# A summary of testing requirement complexities and solutions for smoke flavourings reauthorisations: EFSA's *ad hoc* meeting with industry representatives

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# Introduction - About EFFA

The voice of flavour in Europe, leading a Europe-wide strategy to the benefit of the flavour industry, its customers and consumers alike.

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National Associations with a membership of over 300 SMEs

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Company members - Flavour houses

Firmenich

Givaudan

iff

KERRY

MANE

McCormick

ROBERTET

SENSIENT

Silesia

TAKASAGO

symrise

# European Flavour Sector

**10.000**
industry workers

**30%**
of the global share

**2500+**
flavouring substances included in the EU UL

**€ 3.5 B**
turnover

**1/3**
of products are flavoured

**10%**
Invested in R&D+i

# EFFA Smoke Flavouring Primary Product Task Force

## EFFA authorisation holders & users

- **Kerry:** Stefano F. Liparoto (chair), Mike Gilligan, Zeynep Ilkbahar
- **Symrise**: Gerhard Krammer, Ute Woelke, Melanie Behringer
- **Azelis**: Rachel Serafin, Lotte Kristiansen
- **Profagus**: Benjamin Voss
- **Nactis:** Vincent Ferrari

## EFFA users (non-authorisation holders)

- **Givaudan**: Severin Müller, Nita Nana, Eduardo Moraes
- **Firmenich**: Charlotte Hernandez, Viviane Vijverman
- **Silesia**: Anja Kirstgen
- **Bell-EU**: Nicole Albrecht

# Here's what we would like to discuss today.

## Smoke Flavouring authorisation holders are committed to conducting safety studies necessary to keep consumers safe and fulfill regulatory requirements.

- The EFSA Scientific Guidance on Smoke Flavours doesn't account for time to conduct necessary preferred or alternative testing.
  - Testing design as described is not commercially available at CROs.
    - Academically feasible and scientifically understood, however not OECD GLP nor validated for regulatory submissions.
  - Fit-for-purpose study options
    - What does the preferred OECD 443 address?
    - What does alternative OECD 408 + additional endpoints (ImTx) address?
    - How do we address concerns of data gaps and the potential introduction of additional uncertainty factors?

# Smoke flavouring usages in different food categories; there are 2 primary types of usages smoke flavour products

Smoking process

(atomized, regenerated smoke)

Meat/fish/dairy industry
Smoked products

**Consumer/supermarket**

As an ingredients e.g, plant-based, soups/broths, sauces, savoury snacks

Flavour industry

Food industry

Consumer/ supermarket

# Current Situation of Smoke Flavour Primary Products

- Smoke flavourings are permitted in accordance with **Regulation (EU) No 2065/2003** and Implementing Regulation **1321/2013.** In EU & UK, smoke flavourings (SF) are authorised for a period of 10 years and all **existing authorisations** are scheduled to **expire in January 2024**.

- "…**smoke flavourings are produced from smoke** which is subjected to fractionation and purification processes, the use of smoke flavourings is generally considered **to be of less health concern** than the traditional smoking process." **Regulation (EU) No 2065/2003**

- Smoke Flavours reauthorisations are subject to **new tests and processes** for submission **by June 2022** based upon "Scientific Guidance for the preparation of applications on smoke flavouring primary products" ("EFSA SG") **issued March 2021.**

- Smoke flavourings are used in applications such as **compounded flavours** & uniquely in the **smoking process** by atomization of SF's Regulation (EU) No 1321/2013. **There are no technical replacements.**

# Current Complications Associated with Reapplications

- The 2021 EFSA SG and the Transparency Regulation EC (No) 2019/1381 have created an **impossible timeframe** for application submission of **June 2022.**

- The EFSA SG states on pages 15, 18, and 19 describes e.g, a **preferred study**, "since the performance of an [Extended One Generation Reproductive Toxicity Study according to OECD standards] may **require a time span of approximately two years, for renewal applications**, it is considered **not feasible** to finalise and assess such a study within the **foreseen current legal deadline."**

- The ***alternative*** that has been proposed in the EFSA SG, an **enhanced OECD 408 is not commercially available** (OECD GLP, internationally validated or GLP per global CROs). Many **immunotoxicology** endpoints are **not commercially available.** The *alternative* OECD 408 study design does not address the same toxicologic endpoints as the EFSA *preferred* OECD 443.

