The Challenges in Toxicological assessments for Small Volume Parenteral Packaging system applications

31 March 2022

Koen Van Deun, Dr. Vet. Medicine
European Registered Toxicologist

Consultant for
Nelson Labs
Europe

Table of Contents

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

Table of Contents

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

A. Toxicological evaluation & Endpoints

- **Toxicological evaluation of E&L**
  - **Exposure assessment**
    - SVP packaging (primary or secondary; solvents used, conditions …)?
    - Duration of exposure (< 1 month, < 1 year, lifetime, intermittent…)?
    - Type of patient (age, sex, body mass)?
  - **Hazard assessment: threshold or non-threshold?**
    - Critical/major toxicity endpoints: genotoxicity/carcinogenicity/sensitization …
    - **Point of Departure (**PoD): **NOAEL,** LOAEL, BMDL, TD_{50} …
    - Derived **safety limits**: **PDE,** , ADE, HBEL, RfD, ADI, MRL ….
  - **Risk assessment**
    - Local tolerance: e.g. Irritation/sensitization potential
    - Systemic toxicity : **Safety margin = Safety limit / Max. exposure**

Maximum exposure (µg/day)?

Most critical findings + MOST CONSERVATIVE safety limit (µg/day)?

> 1: OK **< 1 : further testing**

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

A. Toxicological evaluation & Endpoints

- **Exclude/confirm genotoxicity & carcinogenicity**
  - **Genotoxicity:**
    - ICH M7 (2017): The focus is on DNA reactive substances that have a potential to directly cause DNA damage when present at low levels leading to mutations and therefore, potentially causing cancer. According to ICH M7, a risk of 1:100 000 = acceptable (linear or non-threshold).
    - This type of mutagenic carcinogen is usually detected in an **Amest test (bacterial reverse mutation assay)**.
    - A **computational toxicology assessment** should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay.
      Two (Q)SAR prediction methodologies that complement each other should be applied.
  - **Carcinogenicity:**
    - Other mechanisms typically have threshold mechanisms and usually do not pose carcinogenic risk in humans at low concentrations.
    - This is tested in chronic bioassays or other long-term studies.

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

C. Toxicological evaluation & Endpoints

- **Exclude/confirm sensitization & irritation**
  - **Sensitization:**
    - A non-mutagenic leachable which has **potential for irritation or sensitization** should be controlled at **≤5 µg/day** (PQRI, 2020).
    - For leachables, the potential to induce **skin sensitization** is of high relevance as PDP may be administered subcutaneously (Broschard et al. 2016).
    - There are several types of ***in vivo* studies** to investigate the skin sensitizing potential in guinea pigs (HRIPT, GMPT, Buehler Test) and mice (LLNA).
    - ***In vitro* and computational models** are available that can provide **mechanistic pathway information** (e.g. protein binding, keratinocyte/dendrocyte activation, T-cell activation).
  - **Irritation:**
    - In the past, ***in vivo* studies in rabbits for** skin and/or eye irritation were used.
    - Currently, reliable ***in vitro* models** for skin and/or eye irritation are available.
    - Most of these tests are applied **on substance; dilutions may not be irritating**!

B. Toxicological evaluation & Endpoints

- **Calculate safety limits - standard**
  - **PDE: Permissible Daily Exposure**

    (ICH Q3C, 2021; ICH Q3D, 2019; EMA 2014; EVM)
    - Based on NO(A)EL of **repeated dose toxicity studies**, but also **reproductive & developmental toxicity**, **carcinogenicity** and **clinical data** (if available).
    - Modifying factors:
      - F1 = A factor to account for extrapolation between species (default 5 for rats; for RfD factor 10 is used for rats);
      - F2 = A factor of 10 to account for variability between individuals;
      - F3 = A variable factor to account for toxicity studies of short-term exposure;
      - F4 = A factor that may be applied in cases of severe toxicity;
      - F5 = A variable factor that may be applied if the no-effect level was not established;
      - F6 = Extra factor is applied based on ADME data (ICH Q3D).

