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Analyse du guide (draft) FDA « Chemical Analysis for Biocompatibility Assessment of Medical Devices » (Draft of September 20, 2024)

Note d'analyse Tech & Reg, Octobre 2024

La FDA vient de publier le Draft d'un nouveau guide[1] sur la caractérisation chimique pour l'évaluation biologique des dispositifs médicaux. Jusqu'à présent, les exigences de la FDA étaient formalisées officiellement par la reconnaissance de l'ISO 10993-18 (2020, A1 : 2022). Elles étaient aussi formalisées lors de pré-soumissions ou de demande d'informations complémentaires, mais il fallait pour cela avoir un dossier à soumettre. Ceux qui ont eu cette expérience ces derniers temps ont sans doute remarqué que les demandes écrites de la FDA étaient très précises et similaires d'un dossier à un autre. Il était donc attendu qu'un guide de la FDA soit publié sur le sujet.

Ce guide de la FDA a pour ambition « d'améliorer l'uniformité et la fiabilité des études de chimie analytique et sont fondées sur l'expérience de la FDA dans l'évaluation de ces études soumises dans le cadre des soumissions préalables à la mise sur le marché ». Il traite principalement des études de caractérisation des extractibles. Quiconque a déjà lancé de telles études dans différents laboratoires a déjà dû constater des écarts importants sur l'identification et la quantification des substances extractibles. La FDA a fait le même constat et l'a signalé lors des réunions du comité ISO TC194 dont je fais partie, qui travaille sur l'évaluation biologique des dispositifs médicaux. Ces écarts de résultats sont principalement dus à l'absence de directives précises dans l'ISO 10993-18 sur la manière de conduire les extractions et l'analyse des extraits. Les experts du comité ISO TC194 en sont conscients et travaillent actuellement à l'élaboration de deux documents : l'ISO/TS ISO 11967 « Ensuring Quality of Analytical Chemistry in Support of Biological Evaluation » et l'ISO/TS 25364 « Quantification of Medical Device Extractables and Leachables using Non-targeted Analysis (NTA) — Analytical Chemistry Matters Associated with ISO 10993-18 ». La FDA a pris les devants et n'a visiblement pas souhaité attendre la publication de ces documents ISO.

BioM ADVICE a analysé pour vous le guide de la FDA. Le moins que l'on puisse dire, c'est que le niveau des exigences est très élevé, à un tel point que l'on peut se demander quel laboratoire serait actuellement capable de les satisfaire. Ce guide doit être pris en compte dès que possible pour vos soumissions à la FDA, car dès sa publication il sera la référence pour les caractérisations chimiques des extractibles (à noter que les études d'extraction simulée ne sont pas traitées par ce guide et que la FDA conseille de passer par le process Q-submission pour obtenir le feedback de la FDA pour ce type d'étude). De plus, de nombreux points font d'ores et déjà partie des exigences de la FDA, qui s'ajoutent à celles des normes ISO reconnues. Les pages suivantes sont une check-list des principaux points spécifiques de ces exigences et vous permettront d'évaluer les gaps de vos études actuelles et de définir le design de vos futures études de caractérisation chimique pour le marché US. Cette check-list n'est qu'un extrait du guide de la FDA et il est recommandé de lire le document dans son intégralité pour bien comprendre les exigences de la FDA et leurs nuances.

NOTE : Cette *Note d'analyse Tech & Reg* sera mise à jour sur le site internet de BioM ADVICE après la publication du guide final.

[1] Disponible à l'adresse : https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chemical-analysis-biocompatibility-assessment-medical-devices

Aurélien BIGNON
Consultant

a.bignon@biom-advice.com

Sophie BIGNON
Consultant

s.bignon@biom-advice.com

BioM ADVICE
45A rue de Margnolles
Caluire et Cuire (69) - FRANCE
+33 (0)6 79 82 08 22
www.biom-advice.com

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Make standards and regulations your strength to conquer new markets

Check-list of the main tips derived from the FDA Guidance: « Chemical Analysis for Biocompatibility Assessment of Medical Devices » *(Draft of September 20, 2024)*

Type of medical device (§III)

☐ Consult ISO 11979-5, ISO 15798, and ISO 16672 for ophthalmic implants, device specific guidance on contact lenses, ISO 18562-3 and ISO 18562-4 for gas pathway devices, and ISO 217 7405 for dental materials.

