparison of BPOG's and GE's E&L protocols[1]

Test conditions	BPOG protocol (1)	Former GE approach	Current GE protocol	Alignment of BPOG and current GE protocol
Test articles	Components	Systems	Components	Yes
Number of test articles	2 each from different lots	1 test article	2 each from different lots	Yes
Product pretreatment	Pretreatment to model use with sterilization at upper range. Separate study if multiple methods of sterilization.	Gamma irradiation above the specified range. No separate study for multiple methods of sterilization. Autoclave for some filter cartridges.	Pretreatment to model use with sterilization at upper range. Separate study if multiple methods of sterilization.	Yes
Product families	Allowed	Allowed	Allowed	Yes
Solvents	WFI 50% ethanol 0.5 N NaOH 0.1 M phosphoric acid 5 M NaCl 1% polysorbate 80	Solvents for bioreactors: WFI pH 9 pH 5 20% ethanol 1% polysorbate 80 Solvents for non-bioreactor SUS: WFI 20% ethanol pH 13 NaOH pH 2 HCl 0.1% polysorbate 20 5 M NaCl	WFI 50% ethanol 0.5 N NaOH 0.1 M phosphoric acid 5 M NaCl 1% polysorbate 80	Yes
Extraction time	T = 0 all components T = 24 h all components T = 7, 21, 70 d serve as maximum and intermediate time points depending on component application	T = 24 h all components except bags T = 28 d for cell culture/mixing bags T = 120 d mixing and storage bag	T = 0 all components T = 24 h all components T = 7, 21, 70 d serve as maximum and intermediate time points depending on component application	Yes
Extraction temperature	40°C	Bioreactors: 50°C Non-bioreactor SUS: 40°C	40°C	Yes
Surface area/volume	6 cm^2/mL recommended for all non-filter components 1 cm^2/mL recommended for filters	Target is the smallest SA/V ratio to get the worst case. Results are reported as mg extractables/system	6 cm^2/mL recommended for all non-filter components 1 cm^2/mL recommended for filters	Control of SA/V for new GE policy is aligned with BPOG. However, some exceptions are allowed for ease of testing and reducing complexity of study design.
Extraction mode	Dynamic	Static Dynamic for TFF filters and NFF filter cartridges (non ReadyToProcess™ products)	Dynamic	Yes
Analytics	ICP/MS HS GC/MS DI GC/MS LC/MS	Same as BPOG plus: IC, TOC, pH, conductivity, and nonvolatile residue (NVR). Assays performed in the model solvents that do not interfere with the assay.	ICP/MS or ICP/OES HS GC/MS DI GC/MS LC/MS Other assays, such as IC, TOC, pH, conductivity, and nonvolatile residue (NVR) may be added for model solvents that do not interfere with the assay.	Yes Deviations from the BPOG protocol analytical methods are allowed regarding sample preparation, choice of standards, mobile phases, and methodology for quantification.

[1] DI GC/MS = direct injection gas chromatography mass spectrometry; HS GC/MS = headspace gas chromatography mass spectrometry; IC = inorganic carbon; ICP/MS = inductively coupled plasma mass spectrometry; ICP/OES = inductively coupled plasma optical emission spectrometry; LC/MS = liquid chromatography mass spectrometry; NFF = normal flow filtration; SA/V = surface area/volume; SUS = single use systems; TFF = tangential flow filtration; TOC = total organic carbon; WFI = water for injection

FAQs

1. What is the BPOG paper?

Authors representing the Biophorum Operations Group (BPOG) published a paper in *Pharmaceutical Engineering* titled “Standardized extractables testing protocol for single-use systems in biomanufacturing."

Ding, W. *et. al.* Standardized extractables testing protocol for single-use systems in biomanufacturing. *Pharmaceut. Eng.* **34(6)** (2014).

BPOG is a consortium of biopharmaceutical manufacturers and represents over 30 companies (*www.biophorum.com*).

2. What is the paper about?

The paper proposes a standard approach to doing extractables and leachables (E&L) testing on single-use manufacturing components and systems. The need arises out of a difficulty that end users have with respect to obtaining consistent, high-quality data that can be used in assessing product and process risk.

