Johnson & Johnson MEDTECH

Non-Volatile Residue Reconciliation – Expectations vs Reality

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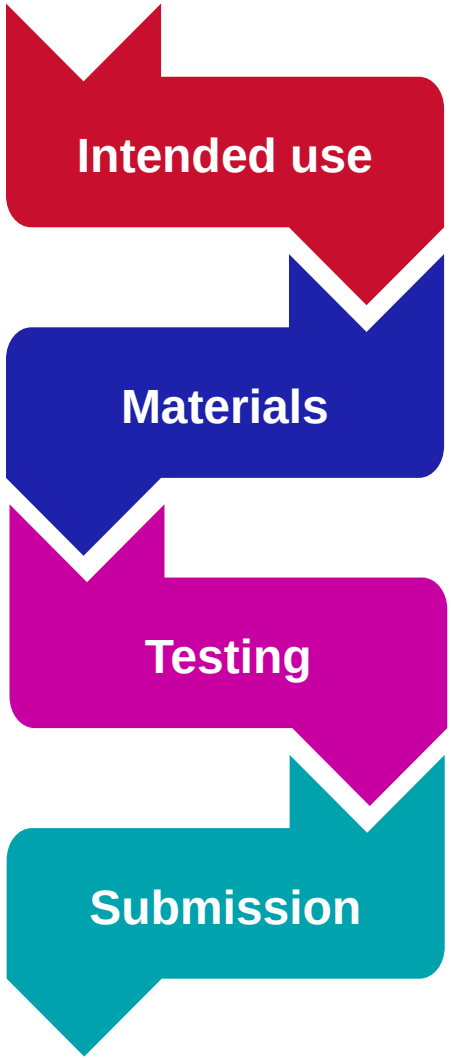
A case study of NVR reconciliation during a recent FDA submission.

Project Details



1. Long-term implantable orthopedic device for use in skeletally mature patients with 1 or 2 devices per patient.
2. Solid, metallic device conforming to ASTM F562 and passivated with nitric acid.
3. Chemical characterization was contracted to US CRO (Lab A) in October 2020, results available in May 2021.
4. US FDA 510(k) submission planned for July 2021.

Exhaustive Extraction Details

- Test articles were not subdivided.
- Extractions occurred in glass vessels.
- NVR measurements were performed through gravimetric analysis.

Extraction Vehicle	Article Amount (cm^2)	Volume of Vehicle (mL)	Extraction Conditions
Purified Water	109.8	270*	50ºC
Isopropanol	109.8	300*	50ºC
Hexane	109.8	520*	50ºC

* Due to the size and shape of the test article, in glass vessels a sufficient volume to cover the test article was used.

Non-Volatile Residue Results

- NVR results were not provided until the study was complete.

Timepoint	Purified Water	Isopropanol	Hexane
	(mg)	(mg)	(mg)
1	0.8	<0.1	0.2
2	1.2	0.2	<0.1
3	0.6	---	---
4	1.1	---	---
5	0.2	---	---
Total NVR	3.9	0.2	0.2

510(k) Submission preparation

- The high level of NVR was concerning, but no further testing could be performed on the residues as they no longer existed.
- The analytical data was assessed for toxicity and the TRA was created.
- Biological testing (*in vitro* and *in vivo*) was leveraged from a sister device comprised of the same materials.

FDA 510(k) Submission in July

Deficiency Questions Received in September

Initial FDA Deficiency Question

- A large mass of NVR (3.9 mg/device) was identified in the purified water extract as part of the assessment of exhaustive extraction. However, the analytical results from the purified water assessment identify only a small mass of identified compounds in the purified water extract. We are concerned that the differences between NVR gravimetric mass and the quantified results from analytical testing may demonstrate that the analytical analysis is not identifying all compounds or accurate quantities of compounds.

  Inaccurate measurement of extractables and leachables can impact the accuracy of the toxicological risk assessment. To ensure the chemical characterization represents worst-case exposure for the permanent implant to support biocompatibility of the subject device, please provide a comparison between the total mass of identified compounds from each of the analytical methods and the results from NVR analysis.

  Please provide a justification that any difference(s) in the masses will not impact the toxicological risk assessment for the subject device.