- The EFSA exposure assessment tool to be implemented in the applications and risk assessment has not been published.

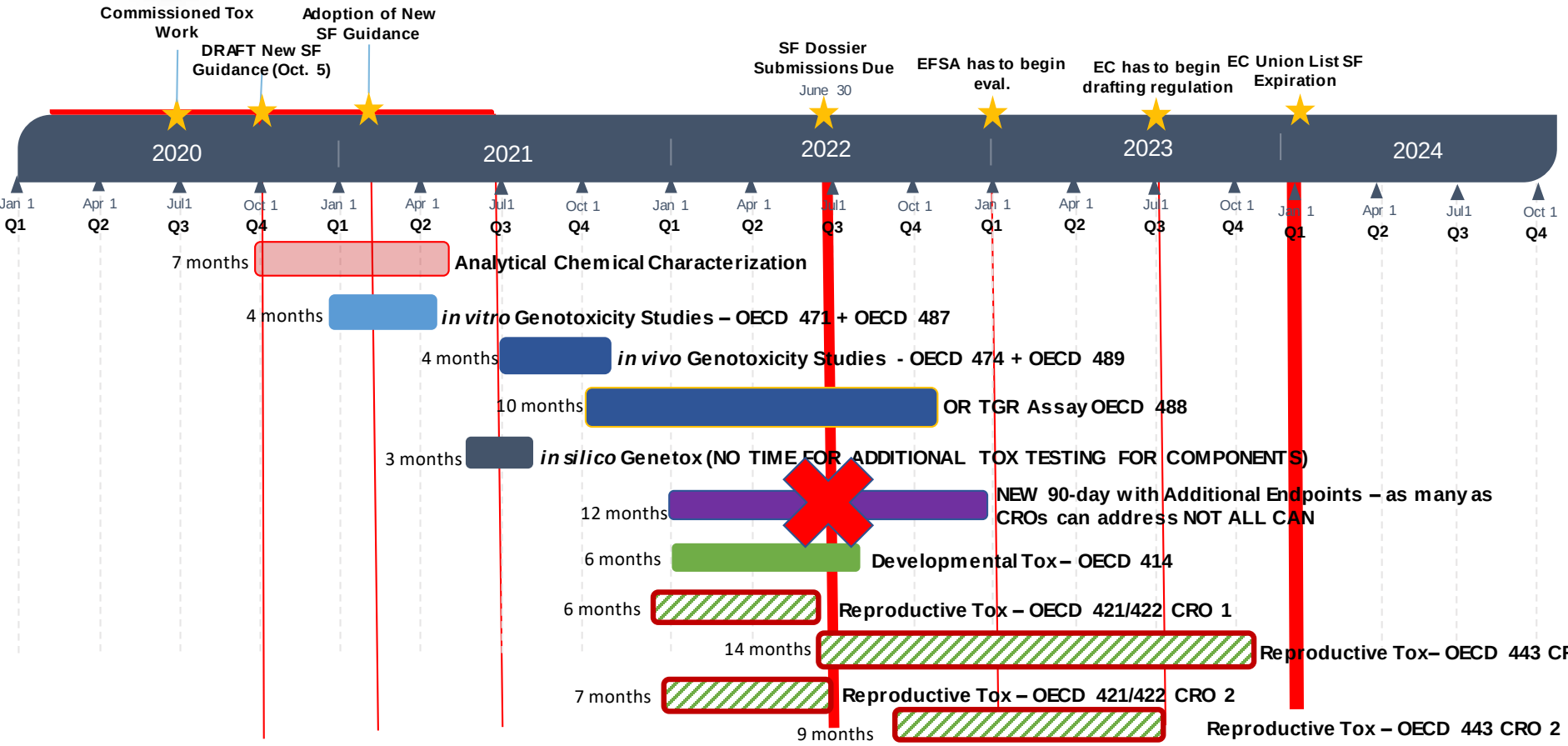
# EFSA-related Primary Questions

- Since **preferred** toxicology studies i.e. **EOGRT** nor the **alternative OECD 408 + Imtx**, can be conducted by the deadline, will EFSA consider a dossier valid without these studies? How will uncertainty factors be applied to SF reapplications submitted lacking the pivotal safety studies?

