Technical Brief

PureFlex™ FILM: Extractables Bioreactivity Safety Evaluation Approach

This paper reviews a risk-based approach followed by a leading biotech customer to perform a bioreactivity safety evaluation of bioprocess container film extractables. Millipore's PureFlex film was evaluated using this approach and qualified for buffer and media filtration and storage applications. The results of the study are summarized in this paper.

SAFETY EVALUATION APPROACH

The customer confirmed all materials of construction used in the manufacture of PureFlex film were 21 CFR Part 177 cleared and reviewed the extractables profile data collected on PureFlex, using the model solvent approach (See document TB1013EN00). Based on the review, the customer determined that PureFlex film did not warrant any further or more extensive extractables analysis. This decision was based on the following factors:

- PureFlex extractables profile was typical of existing Polyethylene films in the market
- Lack of central database for Permissible Daily Exposure (PDE) values for all identified compounds; incomplete data covering PDE values for all known compounds
- Incomplete human impact assessment data for the more obscure compounds
- Excessive time and cost required to identify compounds that are present in limits well below the threshold of toxicological concern

Based on this assessment, the customer's next and final objective was to use their safety evaluation approach to establish that the film extractables did not present any bioreactivity concerns impacting the drug quality and patient safety. The underlying strategy was to determine worst case concentrations of the various BPC components (a 100% extraction) and then use these concentrations to demonstrate biological compatibility per modified USP <87> and <88> methodology.

The bag surface area-to-volume ratio, extraction time and temperature conditions, solvent concentrations and 100% extraction of film components were selected to simulate worst-case conditions.

EXPERIMENTAL DESIGN

- Samples of each film component material were furnished by the film manufacturer in the form of polymer pellets measuring approximately 5 millimeters in diameter.
- Gamma irradiation of the individual components was performed by Steris with a minimum and a maximum dose of 45.7 kGy and 57.0 kGy respectively.
- Accelerated aging of both non-gamma and gamma irradiated components was performed in Millipore's R&D facility in Bedford, MA.
  - Each component sample aged for 3 yrs per ASTM F1980-02

$$A_{AT} = \frac{D_{RT}}{(Q_{10}{}^{(T_{AA}-T_{RT})/10})}$$

Where, A_{AT} = Accelerated aging time
D_{RT} = Desired real time age
Q_{10} = Aging factor for a 10 °C temperature delta
T_{AA} = Accelerated aging temperature
T_{RT} = Room temperature

  - Aging factor of 2.0, Aging temperature of 60 °C, room temperature of 20 °C
- Concentration of the individual components as tested was chosen to be reflective of the concentration which would be present if a 100% extraction of the component occurred in a disposable process container with a surface area to volume ratio of 1,000cm^2 to 1 L.
- Equation 1 and Table 1 show the component concentration calculation
- Equation 2 and Table 2 show the 100% extraction calculations
- USP <87> and <88> testing of un-aged and aged samples was conducted by an accredited laboratory for USP biological testing.
- USP <87>: Elution Method, Agarose Overlay Method
- USP <88>: Intracutaneous, muscle implantation, systemic studies

Component Concentration and 100% Extraction Calculation

Equation 1: Calculation of % Composition of each polymer

$$\%\text{Composition} = \Sigma\, \%\text{Component} \times \%\text{Layer Composition of Total}$$

Layer	1	2	3	4	5	6	7	8	9	% Composition
% Layer Composition of Total	20%	5%	17%	3%	15%	14%	6%	10%	10%	
EVA	-	-	-	-	-	-	100%	100%		16%
PE copolymer A										24%
PE copolymer B										25%
PE copolymer C										25%
EVOH										8%
Slip agent A										1%
Slip agent B										1%

Note: Example only. Table does not represent actual data.

Equation 2 and Table 2 below show the calculations and values used to determine the concentration of each polymer in a worst case 100% extraction scenario. It is important to note that PureFlex film has a weight of 250.5 g/m^2.

Equation 2: Concentration of polymer in a 100% extraction

$$\text{Concentration } {}^{g}/_{L} = 250\ {}^{g}/_{m^2} \times \%\text{Composition} \times {}^{1\ m^2}/_{10{,}000\ cm^2} \times {}^{1{,}000\ cm^2}/_{1\ L}$$

Material (supplier & part number)	SA/V (cm^2/L)	% Composition	Density (g/cm3)	Purity	Concentration (g/L)
EVA	1,000	16%	0.95	99%	3.97
PE Copolymer A	1,000				
PE Copolymer B	1,000				
PE Copolymer C	1,000				
EVOH	1,000				
Slip Agent A	1,000				
Slip Agent B	1,000				

Note: Example only. Table does not represent actual data.

RESULTS AND DISCUSSION

Tables 3 and 4 show the results of the USP <87> and USP <88> tests, respectively. This shows that no signs of reactivity were seen for un-aged material and for material that was aged the equivalent of three years, either before the implantation or after the 72-hour and seven-day implantation period.

Table 3: USP <87> Test Results for Un-Aged and Aged Materials

Test Lab Report #	Test Material	Test Date	Test Result
XX-YYYY-ZZ	EVA	July 2007	No signs of reactivity (grade 0)
	PE copolymer A	July 2007	No signs of reactivity (grade 0)
	PE copolymer B	July 2007	No signs of reactivity (grade 0)
	PE copolymer C	July 2007	No signs of reactivity (grade 0)
	EVOH	July 2007	No signs of reactivity (grade 0)
	Slip agent A	July 2007	No signs of reactivity (grade 0)
	Slip agent B	July 2007	No signs of reactivity (grade 0)

Table 4: USP <88> Test Results for Un-Aged and Aged Materials

Test Lab Report #	Test Material	Test Date	Test Result
XX-YYYY-ZZ	EVA	July 2007	No signs of reactivity in systemic or intracutaneous tests after 72 hours. No signs of reactivity in implantation site after 7 days.
	PE copolymer A	July 2007	
	PE copolymer B	July 2007	
	PE copolymer C	July 2007	
	EVOH	July 2007	
	Slip Agent A	July 2007	
	Slip Agent B	July 2007	

CONCLUSION

The study results provided the following conclusions:

- All components used in PureFlex film are non-toxic in the proportions used to produce the film.
- At 100% extraction, i.e. worst case condition, solvent/solute mixture for all components remains non-toxic.
- The results are valid for gamma irradiated film, both un-aged and aged the equivalent of three years.

The customer followed a logical and reasonable risk-based approach to successfully qualify PureFlex film. This study was completed in a short period with optimal utilization of resources.

TO PLACE AN ORDER OR RECEIVE TECHNICAL ASSISTANCE

For additional information call your nearest Millipore office:

In the U.S. and Canada, call toll-free
1-800-MILLIPORE (1-800-645-5476)

In the U.S., Canada and Puerto Rico, fax orders to
1-800-MILLIFX (1-800-645-5439)

Outside of North America contact your local office.

To find the office nearest you: **www.millipore.com/offices**

Internet: **www.millipore.com**

Technical Service: **www.millipore.com/techservice**

MILLIPORE™

www.millipore.com/offices

ADVANCING LIFE SCIENCE TOGETHER™
Research. Development. Production.

Millipore is a registered trademarks of Millipore Corporation.
The M mark, Advancing Life Science Together and PureFlex are trademarks of Millipore Corporation.
Lit. No. TB2418EN00 Rev. A 05/09 Printed in U.S.A. DP SBU-09-01842© 2009 Millipore Corporation, Billerica, MA 01821 U.S.A. All rights reserved.