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Further Investigation by DePuy Synthes

- Explored the difference in NVR and analytical data.
- NVR in the purified water extract was 3.9 mg/device.
- Total amount of compounds identified through analytical testing was 0.095 mg/device.

Vehicle	NVR (mg/device)	GC-MS (mg/device)	UPLC-MS (mg/device)	ICP-MS (mg/device)	Total Analytical (mg/device)	Difference (mg/device)
Purified Water	3.9	0.00376	0.00314	0.08816	0.095	3.805
Isopropanol	0.2	0.021	0.02156	---	0.043	0.157
Hexane	0.2	0.18527	0.05578	---	0.241	-0.041

DePuy Synthes Response Written with Lab A

- The NVR results are obtained by evaporating the extraction vehicle at high temperature leaving only non-volatile compounds that likely contain many chemicals that are >1,500 Daltons (Da), for example, longer chain polymer fragments, machining fluids and detergents. Such species >1,500 Da would not be detectable by the analytical methods which are designed to look for toxicologically concerning compounds <1,500 Da. This concept is in accordance with ISO 10993-12:2012, Annex D, which indicates that exposure to low-molecular-weight chemical substances are the major toxicological chemical entities of concern. These chemical species >1,500 Da, however, would contribute to the NVR results.

- There is no analytical technique or combination of analytical techniques that is capable of the semi-quantitation or full quantification and identification of any and all organic and inorganic extractable chemical entities known to science. The use of solvents with varying polarities (polar, semi-polar and non-polar) along with exhaustive extraction techniques are used to determine possible extractable substances under aggressive conditions.

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Response Provided in November

Deficiency Questions Received in December

Second FDA Deficiency Question

- In response… you state that the NVR results likely include high molecular weight species (> 1500 Da) that cannot be detected by the performed analytical testing. You further state that the high molecular weight species could include polymer fragments, machining fluids, or detergents. However, it is concerning that a large quantity of residual manufacturing aids may remain on the subject device following passivation and cleaning.

  Furthermore, you have not demonstrated that the analytical testing supports a comprehensive toxicological risk assessment as <1 mg of compounds were quantified through analytical testing compared to 3.8 mg of NVR. In order to ensure that the residual NVR does not present a new biocompatibility risk and demonstrate that the biological testing performed is representative of the final, finished device, please provide additional testing to confirm the identity of the NVR not captured in the analytical testing and demonstrate that this does not present a biological risk for the final, finished subject device.

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Further Investigation by DePuy Synthes

- Cytotoxicity, Irritation, Sensitization, Acute Systemic Toxicity, and Pyrogenicity testing was performed.
- All manufacturing aids were reviewed for systemic toxicity, genotoxicity, and carcinogenicity risk in the TRA.
- Gel Permeation Chromatography / Size-Exclusion Chromatography (GPC/SEC) testing was performed to determine the molecular weight distribution.
  - 2 devices were extracted in Purified Water for 4 cycles and in Hexane for 1 cycle (50ºC for 72 hours) to create 2 samples of each extract.
  - No peaks were detected in the Purified Water samples.
  - One peak was detected in each of the Hexane samples with an average molecular weight of 1701 g/mol.

DePuy Synthes Response

- Provided the results of additional testing:
  - Biocompatibility testing - cytotoxicity, sensitization, intracutaneous reactivity, material mediated pyrogenicity, acute systemic toxicity, genotoxicity
  - Gel permeation chromatography (GPC) results of test article extracts in purified water and hexane
- Updated the TRA to included a review of risks due to potential manufacturing aid residuals.
- **Concluded:**
  - **“Using the weight of evidence approach, a review of the manufacturing aids, the TRA, and the additional biocompatibility testing show that the residual NVR does not present a new biocompatibility risk and is representative of the final, finished device.”**

Response Provided in March

Deficiency Questions Received in April

Third FDA Deficiency Question

- The NVR results for the purified water extract (3.9 mg) reported in the chemical characterization testing in your original submission are significantly higher than the total amount of compounds identified through analytical testing. While you provided a justification that the NVR results likely include high molecular weight species, the GPC-SEC data provided did not identify any high molecular weight species in the purified water extracts.
- Additionally, you have not provided any other data to support the potential identity of the NVR or justification to demonstrate that results of the analytical testing and other biocompatibility testing support a comprehensive toxicology risk assessment. Therefore, we are unable to determine that the analytical testing and toxicological risk assessment are sufficient to address the potential risk of subacute/subchronic/chronic toxicity.