- Since the **EFSA SG preferred** study is the **OECD 443,** will uncertainty factors be applied to the **alternative customized OECD 408** since the **different** data packages address different **toxicological endpoints**?

- Considering the largest, global CRO's have pragmatic **study start constraints** and no one can complete the alternative OECD 408 in the manner requested, what are the **most fit-for-use** endpoints an applicant should seek knowing applicants **can't complete an application on time** (OECD 443), or as requested (OECD 408 + Imtx )?

# Generalized overview of OECD GLP toxicology testing for 1 SF PP application

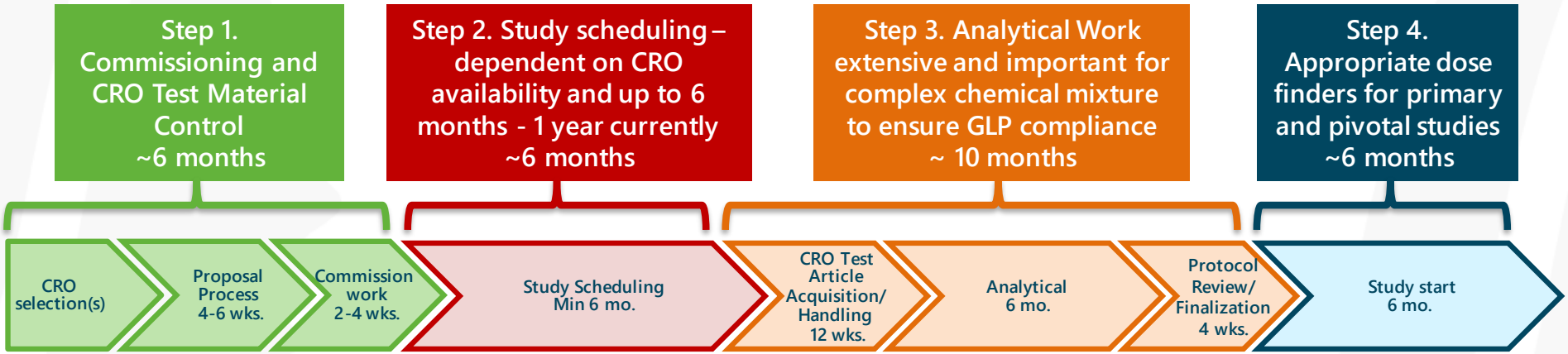



*Schedule for TGR, 90-day and repro studies reflect general timing provided by 2 large global CROs; would need to assume 2 months delay in between the start of another SF product at the lab – IF all 10 SF's went through this process at these 2 CRO's not ALL SFs would even be complete before expiratory

The TGR assay is not necessary, but is accounted for in the timeline in case an applicant must run this assay as a follow-up to an *in vitro* assay

The *in vivo* genetox. bar represents both a comet and/or micronucleus assay

# Timing / Complexities to Commission and Start a study with a CRO



# Timing / Complexities to Commission and Start a study with a CRO

## Key takeaways

- The process to commission a new study with a CRO is strategic **complex and time-consuming.**
- Defining **analytical work is extensive,** in particular for complex chemical mixtures.
- If studies need to be conducted at multiple CRO locations, assays need to be transferred and revalidated.
- Scheduling the restricted and more complex assays is currently **subject to significant delay.**

# For certain requested endpoints, Imtox Assays do not currently exist

| OECD GLP immunotoxicology capability gaps of the largest, global CRO's compared to the EFSA SG (2021) | | | |
|---|---|---|---|
| Imtox Assay/Endpoint: | CRO 1 Capabilities | CRO 2 Capabilities | CRO 3 Capabilities |
| Histopathology of bone marrow cellularity | | | |
| *Histopathology of lymphatic organs** | | | |
| Immunoglobulin isotopes in blood | | | |
| Total serum haemolytic activity | | | |
| C-reactive protein (CRP) | | | |
| Phenotypic analysis of CD4 cells in spleen | | | |
| *Total white blood cell count** | | | |
| *Differential white blood cell count** | | | |
| Phenotypic analysis of CD8 cells in spleen | | | |
| Phenotypic analysis of T reg cells in spleen | | | |
| Phenotypic analysis of B cells in spleen | | | |
| Phenotypic analysis of natural killer (NK) cells in spleen | | | |
| Phenotypic analysis of macrophages | | | |
| Functional analysis of natural killer cells in spleen | | | |
| Phagocytic activity in the spleen | | | |
| Mitogen simulation assays for B and T cells in the spleen | | | |

