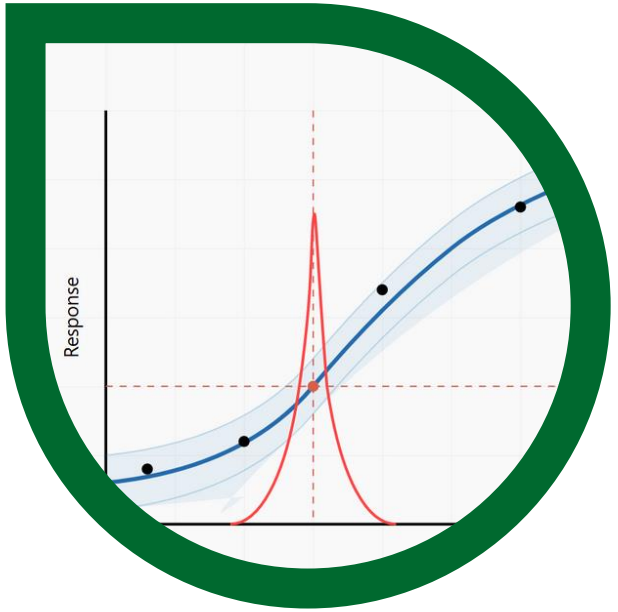
Regulatory Hurdles

Manousos Foudoulakis

(on behalf of the CLE Terr Vert expert team)

Navigating B&M Dossier Development in Varying Regulatory Environments



EFSA BMD Tool Updates and Their Impact on Regulatory Submissions

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BMD challenges overview

Accurate BMD estimation is crucial for:

- Setting EU-agreed B&M toxicity endpoints for Tier I risk assessment
- Developing higher-tier strategies for Birds and Mammals risk assessment
- Finalizing the GAP

BMD is acknowledged that:

- Provides a more precise estimate of dose-response relationships
- Sound method for endpoint derivation, when scientifically applicable and properly performed
- Significant resource investment and technical expertise needed

Process-wise, the implementation of the BMD method will likely involve:

- EU process: Re-evaluation of all active substances through RMS evaluation and EFSA peer-review
- Zonal process: Extending this approach to zonal submissions as well

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Navigating B&M Dossier Development in Varying Regulatory Environments

New EFSA B&M guidance can be used in regulatory process for decision making.
Is this true?

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Current Regulatory Environment

What is the current PPP regulatory environment for both EU and zonal submissions? How clear is the process for BMD evaluation?

Workflow B&M data Development

Regulatory steps industry undertakes to generate B&M data for an EU submission, and how BMD calculation integrates into this process

Case Scenario

Submission Case and Challenges Identified

Policy Gaps and Key Takeaways

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- **Current Regulatory Environment**:
- New EFSA GD 2023 enforced for A.I. and product submission after 1st Oct 2025
- New GD adoption varies due to:
  - National interpretations of EU regulations
  - EU court decisions
  - Resources and expertise concerns

- There are three options of implementing the new GD
  - Full Implementation: MS require compliance with the new GD
  - Partial Implementation: MS selectively apply certain aspects or National interpretations of EU regulations
  - No Implementation: MS still follow older guidelines

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- **EU submissions**
- As BMD is part of the tier 1 risk assessment, it has a substantial impact if confirmed late in the process
  - Late confirmation can hinder the applicant's ability to generate the necessary data, as it may be unclear how many scenarios will fail and to what extent

- For future submission, currently, there is a lack of technical-level pre-submission engagement with the RMS for the BMD process

- For previous AIR submissions, both completed and ongoing, there is no clear proposal or process for how the BMD will be developed

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- **Product submission**
- Agreed LoEP is necessary, currently used EU agreed NOEC values for Tier 1 RA

- Although BMD values are considered active substance endpoints, they have not been previously confirmed in an AIR process

- **Changes of endpoint should follow RMS evaluation + EFSA peer-review according + confirmatory data to the current EU GD SANCO/10328/2004 (rev.9 of 21.10.2021) for all actives. New data evaluations should be conducted post (renewal of) approval of the active substance**

- ***Impact management needed:***
- Potential delays in approvals
- Need for increased resources to generate data tailored to different requirements
- Addressing the risk of rejection of the approval due to procedural challenges and communication gaps