$$PDE = \frac{NO(A)EL \times Mass\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5 \times F6}$$

Adult: 50 kg (45 kg for vaccines)
Child: 10 kg (5 kg for vaccines)

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Toxicological evaluation & Endpoints

- **Calculate safety limits - alternatives**
  - **ADE: Acceptable Daily Exposure**
    (ISPE Risk-Mapp)
    - PoD = Point-of-Departure (NOAEL, LOAEL)
    - BW = Body Weight (kg)
    - AF_C = Composite Adjustment Factor
    - MF = Modifying Factor
    - PK = Pharmacokinetic Adjustment(s)
  - **HBEL: Health Based Exposure Limit**
    (ASTM E3219)
    - F_T = composite adjustment factor
    - PK-AF = Accumulation factor
    - α = Bioavailability for the route of exposure
  - Walsh et al., 2020.

$$\text{ADE (mg/day)} = \frac{\text{PoD} \times \text{BW}}{AF_C \times \text{MF} \times \text{PK}}$$

$$\text{HBEL} = \frac{\text{PoD} \times \text{BW}}{F_T * \text{PK-AF} * \alpha} = \text{mg/day}$$

Interspecies extrapolation (F1)
Interindividual variability; Intraspecies variability; Human variability (F2)
Exposure length AF; Subchronic to Chronic (F3)
Severity of effect; Severity (F4)
LOAEL-to-NOAEL extrapolation (F5)
Route of Exposure (F6)
…

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

Table of Contents

A. Toxicological evaluation & endpoints

B. Hazard evaluation methods

- Data available:
  - Literature search → PDE calculation
- No data available
  - PQRI & TTC limits …
  - Prediction methods
  - Experimental testing

C. Challenges in the toxicological evaluation of SVP E&L

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **Data available → Literature search → PDE calculation**
  - **Public Databases**

...

  - **Non-public databases**

...

  - **General literature search**

ScienceDirect

...

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **Literature search → PDE calculation**
  - **Human health classifications**
  - **Regulatory existing information:**
    - FDA Inactive Ingredient List
    - Generally Recognized as Safe (GRAS)
    - ADI, RfD, MRL … existing regulatory limits!
  - **Typical toxicity endpoints:**
    - (Acute toxicity)
    - Skin/Eye irritation
    - Skin/Respiratory sensitization
    - Genotoxicity (bacterial & mammalian gene mutation, chromosome aberration)
    - Carcinogenicity →
    - Repeated dose toxicity (subacute, subchronic, chronic) →
    - Reproductive & Developmental toxicity →
    - ADME (Absorption, Distribution, Metabolism, Excretion)
  - **Clinical studies/effects** (if applicable) →

Quality
Dose response
Mechanism of action

Critical effects?
NO(A)ELs?
PDE!

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **Literature search → PDE calculation: example '2,4-Di-*tert*-butylphenol'**

  First genotoxicity (mutagenicity), sensitization & irritation potential are evaluated; then PDE is derived.

Leachable	Species	Departure point	Assess-ment Factors *	Total factor	Systemic lifetime adult oral PDE	F6 factor **	Total factor	Systemic lifetime default IV PDE
2,4-Di-*tert*-butylphenol (CAS No. 96-76-4)	Rat	NOAEL 150 mg/kg (13-week oral one-generation reproductive toxicity study in rats)	F1=5, F2=10, F3=5, F4=10, F5=1	2500	3000 µg/day	2	5000	1500 µg/day

* F1 = A factor to account for extrapolation between species (default 5 for rats; for RfD factor 10 is used for rats);
F2 = A factor of 10 to account for variability between individuals;
F3 = A variable factor to account for toxicity studies of short-term exposure;
F4 = A factor that may be applied in cases of severe toxicity;
F5 = A variable factor that may be applied if the no-effect level was not established;

**F6 = Extra factor is applied based on ADME data.

Note: Further refinement may be needed depending on duration of application, or if new data become available.