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- Additionally, you have not provided any other data to support the potential identity of the NVR or justification to demonstrate that results of the analytical testing and other biocompatibility testing support a comprehensive toxicology risk assessment. Therefore, **we are unable to determine that the analytical testing and toxicological risk assessment are sufficient to address the potential risk of subacute/subchronic/chronic toxicity.**

Third FDA Deficiency Question

- Please **provide a justification that the performed testing supports the identity of the NVR** from the purified water extract **that was not captured in the analytical testing**.
- Additionally, please **provide a justification to demonstrate that the analytical testing results support a comprehensive toxicological risk assessment**.
- We recommend that your justification include **consideration of the potential manufacturing residuals** from the manufacturing and processing of the subject device.
- Please note, **if this risk cannot be mitigated through justification, additional information or testing may be needed to address subacute/subchronic/chronic toxicity** of the final, finished device**.**

Further Investigation by DePuy Synthes

- Additional NVR testing was performed to determine if the residue measured in the exhaustive extraction was representative of the final, finished device.

Lot Number	Test Cycle (50ºC)					Total NVR (mg)
	1	2	3	4	5	
GM59076	1.3	0.1	---	---	---	1.4
	<0.1	1.0	<0.1	---	---	1.0
	<0.1	<0.1	---	---	---	<0.1
GM59041	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
GM59077	<0.1	4.2	<0.1	---	---	4.2
	<0.1	<0.1	---	---	---	<0.1

Further Investigation by DePuy Synthes

- Samples were discarded immediately after weighing, no additional analysis was performed.

Lot Number	Test Cycle (50ºC)					Total NVR (mg)
	1	2	3	4	5	
GM59076	1.3	0.1	---	---	---	1.4
	<0.1	1.0	<0.1	---	---	1.0
	<0.1	<0.1	---	---	---	<0.1
GM59041	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
GM59077	<0.1	4.2	<0.1	---	---	4.2
	<0.1	<0.1	---	---	---	<0.1
GM57111	0.8	1.2	0.6	1.1	0.2	3.9

Further Investigation by DePuy Synthes

- Another round of NVR testing was performed at a different US Laboratory (Lab B).

Lot Number	Test Cycle (50ºC)					Total NVR (mg)
	1	2	3	4	5	
GM59041	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
GM59076	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
GM59077	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
GM59040	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
GM59110	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1

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	<0.1	<0.1	---	---	---	<0.1
GM59077	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
GM59040	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1
GM59110	<0.1	<0.1	---	---	---	<0.1
	<0.1	<0.1	---	---	---	<0.1

NVR from Lab A = <0.1 mg

NVR from Lab A = 4.2 mg

DePuy Synthes Response

- It can be considered that the results of the NVR testing shown are artifacts, and not indicative of the actual residuals that remain on the part after final cleaning and packaging, as cleaning validation studies have been performed on challenge devices that undergo the same cleaning process showing acceptable results.

- In conclusion, the analytical chemistry was analyzed for toxicological risks, and showed that there were no concerns toxicologically. Further, biocompatibility testing (cytotoxicity, sensitization, irritation, pyrogenicity, acute systemic toxicity, bacterial reverse mutation assay, and mouse lymphoma assay) were performed and all testing passed. The data generated from this testing points to the fact that the devices are biocompatible and have no risk of systemic or long-term toxicological issues.

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Response Provided in August

510(k) Approval Received in September

Lessons Learned…

1. NVR matters! Be prepared for the FDA to question discrepancies between NVR levels and analytical results.
2. Your laboratory partner is important and effective communication is needed.
3. The NVR results should be communicated when complete, not in the final report. Request that measurable residue is documented in photographs and run FTIR (if possible).
4. Some labs use chromatographic techniques for exhaustive extraction measurements, but it lengthens the TAT and increases the cost.
5. Additional NVR testing to show variations between lots may be an option to deal with NVR reconciliation.

Thank you


DePuy Synthes
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