☐ For absorbable/resorbable/degradable devices, combination products, devices that include animal tissues, or devices intended to change phase or other physical state (e.g., expansion) during use, additional considerations may apply and it is advised to use the Q-submission process to obtain FDA feedback regarding the study design.

Test article (§VIII.B)

☐ FDA is expected a statement that the test article is the **device/component in its final, finished form** (including sterilization and packaging, if applicable). Alternatively, an explanation for why the test article accurately represents the device/component in its final finished form.

☐ FDA recommends providing additional information describing that the test article represents the worst-case tissue exposure scenario:

- **Complete whole (not partial) device** (or multiple complete devices)
- Typically, the device with the **largest surface area should be used** because larger devices tend to contain greater quantities and/or numbers of extractables. In most cases, it is not considered worst-case to extract smaller devices and extrapolate based on the direct proportion of extraction surface area.
- **When applicable, the worst-case manufacturing process** should be applied (e.g., the device that undergoes the greatest number of sterilization and/or reprocessing cycles).

Test Article Processing Prior to Extraction (§IV.C)

☐ Test article preparation should **mimic the clinical preparation of the device prior to extraction**, if applicable, to account for physical transfer of chemicals onto the test article. For example, this may include contact of the test article with all delivery systems, accessories, and packaging materials and any other preparation or processing steps (e.g., rinsing procedure) per the device's instructions for use.

Test Article Extraction (§V)

☐ For long-term contact devices, a **semi-polar solvent** should be used in addition to polar and non-polar solvents.

☐ It is recommended to conduct extractions using a **sealed container with minimal dead space** (i.e., empty space above the solvent and test article) and temperature control, with **continuous mechanical agitation** during extraction.

☐ For each solvent, it is recommended that **extractions be performed in triplicate** and the analyses be conducted on each separate extraction, unless otherwise justified. Triplicate extraction may not be necessary if three or more devices need to be pooled for the extraction studies. For example, pooling may be warranted in some cases, such as for very small devices, to generate sufficient extract volume for subsequent chemical analyses. However, if there is other data (e.g., engineering data) that suggests potential unexpected variability across devices, pooling devices instead of conducting triplicate extractions may not be appropriate.

☐ When conducting replicate extractions, FDA recommends reporting the identity of the extractables and amounts from all replicates separately. Additionally, FDA recommends using the **highest amount for each extractable** from any replicate as a worst-case exposure estimate.

☐ **Extraction volumes** should be minimized and justified based on relevant published documents and/or the sensitivity needed for the chemical analysis and the subsequent TRA. For example, extraction ratios as described in ISO 10993-12 could be considered if the extraction is not overly dilute (i.e., the limit of quantification **(LOQ) is lower than the analytical evaluation threshold (AET)**). The test article should be completely covered by solvent.

☐ While **some swelling can be acceptable** if there is no device destruction, high levels of swelling/solvent uptake can cause a reduction in the accessible volume of extraction solvent. Compensating for solvent loss by adding more solvent after extraction is complete is not recommended as it could adversely impact the concentration of extractables. If replenishing the solvent, a justification should be provided.