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **No data available: PQRI limits (Paskiet et al., 2013; PQRI, 2020):**

Proposal	Class I No Genotox	Class II No Genotox	Class III Genotox M7
Threshold (µg/day)	~~50~~ If Systemic	5 If Irritant/Sensitizer	1.5 To **Identify**

- **Genotoxic/Carcinogenic TTC (ICH M7, 2017; PQRI, 2020):**

ICH M7 allows adjustment of acceptable daily intake for individual DNA-reactive impurities based on treatment duration

Duration of treatment	≤ 1 month	> 1-12 months	> 1-10 years	> 10 years to lifetime
Daily intake (µg/day)	120	20	10	1.5

While it is recognized that PQRI PODP has proposed higher qualification threshold levels for leachables, **the FDA recommends 5 µg/day** as the qualification threshold for non-genotoxic Leachables.

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **Safety thresholds and best demonstrated practices (PQRI, 2021):**
  - **SCT = 1.5 µg/day** can be used to calculate AET
  - **QT = 5 µg/day** can be used in absence of data, when no genotoxic or carcinogenicity potential
  - **Cramer classification could not be recommended at this time**.
- **Duration-Based Non-Mutagenic TTC relevant to Parenteral E&Ls (Masuda-Herrera et al., 2021)**
  - **ELSIE derived TTC values** (lower 5th percentiles) for organic, non-mutagenic E&L substances administered parenterally (488 E&L were analyzed; parenteral POD estimates from 252 compounds).

Duration of treatment	>10 years	>1-10 years	≤ 1 year
TTC (µg/day)	35	110	180

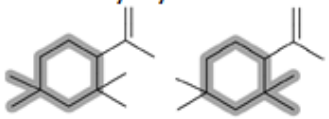
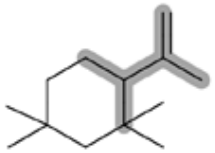
Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **Prediction methods: example '$C_{13}H_{24}$ Rubber oligomer'**

Rule Based (Q)SAR Model

Alert found	$C_{13}H_{24}$ Rubber oligomer (CAS No. 63251-38-7)
Mutagenicity in vitro in bacterium	INACTIVE No misclassified or unclassified features
Nephrotoxicity in human/mammal	EQUIVOCAL Alert matched: RapidPrototype065 1,1-Dimethylcyclohexane 
Skin Sensitisation in human/mammal	EQUIVOCAL Alert matched: 894 Tertiary allylic hydroperoxide precursor  Insufficient data to make EC_3 prediction Similarity: 16-47%

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **Prediction methods: example '$C_{13}H_{24}$ Rubber oligomer'**

Statistical Based QSAR

Endpoint	$C_{13}H_{24}$ Rubber oligomer (CAS No. 63251-38-7)	
Mutagenicity		
Prediction with Model: GT1_BMUT (Bacterial Mutagenicity by OECD 471 Test)	Negative	(positive probability = 6.5 %)
Konsolidator Report Bacterial Mutagenicity	Negative	
Irritation		
Prediction with Model: EYE_DRAIZE (Draize eye irritation test, rabbit)	Negative	(positive probability = 31.6%)
Prediction with Model: EYE_IRR (sensory irritation, mouse)	Inconclusive	(positive probability = 57.7 %)
Prediction with Model: SKIN_CORROSION (*in vivo* skin corrosion)	Negative	(positive probability = 38.8%)
...		

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **Experimental testing: some typical assays**
  - **Genotoxicity**
    - *In vitro* Ames test (Bacterial reverse mutation study)
  - **Sensitization**
    - *In vivo* LLNA or GPMT
    - *In vitro* battery covering 3 Key pathways
      - Key event 1 Peptide/protein binding
      - Key event 2 Keratinocyte response
      - Key event 3 Monocytic /Dendritic cell response
  - **Irritation**
    - *In vitro* models for skin irritation
    - *In vitro* models for eye irritation
  - **Repeated dose toxicity**
    - *In vivo* 14-90 days toxicity in appropriate species (ICH Q3B, 2006).