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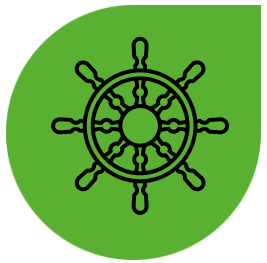

- **Workflow for B&M data Development in Industry**

- *What regulatory steps does industry undertake to generate B&M data for an EU submission, and how is BMD calculation integrated into this process?*

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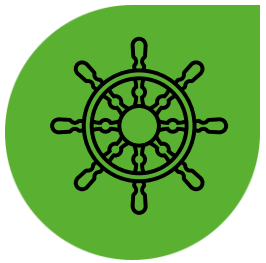
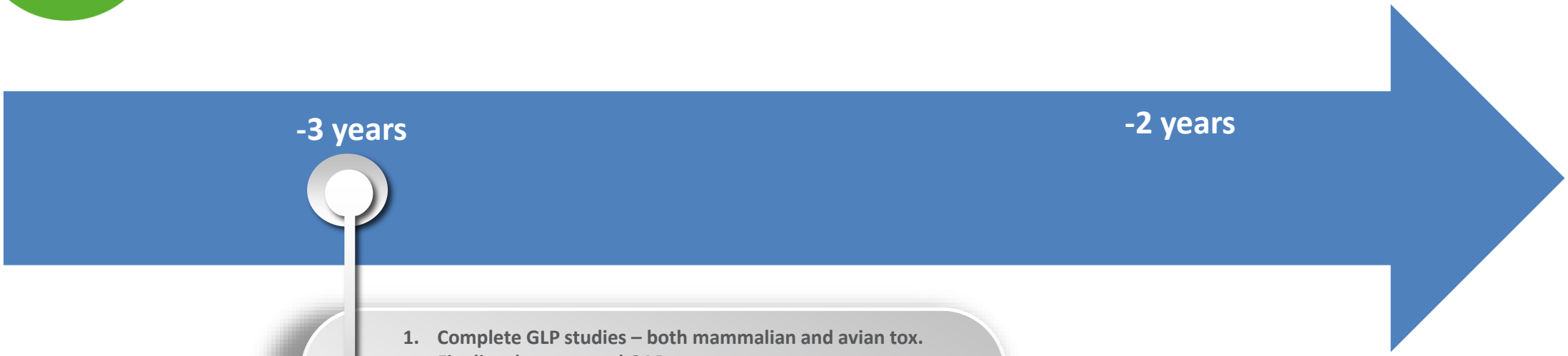
B&M Regulatory submission EU process - Applicant evaluation





1. Complete GLP studies – both mammalian and avian tox. Finalise the proposed GAP
2. Review bird and mammal studies, **calculate BMD for ALL relevant endpoints.** Contract out work (studies review and BMD modeling) if internal resources are not sufficient to support
3. Run tier I risk assessments
4. <u>If tier I risk assessment fails</u>: **Plan for higher tier testing or adjust the GAP**

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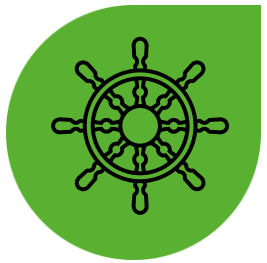
B&M Regulatory submission EU process- Applicant evaluation



-3 years

1. Complete GLP studies – both mammalian and avian tox. Finalise the proposed GAP
2. Review bird and mammal studies, calculate BMD for ALL relevant endpoints. Contract out work (studies review and BMD modeling) if internal resources are not sufficient to support
3. Run tier I risk assessments
4. <u>If tier I risk assessment fails</u>: Plan for higher tier testing or adjust the GAP

-2 years

1. Run relevant higher tier studies (FS), and plan higher tier studies for next year

-2 years

1. No BMD version control: Re-run BMD calculations to check if BMDs are still the same. If BMD10s changed, repeat steps 3 and 4 from year -3 !!
2. Run relevant higher tier studies (FS), and plan higher tier studies for next year

-1 years

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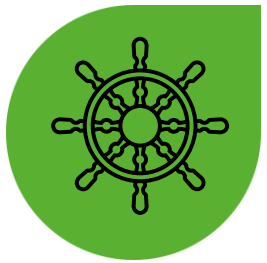
B&M Regulatory submission EU process - Applicant evaluation



-3 years

3. Run tier I risk assessments
4. If tier I risk assessment triggered: Adjust the GAP

-2 years

1. Run higher tier studies (FS), and plan higher tier studies for next year

1. No BMD version control: Re-run BMD calculations to check if BMDs are still the same. If BMD10s changed, repeat steps 3 and 4 from year -3
2. Run higher tier studies (FS), and plan higher tier studies for next year

-1 years

1. Run relevant higher tier studies (PD, PT)
2. Pre-submission meeting with RMS and adjust strategy if needed !Endpoints usually confirmed (previous AIR). Tier 1 RA confirmed!