☐ Extraction **should not cause destructive swelling** of the test article (e.g., severe swelling, particulate generation, degradation, and/or dissolution). […] However, if unintended destructive swelling occurs in an aqueous extraction solvent, the clinical implications should be considered. […] If destructive swelling occurs due to solvent effects, FDA recommends evaluating at least two additional alternative solvents that are representative of similar polarity (e.g., semi-polar) and varying chemical functionality (e.g., alcohols, esters) and providing photographic evidence of the solvent effects on the test article. For example, if alcohols are incompatible with your device, FDA recommends that solvents with different functional groups (e.g., butyl acetate, acetonitrile) be evaluated. Similarly, if hexane is incompatible with your device, FDA recommends longer-chain solvents (e.g., heptane, iso-octane) and cyclic solvents (e.g., cyclohexane) be evaluated. […] For devices with limited or prolonged contact, where use of two solvents (i.e., polar and non-polar) are recommended for extraction studies, occurrence of destructive swelling may be an appropriate justification for the use of a semi-polar solvent instead of the solvent (e.g., non-polar) that resulted in destructive swelling. (+§IX.A.3)

☐ The **temperature and duration of the extraction**, including the duration of extraction cycles if conducting an exhaustive extraction, should be provided and justified. Justifications should address how the conditions result in a worst-case exposure estimate. While the recommendations in ISO 10993-12 could be used as a starting point for choosing the temperature and time (e.g., 50 °C with 72-hour cycles), other recommendations in this guidance should also be considered when choosing the temperature and time. For example, for exaggerated extractions FDA recommends that **both the temperature and time exceed clinical use**.

☐ When conducting exhaustive extractions, FDA recommends that **all cycles have the same duration** and that the same extraction schedule (i.e., duration and number of cycles) be used when preparing extracts for all analyses (e.g., GC-MS, LC-MS, ICP-MS), unless justified. For example, when analyzing extracts using HS-GC-MS it might be appropriate to use **a different extraction schedule to avoid the loss of volatile organic compounds (VOCs)**.

☐ When **particulates are observed in test extracts**, FDA recommends characterization of the particulates to determine the likely source and chemical composition of the particulates, and whether tissue could be exposed to particulates from the final finished device.

☐ A justification should be provided to support that any **particulate removal steps** (e.g., filtration, centrifugation) do not alter the extractables profile. However, if particulates are thought to be precipitated extractables, re-dissolution is recommended prior to subsequent analysis. Additionally, particulates should be accounted for when determining the exhaustive endpoint (i.e., particulates may raise the apparent NVR mass in the initial extraction cycle, leading to an underestimate of the number of cycles needed to reach exhaustion).

☐ FDA recommends the use of **gravimetric NVR analysis to determine the endpoint of an exhaustive extraction**. NVR analysis provides an estimate of the amount of non-volatile and some semi-volatile extractables. Other approaches can be used to determine the exhaustive endpoint, if justified (e.g., use of device-specific guidances).

☐ If NVR analysis is used to demonstrate that exhaustion has been achieved (§IX.B):

- **use of replicate extractions for NVR** (e.g., triplicate), unless otherwise justified. It is recommended **drying the entire volume of an extraction** for NVR analysis.
- Use of extraction conditions (including temperature, time, solvent volume, and number of test articles) that **produce a measurable NVR amount during at least the first extraction cycle.** If the NVR amount from the first extraction cycle is not measurable, it may be challenging to demonstrate that exhaustion has been achieved, unless justified. For example, justifications could include that the materials of construction are expected to yield very low extractable amounts under the extraction conditions (e.g., some polymers in water).

- Use of a **balance with the capability to precisely measure NVR in the 10-100 µg range**.
- **Extractions should be conducted for exhaustive endpoint determination and for analytical testing in an identical manner** (i.e., use the same temperature, cycle duration and number, extraction solvent, extraction ratio, and number of test articles).

☐ **NVR expression:** in total mass for the sample (e.g., for extractions of multiple devices) and mass per device for each replicate for each extraction cycle (§XI.D)

☐ Per the FDA, it is not necessary to separately perform chemical analysis on the extract from each iteration of an **exhaustive extraction**. **Sequential extractions can be combined (i.e., pooled), and the total combined volume can be used for an AET calculation** (i.e., the B parameter) as described in ISO 10993-18, and chemical analysis.