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

Table of Contents

Note: Examples given in current presentation are only meant for illustration, not as reference material for any regulatory documents. Although existing substances are used, any figures and calculations here applied are just fictive for current presentation.

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

C. Challenges in the toxicological evaluation of SVP E&L

1. Data-poor substances

- **Oligomers from plungers in syringes or rubber stoppers or on vials:**
  - Typically, **bromo-butyl or chloro-butyl rubbers** are used (Zdravkovic, 2019).
  - E&L consist of 2 compound classes: **rubber oligomers** (low molecular weight termination byproducts of the polymerization reaction) and the antioxidant **butylated hydroxytoluene** (BHT).
  - **Adducts** may form with the API.
- **Polymer materials containing several sources of E&L:**
  - Various chemicals are used during plastic manufacture, including **plastic monomers, catalysts, plasticizers, dyes, lubricants, slip agents and various stabilizers** (Bolgar et al. 2007; Olivieri et al. 2012; McKeen 2014).
  - Siliconization of barrel & plunger is often applied to become a ‘slippery inner surface’ (Sacha et al., 2010).

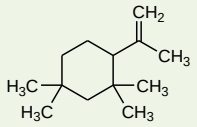
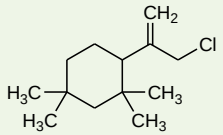
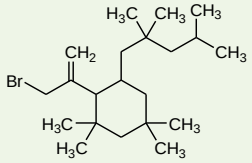
Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

C. Challenges in the toxicological evaluation of SVP E&L

- Example – Oligomers from plungers in syringes or stoppers on vials

  Dosing: 1 mL/d; long-term intramuscular application for a 50 kg patient

No.	Substance	ID	Structure	Formula	Max. Exp. [µg/day]*	PQRI limits [µg/day]	*Intial safety margins*
1	C13-Oligomer (C13H24)	CAS No. 63251-38-7		C13H24	225	PQRI: 1,5/5 ELSIE: 35/110/180 PDE: …	*0,02/ 0,07* … …
2	C13-Cl-Oligomer (C13H23Cl)	ToxID 1/2/3		C13H23Cl	25	PQRI: 1,5/5 ELSIE: 35/110/180 PDE: …	*0,06/0,2* … …
3	C21-Br-Oligomere (C21H39Br)	ToxID 47/48/49		C21H39Br	4,5	PQRI: 1,5/5 ELSIE: 35/110/180 PDE: …	*0,33/* … …

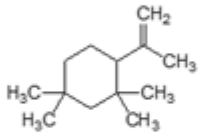
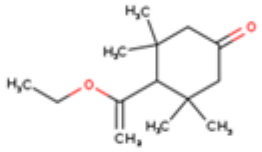
* Values based on extractable study (highest values, taking into account measurement uncertainty)

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

- **Read-across + justification: example '$C_{13}H_{24}$ Rubber oligomer'**

Substances	Non-halogenated Rubber Oligomers and source substance		
	Target	Source	
Molecular structure /weight **+** **Similarity to source substances**	**$C_{13}H_{24}$ Rubber oligomers = Cyclohexane, 1,1,5,5-tetramethyl-2-(1-methyl-ethenyl)- (CAS 63251-38-7)**  MW: 180.34	**…** **(CAS …)**  MW: 224.342 ChemIDplus (2020): 66.1458% vs $C_{13}H_{24}$ Rubber oligomer	
Physicoch.properties	EpiSuite v4.11:	EpiSuite v4.11:	Public Databases:
Water solubility	0.07507 mg/L (EST)	39 mg/L (EST)	51 mg/L (EXP ; study report, 2015)
Log P (octanol-water)	6.237 (EST)	3.422 (EST)	4.3 (EXP; study report, 1996)
Melting point			<-80°C (EXP; study report, 2015)
Boiling point			272°C (EXP; study report, 2015)

Read-across justification!