1. No BMD version control: Repeat steps 1., 2. from year -2 (see also year -1)
2. Run relevant higher tier studies (PD, PT)
3. Pre-submission meeting with RMS and adjust strategy if needed !Endpoints & BMD discussion NOT CONFIRMED. Tier 1 RA NOT CONFIRMED!

0 years

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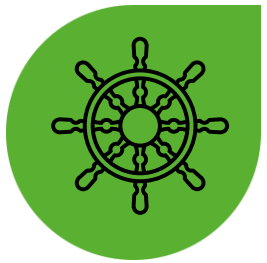
B&M Regulatory submission EU process - RMS/EFSA evaluation



0 years

Compile information, write & submit dossier

+1 years

1. Review studies, and calculate BMD10 for relevant endpoints
2. Run tier 1 risk assessments

+2 years

1. No BMD version control: Review studies, and calculate BMD10 for relevant endpoints
2. Run tier 1 risk assessments. !Endpoints & BMD discussion NOT CONFIRMED. Tier 1 RA NOT CONFIRMED!

+3 years

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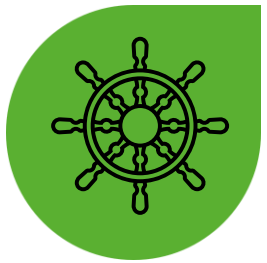
B&M Regulatory submission ZONAL process - zRMS evaluation



1. Run tier 1 risk assessments

+2-3 years

EFSA conclusion or ongoing evaluation

+6 months

... years

1. Different MS are at varying stages of implementing the new GD
2. Lack of BMD process and agreed endpoint for zonal submissions

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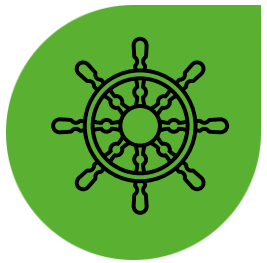
Navigating B&M Dossier Development in Varying Regulatory Environments



- **Conclusions – Consequences**

- GAPs may need to be adapted regularly
- Issues with reproducibility and reliability of results
- Significant higher workload/resources expected for both authorities and industry
- Outcome of Tier 1 RA unclear until very late in the process. Predictability of requirements for higher tier refinements is affected. Higher tier strategy may need to be updated regularly
- High potential for unharmonized approaches

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Navigating B&M Dossier Development in Varying Regulatory Environments

Case scenario

- **Submission Case:** A company submits a zonal pesticide dossier in 2025 across all zones with complex risk assessment scenarios requiring clarification on BMD

- **Outcome**:
- EFSA agreed endpoints cannot be used anymore. Not clear process identified for BMD derivation-different approaches proposed as following:
  - Two zRMS establish inconsistent BMD values for the active
  - cMS requests additional zonal or country specific-based data (expert judgement)-not previously aligned with zRMS or RMS
  - Third zRMS develops tox BMD values for the active at EU level (RMS + EFSA peer review + Confirmatory data)

- **Impact**:
  - **Lack of a BMD process** and/or contradictory feedback from evaluators creates confusion and delays, leading to missed regulatory timelines and increased costs. The applicant faces difficulties adapting to feedback late in the process, risking rejection
  - **Toxicity endpoint for zonal submissions is a key topic. It is not clear which endpoint is relevant for zonal submission**