☐ While both neat alcohol and alcohol-water mixtures (e.g., 50% isopropyl alcohol) could be considered "semi-polar" by definition, if using an alcohol as a semi-polar solvent for extractables studies, FDA recommends **neat alcohol be used** unless otherwise justified. **DMSO** and **Dichloromethane** may raise technical issues. (§IX.A.2)

☐ FDA recommends providing **information on physical appearance of extracts and test articles before and after extraction,** including photographs: color changes, increases in turbidity, particulates and test article integrity changes/destruction.

Extract processing (§X.A)

☐ There are various situations where sample processing (e.g., **solvent exchange, dilution, or concentration**) may be needed. FDA recommends that any extract processing methodologies are accompanied with method qualification and verification information, which generally involves a spike and recovery report. FDA recommends at least 5 reference standards be used to assess recovery. Additionally, FDA recommends including the reference standards used for semi-quantification in the set of reference standards used to assess recovery. Moreover, the concentration of the reference standards used to assess recovery should be justified. FDA recommends using concentrations near the middle of the linear range of the calibration curve. If **adequate recovery (e.g., 80-120%)** is not achieved, you should take steps to improve recovery.

AET (§XI.A)

☐ For a device that **contacts the tissue for 30 days or more, a DBT based on a 1.5 µg/day TTC** would be conservatively protective.

☐ FDA recommends describing the **approach used to calculate the UF** for each analytical method (e.g., GC-MS, LC-MS positive/negative modes) or extraction processing condition (e.g., dilution/concentration).

☐ A default **UF value for GC-FID and GC-MS as low as 4 can be used** without further justification. A UF value for LC-MS analysis can be much higher than for GC-MS due to greater RF variability. **A default UF value for LC-MS has not been established**, though methods describing how to calculate one are available. For example, the formula UF = 1/[1-(RSD)] can be used, where RSD is the relative standard deviation of RRFs of an RF database representing a wide range of chemical properties.

☐ If applicable, a justification should be provided to indicate **cohort of concern substances** are not expected to be present and that a TTC can be applied without targeted evaluation for excluded compounds. An example of a rationale is one that addresses the material suppliers and manufacturing process.

☐ **"AET" for elemental Analysis:** The LOQ for each analyzed element should be low enough to quantify that element at or below the relevant chemical-specific toxicological threshold. A toxicological threshold given in units of µg/day can be converted into concentration units to compare with the LOQ using a calculation analogous to the AET equation (Eq. 1). For example, threshold [µg/mL] = threshold [µg/day] × A/BCD, where A, B, C, and D have the same meaning as Eq. 1 (UF = 1 because ICP-MS is a targeted approach). (§XI.A.2)

Chemical Analysis (§VI)

☐ In general, FDA recommends profiling of extractables through a **non-targeted analysis** with subsequent use of targeted analysis to identify and quantify appropriate extractables, as necessary.

☐ FDA recommends **initiating the analysis as soon as is practically possible** after performing the extraction to avoid deterioration of the extracts **(e.g., within 24 hours).**

☐ **Similarity in NVR and total amounts determined by analytical methods** (e.g., GC, LC, ICP) should be checked, recognizing that these methods are not sensitive to the same analytes, so achieving 100% mass balance is not expected.

☐ FDA recommends providing sufficient information to describe the **analytical system operation, including instrument configurations and operating parameters.** (§XI.E)

☐ FDA recommends the use of **electrospray ionization (ESI) in both positive and negative modes as the primary LC-MS analysis technique.** (§X.B.2)

☐ **Additional detectors** (e.g., ultraviolet (UV), charged aerosol detector (CAD), evaporative light scattering detector (ELSD)) can complement MS to assist with detection of non-ionizable analytes.

☐ **Mass range** should allow for identification of low and high molecular weight analytes.