3. What is GE’s view on the BPOG proposal?

BPOG member companies have taken the BPOG protocol and transformed it into a Standard User Requirement (SUR) Pack which contains three documents:

1. A supplier questionnaire to capture critical product documentation
2. The standardized extractables testing requirements, which are identical to the published protocol (1)
3. A spreadsheet for reporting the results in a uniform way

The SUR pack has been sent out with a letter to GE from several BPOG member companies. As stated in the letter, the sender will give preference in selection to those components that meet the user’s extractable requirements.

The requirement is not retrospective for products already validated into users’ processes. Use of launched products in new processes/applications requires fulfilment of the SUR pack.

4. What is GE’s view on the BPOG protocol?

GE acknowledges end user motivation to make conducting patient safety risk assessments less complex and more intuitive. We understand the desire for a standardized treatment of E&L testing and reporting.

Trying to align multiple suppliers’ data sets for E&L, all of which may have been generated using unique protocols, can be very confusing. Each supplier may have used different methods for pretreatment, solvent selection, extraction conditions, analytics, and data reporting. We have been in contact with BPOG since early 2013, so the content of the protocol was not surprising to us. We support the BPOG objectives around standardization, but we have concerns over some of the specifics of the protocol. Table 1 compares our protocol with BPOG’s.

5. Has GE adopted the BPOG protocol?

The current GE protocol is closely aligned with the BPOG protocol to fulfill the SUR Pack requested by several BPOG member companies. Some principles of the protocol are still being debated in the industry as to their technical correctness, practicality, or alignment with fundamental objectives of an E&L study. GE is contributing actively to the industry discussion; we are evaluating the evolution of opinion on these issues; and we reserve the opportunity to evolve our policy over time.

6. What is GE doing about E&L testing of its products?

GE is committed to improving the current state of our E&L data. We initiated a vast effort in 2013 to refresh our E&L support documentation with a more consistent and thorough approach. In addition, GE has invested in an in-house extractables test lab located in Uppsala, Sweden. The current protocol is followed for newly launched products or those that require repeat E&L testing as a result of product changes. Given the time and resource commitment associated with execution of the BPOG protocol, it will not be possible for us to administer this protocol for launched GE single-use products in short order. Therefore, we are taking a risk-based approach to the order in which products/components are tested. Accordingly, we will begin the process by testing the films in our portfolio. We anticipate that extensive coverage of our products will require a number of years. In addition, we will be working with our critical raw material suppliers to communicate the GE E&L policy and our desire to have them provide high-quality data that are in line with our protocol. Our view is that E&L testing of components should be the responsibility of the component manufacturer; component manufacturers who provide this added support will be favored.

7. Is the BPOG protocol now an industry standard?

No. Time will show if it is going to be broadly adopted and if, perhaps, a standards setting organization will formally translate it into a consensus standard. At present, it is a peer-reviewed publication of a proposal for a de facto standard for suppliers to follow. This does not have unanimous support in the industry. Neither the Product Quality Research Institute (PQRI) nor USP aligns with it. The same is true of the Bio-Process Systems Alliance (BPSA), of which GE is a member, as an organization and as individual member companies, most of whom are suppliers to the industry. *BPSA has published their position*, which is that E&L testing is still in a state of flux until the industry has reached true consensus, BPSA's position was written by four authors, two of which are from GE. There are no listed authors in the published article because it is a BPSA position, having been voted on by BPSA members (100% in favor of publication). In the absence of a standard, several BPOG member companies have, however, taken the BPOG protocol and transformed it into a Standard User Requirement (SUR) Pack, which is sent to suppliers (see above).

References

1. Ding, W. *et. al.* Standardized extractables testing protocol for single-use systems in biomanufacturing. *Pharmaceut. Eng.* **34(6)** (2014).
2. Mahajan, E. et. al. Standardization of single use components' extractable studies for industry. *Pharmaceut. Eng.* **32(3)**, 54–56 (2012).

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