1. **Molecular comparability?**

2. **Physicochemical comparability?**

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

B. Hazard evaluation methods

LD50 values	EPA TEST: Rat LD50 oral Rat oral 7426 mg/kg (EST)	EPA TEST: Rat oral 3179mg/kg (EST) ChemIDplus (2020): Rat oral > 5000 mg/kg (EXP; Fragrance raw materials monographs, 1982) Rabbit skin > 5000 mg/kg (EXP; Fragrance raw materials monographs, 1982)	
Sensitization	Equivocal (Derek Nexus)	No indication for sensitisation (ECHA study reports, 2016, 1980, 1973). The *in vitro* DPRA and KeratinoSens assay were both negative (exp; ECHA).	
Genotoxicity & Carcinogennicity	No experimental data **Derek Nexus & CASE Ultra: not mutagenic**	Negative Ames, Micronucleus & Mammalian gene mutation (study reports, 2003; 2014; 2015). No evidence of carcinogenicity.	
Safety limits	No experimental data **PDE oral:** 97/(250x**2** for read-across= 500) = 0.194 mg/kg = 9.7 mg/day (for 50 kg body weight) Absorption oral: 50% **PDE IV = 4.85 mg/day = 4850 µg/day**	Based on combined repeated dose/reproductive toxicity (OECD 422; study report, 2016): NOAEL: 97 mg/kg bw/day **PDE oral:** 97/250 = 0.388 mg/kg = 19.4 mg/day (for 50 kg body weight) Absorption oral: 50% **PDE IV = 9.7 mg/day = 9700 µg/day**	**ICH Q3 (2016): assessment factors:** F1 = 5 interspecies factor rat to human F2 = 10 intraspecies factor F3 = 1 based on a subacute study versus single exposure F4 = 5 for absence of developmental tox F5 = 1 because based on NOAEL **Total= 250**

3. Toxicological comparability?

Mitigation or testing of sensitisation potential?

~ predicted 'potency' of target & results of source substance.

~ concentration of target substance.

4. Extrapolate safety limit?

Adapt PDE based on duration of testing?

~ Haber's rule: C x t = constant.

~ The dose rate/level matters.

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

D. Conclusions

- **Toxicological approach for SVP:**
  - **Analytics** of E&L Identity & quantity
  - **Exposure assessment** of individual substances or categories
  - **Hazard assessment:** combine toxicological tools to reach safety limits:
    - PQRI limits & TTC
    - Literature search
    - (Q)SAR predictions
    - *Read-across justification*

    Data-poor → data-rich substances
    Mitigation of sensitization potential
    Duration based adaptation (Haber's rule)
  - **Risk assessment:** assess local tolerance and systemic safety margins:
    - Conclude on human safety (any concerns left)?
    - If specific hazards are not covered, or safety margins are not sufficient, optimize approach:
      - improve toxicological tools
      - consider toxicological testing
      - further targeted analytical testing.

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

E. Glossary

- ADI: Acceptable Daily Intake
- ADE: Acceptable Daily Exposure
- ADME: Absorption, Distribution, Metabolism, Elimination
- AET: Analytical Evaluation Threshold
- ASTM: American Standard Method(s)
- BMDL: Benchmark Dose Level
- E&L: Extractables & Leachables
- ELSIE: Extractables and Leachables Safety Information Exchange
- EMA: European Medicines Agency
- EVM: European Vaccine Manufacturers
- EST: Estimated
- EXP: Experimental
- DP: Drug Product
- GMPT: Guinea Pig Maximization Test
- HBEL: Health Based Exposure Level
- HRIPT: (Human Repeat Insult Patch Test
- ICH: International Conference on Harmonisation
- ISPE: International Society for Pharmaceutical Engineering
- LO(A)EL: Lowest Observed (Adverse) Effect Level
- LLNA: Local Lymph Node Assay
- MDD: Maximal Daily Dose
- MRL: Maximum Residue Limit
- MST: Method Suitability Test
- NO(A)EL: No Observed (Adverse) Effect Level
- PDE: Permitted Daily Exposure
- PDP: Parenteral Drug Products
- PoD: Point of Departure
- RfD: Reference Dose
- SVP: Small Volume Parenterals
- TD50: Tumorigenic Dose in 50% of the animals
- TTC: Threshold of Toxicological Concern

