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Risk Assessment of Leachables from a Drug Coated Balloon Catheter Combination Product

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INTRODUCTION

As part of a toxicological risk assessment (TRA), an extractables/leachables (E/L) analysis was conducted for a **drug coated balloon (DCB) catheter**, a medical device used to mechanically dilate an obstructed blood vessel concurrent with the release of a drug product which promotes an ancillary effect of reducing restenosis. The device has direct intravascular tissue and blood contact for the duration of the clinical procedure, which involves <10 minutes of balloon inflation. Since the drug component is absorbed onto the artery walls, the device is considered a permanent implant under ISO 10993-1.

COMBINATION PRODUCTS: GENERAL CONSIDERATIONS

Combination products (under 21 CFR Part 3) include any combination of a drug and device, and are covered by more than one FDA product center. Study design involves feedback/review from appropriate FDA agencies (CDRH, CDER, or CBER), with roles of each agency assigned by the Office of Combination Products. Jurisdiction is governed by the Primary Mode of Action, which is the therapeutic action that is expected to make the greatest contribution to the overall intended effect of the combination product.

It is important to involve toxicologists and chemists in study design and for consultation on FDA feedback for any combination product, as the objectives and requirements for drug product analysis must be integrated and harmonized with those for device analysis.

- Customized extraction methods may be needed for DCBs & other products
- Time profile data relating to the in vivo absorption of resorbable products is important to risk assessment
- FDA can require exhaustive extractions of drug-eluting devices
- FDA might require testing even for components having a brief period of patient contact

E/L testing of a combination product can be applied: (1) to evaluate leachables released from the device components, and (2) for detection of compounds to provide a measure of the stability of the drug product, excipients, and potential impurities and degradants.

ANALYTICAL APPROACH

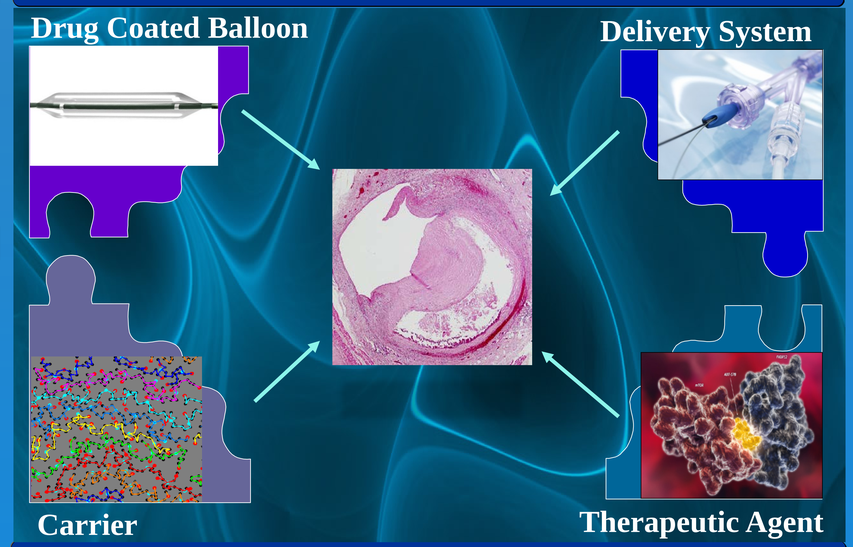
The drug coated and uncoated balloon were separated from the delivery catheter and extracted with polar, nonpolar, and amphipathic solvents, using water, hexane, and 50% isopropanol (50% IPA) to bracket the range of leaching behaviors possible under different conditions. Extractions were conducted following ISO 10993-12, using a surface area-to-solvent ratio of 6 cm^2 per 1 mL solution. All extractions were performed in triplicate.

Preliminary sequential extractions were conducted to determine the duration for a prolonged extraction to capture all of the analyte mass that could be leached from the device. Extractions were conducted for 72-hours at 50ºC, and followed by solvent removal and analysis for non-volatile residue (NVR). Fresh extraction solvent was added and a second sequential extraction was performed along with another NVR analysis. The process was repeated until extracted NVR had declined to a level <10% of the initial concentration (criteria specified by ISO 10993).

Extracts were analyzed for volatile organic compounds (VOCs) and semivolatile organic compounds (SVOCs) by GC/MS, non-volatile organic compounds (NVOCs) by LC/MS, and metallic elements by ICP.

Exhaustive extractions at 50ºC in 3 solvents provide key data for risk evaluation; however, such extractions are more aggressive than clinical conditions (37ºC, 5-10 minutes deployment, and contact with blood), and so might enhance drug product degradation.

COMPONENTS OF A DRUG COATED BALLOON SYSTEM



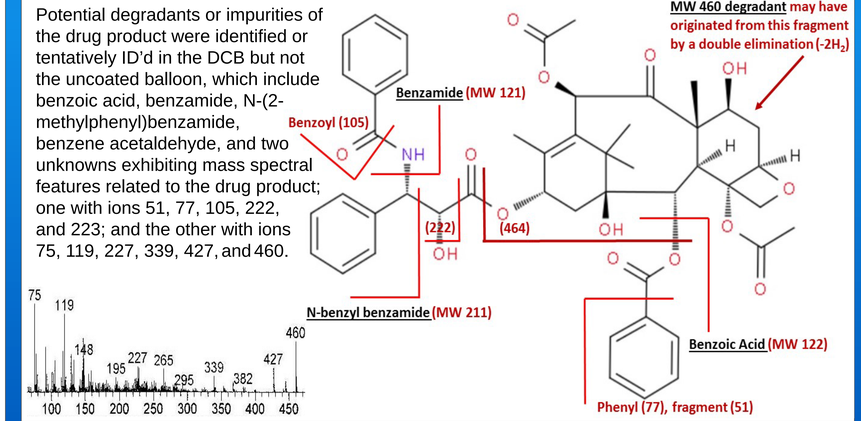
HISTORY OF DRUG ELUTING BALLOONS

Drug delivering balloons and drug eluting stents have been developed for various endovascular treatments, applicable to either coronary or peripheral vascular disease. There have been numerous clinical trials in the past decade involving a small group of drugs, which have demonstrated efficacy in preventing restenosis.

