Technical Note

Thermo Scientific Nunc Cell Factory System extractable review - How product design influences an extractable profile

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Key Words
Cell Factory System, extractables, UV-cured adhesive, ultra-sonic welding, product design, risk, safety

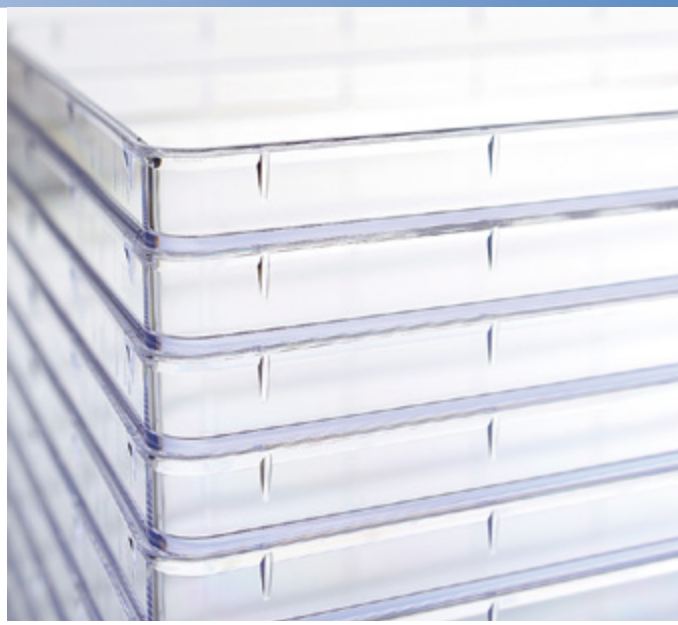
Introduction

Biopharmaceutical manufacturers have an obligation to ensure the safety and efficacy of the products they produce. This requirement drives the selection of products and materials used in manufacturing operations and define the necessary risk assessment of those materials.

One of the areas of concern are the chemicals that can be extracted from cell culture vessels and other containers used in the storage and manufacture of the pharmaceutical. To mitigate these risks, biopharmaceutical manufacturers often use extractables data to perform a risk assessment to determine if they need to take action to reduce risk or if further studies are required. These studies are performed using conditions which are exaggerated to ensure that the list of potential extractables is comprehensive.

Suppliers can assist manufacturers by incorporating an understanding of extractables into the design of their products. Not only is the selection of materials important, but designing products in a way that minimizes the number of materials can reduce the amount of time it takes to assess risk and help save manufacturers' time. The more individual materials you incorporate into a product design, the greater the potential to increase the number of extractables observed.

Thermo Scientific™ Nunc™ Cell Factory™ systems reflect an understanding of the impact of product design on the potential to generate extractables. The Nunc Cell Factory System minimizes the number of materials that could generate extractables by relying on ultrasonic welding to fuse individual layers of the Cell Factory system together. A Competitor uses an adhesive to bond individual layers



of their multilayer vessel, creating the potential for materials from that adhesive to migrate from the vessel into the cell culture media. The Nunc Cell Factory system has no adhesives; therefore, extractables associated with UV-cured adhesive are absent from this system.

An extractable study was conducted to demonstrate the potential for an adhesive to leach from the Competitor's multilayer cell culture vessel in comparison to the adhesive-free Nunc Cell Factory and Thermo Scientific™ EasyFill™ Cell Factory™ systems.

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Materials

Nunc Cell Factory 4-Layer Standard System; Catalog number 140004; Lot number 1099245; Dates of Manufacture: July 03 to 09, 2013

Nunc EasyFill Cell Factory 4-Layer System; Catalog number 140360; Lot number 136652; Dates of Manufacture: November 2013

Competitor 5-layer vessel; Date of Manufacture: December 17, 2013

Methods

The Nunc Cell Factory Standard System, Nunc EasyFill Cell Factory System, and a Competitor's multilayer vessel were filled with 800mL of phosphate buffered saline (PBS, pH 7.4), or 20% isopropyl alcohol (IPA), and were incubated for 20 days at 40°C to exaggerate conditions of use (n=1 per test condition[1]). PBS was chosen because it is very similar in ionic strength and polarity to cell culture media and to human biological fluids, and as a result should represent a physiologically relevant solution. IPA is slightly more aggressive than PBS in terms of its ability to dissolve certain chemicals.

All extractions and analysis were performed at a third-party laboratory.

The extractions were analyzed by Direct Injection GC/MS, Headspace GC/MS, and LC/MS for semi-volatile organic compounds, volatile organic compounds, and non-volatile organic compounds, respectively.

No assessment was made of the toxicological implications of the presence or quantity of the extractables detected in any vessels. No suggestion of suitability or unsuitability for any application should be implied based on these analyses.

Results and Discussion

The extractables profile of the Nunc Cell Factory Systems differed as expected (Table 1). Additional extractables were detected in the competitive device. The compounds detected in the competitor's vessel are consistent with what would be expected from an adhesive (Table 2). No adhesive is used in the construction of the the Nunc Cell Factory systems. As expected, no extractables from adhesive were detected in the Cell Factory products.

Table 1. Extracted Materials Identified in the Nunc Cell Factory and EasyFill Cell Factory Systems

Nunc Cell Factory 4-Layer Standard System		Nunc EasyFill Cell Factory 4-Layer System	
IPA Extracts	**PBS Extracts**	**IPA Extracts**	**PBS Extracts**
Benzaldehyde	None Detected	Benzaldehyde	None Detected
Styrene		One Unknown Compound	
Two Unknown Compounds			

Table 2. Extracted Materials Identified in the Competitor 5-layer vessel

Competitor's Multilayer Vessel	
IPA Extracts	**PBS Extracts**
(1-hydroxycyclohexyl)phenyl-methanone*	(1-hydroxycyclohexyl)phenyl-methanone*
2,4,6-Trimethylbenzaldehyde	N,N-dimethyl-2-propenamide*
Benzaldehyde	Four Unknown Compounds
Exobornyl Acetate*	
Isobornyl Alcohol*	
N,N-dimethyl-2-propenamide*	
Silicone	
16 Unknown Compounds	

* Known components of adhesives

[1] We expect from reasonable scientific principles that we should find the signature of an adhesive in an extractables report for the competitive product and not in the Cell Factory product. The sample size of one is confirmatory.

Conclusions

Specific design features have trade-offs. In the present example, the use of an adhesive to bond layers of a multilayer tray together imparts certain advantages in manufacturing and makes these joints more resistant to breakage under certain conditions. However, the presence of this additional material also carries with it other consequences that may or may not introduce a risk to the products produced in that device. This study demonstrates that the presence of an additional material alters the extractable profile of that device by generating additional extractables. The magnitude and significance of the risk posed by these additional extractables must be assessed where that product is used to produce a biopharmaceutical. Risk assessment can be a time-consuming process and can lead to the decision to perform expensive follow-up tests, which can delay the introduction of a product to the market.

Minimizing the number of materials in the product design is one way suppliers can assist customers in simplifying the risk assessment process.

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