☐ **LC-MS mass accuracy and mass resolution** should meet the criteria detailed in (§X.E), considered achievable on most quadripole time-of-flight (qTOF), triple TOF, and Orbitrap instruments.

☐ The sensitivity of the analysis methods **(i.e., limit of detection (LOD), and limit of quantification (LOQ))** should be established. The **LOQ for each reference standard should be lower than the reporting threshold (e.g., AET).** FDA recommends that you support the LOQ determination by providing experimental evidence, including the calibration curves and calibration chromatograms of the reference standards used and the blank control, and the analysis of a suitable number of samples prepared near the LOQ for each analytical method. (§X.D.7)

☐ FDA recommends determining the chemical identity of extractables above the reporting threshold (e.g., AET) and the **confidence of each identification (i.e., unknown, tentative, confident, confirmed).** Confident and confirmed identifications are recommended for TRA, unless otherwise justified. FDA recommends reporting of all plausible candidate identifications when multiple candidate identifications are found, unless otherwise justified (§X.E).

☐ **Identification approach should be described**: see (§X.E) for details.

☐ FDA recommends **at least 3 surrogate reference standards for direct injection GC-MS** and **at least 5 for LC-MS**. If the 5 surrogate reference standards used for LC-MS do not ionize in both positive and negative modes, additional surrogate reference standards are recommended so that there are at least 5 that ionize in each polarity mode to address possible differences in RFs. (§X.C)

☐ FDA recommends **a description of the calibration method** be provided in your test report. For details, refer to (§X.D.6).

☐ FDA recommends including in your submission, a **description of the semi-quantification method** used and information to demonstrate that the method does not result in underestimation of the concentration of analytes. We also recommend describing how specific reference standards and their RFs were used for semi-quantification of specific analytes. For example, information to support the semi-quantification method used may be based on one or more of the following (§X.D.8):

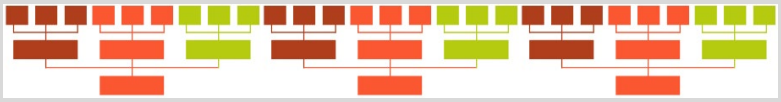
- nearest RT
- similarity in chemistry between the analyte and the surrogate reference standard
- worst-case (i.e., minimum) RF
- an RF database based on prior analysis of a reference standard (i.e., RRF approach)

☐ For each solvent, identified and quantified/semi-quantified **extractables above the AET should be tabulated, including:**

- RT
- chemical name (e.g., International Union of Pure and Applied Chemistry (IUPAC) name)
- Chemical Abstracts Service Registry Number (CASRN), when available
- structural descriptor (e.g., international chemical identifier (InChI), simplified molecular-input line-entry system (SMILES)) or image of chemical/compound molecular structure, particularly if a CASRN is not available
- major ions observed (m/z)
- type(s) of data used to establish analyte identity (e.g., library match, RT, manual spectral interpretation)
- identification confidence level (i.e., unknown, tentative, confident, or confirmed)
- amount in units of µg/device
- quantification method and reference standard
- extraction iteration (if not all extracts are pooled for analysis)

BioM ADVICE peut vous aider à réaliser les différentes étapes de la démarche d'évaluation biologique

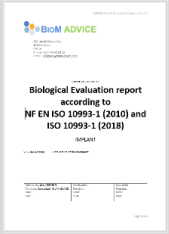
- ✓ **Analyse de votre process, définition des familles de produits et de leurs produits représentatifs**



- ✓ **Mise en relation avec les laboratoires de caractérisation chimique, calcul d'AET et vérification des protocoles des laboratoires**

- ✓ **Interprétation des résultats d'analyse chimique (TRA) selon l'ISO 10993-17**

- ✓ **Établissement du dossier d'évaluation biologique (BER) selon l'ISO 10993-1**



- ✓ **Formation à l'évaluation biologique**

Abonnez-vous aux notes d'analyse Tech & Reg
https://www.biom-advice.com/documents-à-télécharger/