Drug delivering balloons, derived from the principles of drug coated stents, are a relatively new development in the field of balloon angioplasty. The basic principle of drug eluting balloons involves the local release of a drug to resist smooth muscle proliferation after dilatation of the artery. Currently, there are at least nine coronary DCBs that have CE Mark approval in Europe. FDA approved the first DCB to treat peripheral artery disease in 2014.

LEACHABLES RELATED TO DRUG PRODUCT

Potential degradants or impurities of the drug product were identified or tentatively ID'd in the DCB but not the uncoated balloon, which include benzoic acid, benzamide, N-(2-methylphenyl)benzamide, benzene acetaldehyde, and two unknowns exhibiting mass spectral features related to the drug product; one with ions 51, 77, 105, 222, and 223; and the other with ions 75, 119, 227, 339, 427, and 460.



TOXICITY THRESHOLDS USED TO ASSESS LEACHABLES

Three types of toxicity thresholds were used to evaluate the E/L data in the risk assessment:

- **Threshold of Toxicological Concern (TTC):** Used to evaluate unknowns or identified compounds lacking toxicity studies, and to screen data falling below a level of concern. A QSAR analysis identified alerts for mutagenicity (TTC = 120 µg/day), skin sensitization (TTC = 5 µg/day), or noncancer toxicity (Cramer Class 1, 2, 3 TTCs = 150, 50, 5 µg/day).
- **Tolerable Exposure (TE) level:** Allowable limits were derived for identified chemicals following ISO 10993-17, using NOAELs from subchronic/chronic animal studies, and applying uncertainty factors and bioavailability adjustments to estimate parenteral toxicity from oral data: TE = (NOAEL or LOAEL × % bioavail.) / ($UF_1 \times UF_2 \times UF_3$) × (body weight)
- **Qualification Threshold (QT):** Applied to substances that originate from a drug product or excipient (not present in uncoated balloon catheter). Based on ICH Q3B guidance for impurities and degradants in new drug products, the QT represents a fraction of the daily dose of the drug product. For drug products with a daily dose of >10 mg to 100 mg/day, the QT for one impurity is 0.5% or 200 µg total daily intake, whichever is lower.

RISK ASSESSMENT

Risk assessment was performed according to ISO 10993-17. It was assumed that patients could be exposed to a maximum of 50% of the amount of extractable compounds released by an exhaustive extraction at 50ºC over an extended duration (120 hours for water, 168 hrs. for 50% IPA, and 96 hrs. for hexane). In contrast, clinical use of the DCB is at 37ºC over 5-10 minutes during balloon inflation.

Estimated Exposures to Extractable Organics and Tolerable Exposure (TE) Levels.

Substance	Extract	Exposure (µg/day)	TE (µg/day)	Margin of Safety (MOS)
Uncoated Balloon Catheter				
Acacyclotridecan-2-one	PW	9.7	1,800	190
	50% IPA	85		21
	Hexane	19.9		90
Azacyclotridecen-2-one	PW	1.21	580	480
	50% IPA	22.3		26
	Hexane	12.6		46
Acacyclotridecan-2-one Dimer	50% IPA	93.5	580	6.2
Unknown – mol. formula C13H25NO	50% IPA	3.55	5+	1.4
Drug Coated Balloon Catheter				
Tetrahydrofuran	PW	27.5*	5,300	190
	50% IPA	31.1*		170
Benzoic Acid	PW	134*	175,000	1,300
	50% IPA	473*		370
Benzamide	PW	2.3*	70++	30
	50% IPA	5.75*		12
1,3-Diphenyl-2,3-epoxy-1-propanone	PW	3.91*	70++	18
	50% IPA	13.9*		5.0
Acacyclotridecan-2-one	PW	11.6	1,800	160
	50% IPA	86.5		21
	Hexane	16.3		110
Azacyclotridecen-2-one	PW	7.55	580	77
	50% IPA	23.9		24
	Hexane	11.7		50
Acacyclotridecan-2-one Dimer	50% IPA	93	580	6.2
Unknowns - Maximum of 3 results	PW	16*	70++	4.4
Unknowns - Maximum of 6 results	50% IPA	56.5*		1.2

* Analyte found only in drug coated balloon catheter (not in uncoated balloon catheter)
TE values are derived in Appendix I based on toxicity studies for each chemical.
\+ TE is based on SCT of 5 µg/day.
++ TE is based on Q3B impurity qualification threshold of 0.5% of drug product amount (70 µg).

CONCLUSIONS

Concentrations of extractable compounds from a DCB catheter were evaluated with respect to potential patient exposure, with the use of Tolerable Exposure (TE) levels and other toxicity-based thresholds. Risk estimates for all identified organic compounds yielded margins of safety greater than 1. TE values could not be derived for substances where toxicological data were unavailable. In such cases, margins of safety were shown to be acceptable based on comparison to a TTC, or a QT of 70 µg/day that is applicable to drug product impurities.