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

F. References

- Bolgar M., Hubball J., Groeger J. and Meronek S. (2007) Handbook for the Chemical Analysis of Plastic and Polymer Additives, pp. 3–9. CRC Press, Boca Raton
- Broschard TH, Glowienke S, Bruen US, Nagao LM, Teasdale A, Stults CL, Li KL, Iciek LA, Erexson G, Martin EA, Ball DJ. Assessing safety of extractables from materials and leachables in pharmaceuticals and biologics - Current challenges and approaches. Regul Toxicol Pharmacol. 2016 Nov;81:201-211. doi: 10.1016/j.yrtph.2016.08.011. Epub 2016 Aug 26. PMID: 27569203..
- EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (EMA/CHMP/ CVMP/ SWP/169430/2014).
- EVM reflection paper on the Safety Assessment of Residuals and Contaminants in Vaccines.
- ICH M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Rsk. Current Step 4 version, dated 31 March 2017.
- ICH Q3B (R2) Impurities in New Drug Products. Current Step 4 version data 2 June 2006.
- ICH Q3C (R8) Harmonised Guideline on Impurities: Guideline for Residual Solvents. Final version Adopted on 22 April 2021.
- ICH Q3D (R1) Harmonised Guideline for Elemental Impurities. Final version Adopted on 22 March 2019.
- ISPE Baseline Guide Vol 7: Risk-Based Manufacture of Pharma Products 2nd Edition (2017).
- McKeen L. W. (2014) Plastics Used in Medical Devices, in Handbook of Polymer Applications in Medicine and Medical Devices (Modjarrad K. and Ebnesajjad S., eds), pp. 21–53. William Andrew Publishing, Oxford.
- Olivieri A., Degenhardt O. S., McDonald G. R., Narang D., Pau lsen I. M., Kozuska J. L. and Holt A. (2012) On the disruption of biochemical and biological assays by chemicals leaching from disposable laboratory plasticware. Can. J. Physiol. Pharmacol. 90, 697–703.

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company

F. References

- PQRI Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (IV, IM, SC). ISBN: 978-1-945584-30-5, 28 October 2021.
- Paskiet D, Jenke D, Ball D, et al. The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP). PDA J Pharm Sci and Tech, 67, 2013, 430-447.
- PQRI Parenteral and OpthalmicDrug Product Leachables and ExtractablesWorking Group Update 9 September 2020. Safety Thresholds and Best Demonstrated Practices for Extractablesand Leachablesin Parenteral Drug Products(Intravenous, Subcutaneous, and Intramuscular).
- Sacha GA, Saffell-Clemmer W, Abram K, Akers MJ. Practical fundamentals of glass, rubber, and plastic sterile packaging systems. Pharm Dev Technol. 2010 Jan-Feb;15(1):6-34. doi: 10.3109/10837450903511178. PMID: 20088708.
- Wang DM & Firor RL. Analysis of Extractable/Leachable Compounds From Plastic Intravenous Bag Sets Using GC/MSD Systems. Application Note, Agilent Tehcnologies. 2015.
- Walsch A, Altmann t, Bercu J, Canhoto A, Dolan DG., Flueckiger A., Gorsky I, Graham J, Lovsin Barle E, Mohammad O, Neverovitch, M and Shirokizawa O. Introduction To The ASTM E3219 Standard Guide For Derivation Of Health Based Exposure Limits (HBELs). Pharmaceutical Online, July 2020.
- Zdravkovic SA. Understanding Leaching from Stoppers into Lyophilized Drugs. BioPharm International Volume 32, No. 2, February 2019.

Nelson Labs® A Sotera Health company

Sterigenics® A Sotera Health company