- Underlined, italicized* endpoints are standard endpoints within an OECD 408
- GREEN – indicates that the CRO has the availability to address these endpoints as stated (i.e., relevant species from OECD 408 outline) in EFSA guidance

  RED – Indicates the CRO does not have endpoint validated in the proper species or doesn't possess or intend to possess the capabilities

# For specifically requested immunotoxicology endpoints, assays do not currently exist

## Key takeaways

- Specific **functional assays** or assays conducted on freshly isolated tissues or matrices are **not currently feasible** in the alternate OECD 408 study design. While Burleson et al and other primary publications cite the assays, they are not offered in a GLP, nor OECD context.

- The **largest, global CRO's** queried that represent **~90% or more of GLP** work conducted **can not address** the requests.

# DART Data Requirement Comparison

| Endpoint | EFSA Preferred (443) | EFSA ALT. (408+; 414) | CR0 Proposed (408 with DART; 414?) |
|---|---|---|---|
| All DART screen endpts (421) | • | X | • |
| 70-day Male exposure (full spermatogenic cycle) (not fertility) | • | • | • |
| Spermatogenesis/sperm measures | • | • | • |
| Female estrous cyclicity | • | (optional) | • |
| Female fertility | • | X | • |
| Postnatal Development to weaning | • | X | • |
| F1 AGD, Nipple retention | • | AGD in fetuses | • |
| Dam dosing to weaning | • | X | • |
| Terminal necropsy of P0 | • | X | • |
| F1 cohort repro hormones (EAT) | •young adult | X | ~(pnd 4, 21) |
| F1 male sperm parameters | • | X | X |
| F1 cohort neurotox | • | X | ~ (pnd 21?) |
| F1 cohort immunotox | • | X | ~ (pnd 21?) |
| F1 Sexual maturation | • | X | X |
| Effects on implantation | • | X | • |
| Animal Numbers | 1400 | 1224 | 1784 |
| Study Start | Oct 2022* | Not Feasible | Jan. 2022 |
| Study Duration (not including reporting) | 9 months | 7 months | 7 months |
| Complete for June 2022 Deadline | No | No | No |

• Indicates included in study
X Indicates not included in study
GREEN – Included in protocol
AMBER – Partially covered in protocol
RED – Not included in protocol
*Study start is precluded by dose-range finder which can take up to 7 months

# Pivotal DART-related assays

## Key takeaways

- **None** of the studies described **can be completed by June 2022.**

  ***Scheduling and capacity are limiting*** *in the preferred OECD 443, the alternative is not a commercially viable option as attested by CRO's*

- **Alternatives** fall significantly **short** of the **preferred OECD 443 data**.

- **Animal use numbers** may vary but are generally substantial. If the OECD 443 will ultimately be the standard, running alternatives + the preferred will consume large animal numbers.

# Conclusions and proposed solution(s)

- EFFA SF authorisation holders are **committed** to submit the most fit-for-use, robust study data given the **necessary time** and **commercial availability**.
- EFSA's *preferred* study (i.e. OECD 443) **has significant complexity** with regards to **study placement capabilities** and **study start.**
- The alternative proposal (i.e. OECD 408 + ImTx) by EFSA is **not available** commercially**.**
- Therefore, completion as per the EFSA SG is **not possible by the deadline** of June 2022. Since the **deadline cannot be met**, a continuance of authorisation is sought while studies are notified and conducted.
- The 2013 Union List of Smoke Flavours were approved ***with Restrictions***

  *The **restrictions** could be interpreted to permit the reAuthorisations with conditions, ie study notifications via the Transparancy legislation etc.*

# Appendices and Premeeting submission Questions

# Summary of Pre-Submission Questions

1. The exposure tool is not yet available as previously suggested, by June 2021. What is status of the tool?

    a. Will EFSA please clarify which exposure estimate will be used to calculate the initial MOS (e.g., the highest 95th percentile estimated from all applicable surveys for the age group with the highest exposure)? The guidance states that the risk assessment will be based on dietary exposure estimates for high consumers (95th percentile) across relevant population groups and countries and that EFSA will refine the exposure estimates if the MOS is insufficient.

    b. Will EFSA please outline the prioritization of refinements that will be done to the exposure assessment? The guidance identifies three possible refinements to the dietary exposure assessment based on maximum use levels: typical use levels, market share (GNPD) data, and facets in FoodEx2 nomenclature.

2. Previously Smoke Flavouring PP's were regulated at a MOS of 300 because of the absence of specific toxicology data that is being requested now. Could you explain how additional uncertainty factors due to different toxicological data especially regarding immunotoxicological endpoints will affect the MOS.

3. What will occur on June 2022 knowing that neither the preferred OECD 443 nor the OECD 408 with additional immunologic endpoints will be feasible?

    a. Will EFSA apply uncertainty factors accounting for the absent data, provide an opinion to the commission, nullify the application or other outcome? As stated in the EFSA SG, there is not the necessary time to request additional data.

    b. Could EFSA accept an application as complete, when intended studies cannot be finished, due to the legal deadline for renewal applications (June 22) and the resulting timeline constraints? Missing information could be uploaded to the e-submission system as soon the remaining / intended studies are finished and reports finalised.

    c. If the applicant submits as much data as time allows, and notifies the additional studies under the Transparency Regulation requirements including co-notification by the laboratories, will the submission be considered valid?

# Summary of Pre-Submission Questions *cont'd*

4. Several CRO's and consultants are proposing various studies as alternatives in a manner consistent to an open comment period to the EFSA SG and it has been suggested that an alternative to the EFSA SG alternative is being proposed.

    a. How will EFSA consider these additional options for implementation considering there is less than one year to conduct the studies?

    b. If EFSA is in fact willing to consider other options, by what mechanism will adoption of alternatives be codified into the Scientific Guidance document such that applicants are not proceeding at risk against the guidance of the EFSA SG?

5. As part of the Transparency Regulation (Regulation (EU) No 2019/1381), applicants must submit list of all intended studies for renewal according to Article 32c1 prior to commissioning studies. Due to the current time constraints, SF applicants need to notify and commission studies immediately raising concerns that study start dates will be impacted and delayed if they follow the notification process for renewals which could take up to 5 months to notify.

    a. Can SF applicants simultaneously submit list of intended studies (32c1) and notify these studies under Article 32b (for NEW applications) to ensure promptness in study commissioning?

    b. The Transparency Regulation only applies to EU-based laboratories, but are UK-based, non-EU CROs under the oversight of the Transparency Regulation and require co-notification?

# Summary of Pre-Submission Questions *cont'd*

6. EFSA has stated in the recent May FAF meeting minutes that the additional immunotoxicology endpoints in alternatives study design were added to allow a full investigation of the potential effects on the immune system. However, the OECD 443 doesn't perform this extensive immunotoxicology assessment and the alternative 408 + immunotoxicology endpoints excludes the assessment that would be generated in the OECD 443 (developmental immunotoxicology).

    a. As an applicant and toxicologist, we have concerns on allowing a lack of historical control data (e.g., validated endpoints) for certain immunotoxicology endpoints subject to interpretation and relying solely on concurrent controls of unvalidated, non-GLP methods. While the endpoints requested by EFSA have been in academic use, they have not been implemented in standard regulatory toxicology submissions and are not available among queried CRO's that represent ca 90% of the global GLP capacity. Historical data is vital to interpretation of endpoints and an appreciation of treatment related effect(s) or within the range of stressors. Magnitudes of changes in relation to effects would also not be readily available.

    b. Applicants have contacted Burelson labs that have been cited by EFSA to determine capabilities to perform suggested assays (e.g., alternative OECD 408 + immunotox parameters) as stated in the final guidance and they could not address them as requested by EFSA. While Burelson and other laboratories have the capabilities to do an alternate 28-day immunotox study to include all additional immunotox endpoints indicated by EFSA they do NOT have the capabilities to perform them in a 90-day study. Alternatively, an ICH S8 Immunotoxicolgy study could be considered by an applicant but this does not address developmental immunotoxicology.