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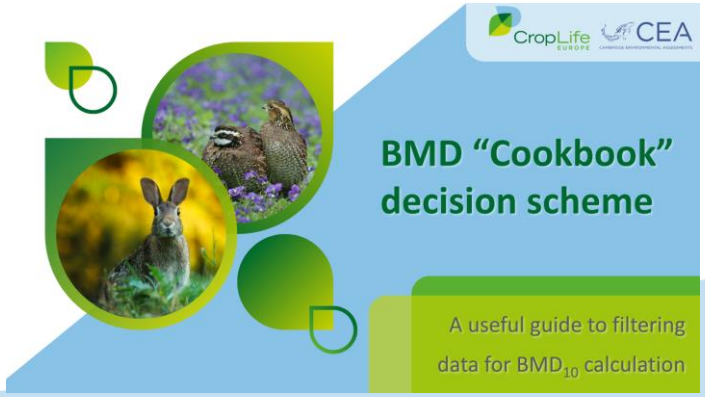
Navigating B&M Dossier Development in Varying Regulatory Environments
Case scenario

- **Policy Gap:**
  - ***Pre-Submission Engagement****: Which is the* ***process*** *to discuss with zRMS and cMS to align expectations and discuss technical BMD challenges?*
  - ***Harmonized Communication****: How can we ensure that RMS, zRMS, cMS are aligned during transition?*

- **Key Takeaways**
  - **Timelines:** Data generation is long-lasting process, BMD to be agreed at early stage to ensure consistent & predictable outcomes
  - **Enhanced Communication Framework and Process Efficiency:**
  - Streamlined processes, e.g. pre-submission meetings, efficient communication process including in depth discussion and if possible, confirmation of BMD and clear timelines for feedback, can significantly enhance regulatory process
  - Early engagement with cMS is critical to understand varying requirements & avoid back-and-forth discussions
  - **BMD "Cookbook" decision scheme can provide further clarity**
  - **Harmonized communication**: Stakeholder collaboration is critical to ensure consistent and fair evaluations and preventing the process from transitioning to national submissions



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Navigating B&M Dossier Development in Varying Regulatory Environments
Case scenario

- **Policy Gap:**
  - **Key topic for alignment:** Toxicity endpoint for zonal submissions is a key topic. It is not clear which endpoint is relevant for zonal submission

- **Key Takeaways**
  - **Relevant scenarios** until the renewal of the approval of the active substance using the new B&M GD:
  - No impact on timelines: Determine whether the previously agreed NOEC should be used
  - Interim step: Clarify if an EU BMD is needed for the parameter driving the toxicity endpoint (NO(A)EL) as confirmed at the EU level (DAR/RAR). BMD can be updated once EFSA peer review completed
  - Significant impact on timelines: Follow up the official proposal (RMS + EFSA peer review + Confirmatory data)
  - Confusion: If no further guidance provided, zRMS, cMS will proceed based on their own interpretations & decisions

Toxicity endpoint for zonal submissions is a key topic. Clarity is needed!

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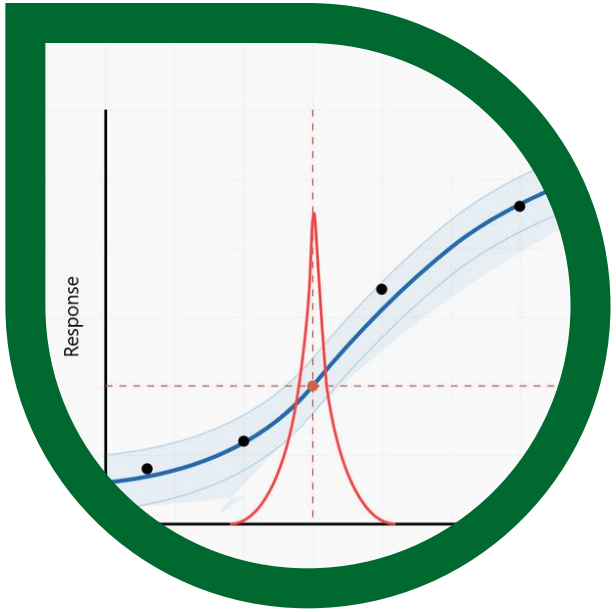

EFSA BMD Tool Updates and Their Impact on Regulatory Submissions

The EFSA online BMD tool is available so it can be used as proposed for BMD derivation.
Is this true?

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Current Regulatory Environment

Is the EFSA online calculator currently fit for purpose for regulatory submissions?

EFSA – CLE meeting (Nov 2024)

How important is a reliable and stable online EFSA BMD tool for regulatory submissions?

Case Scenario

Submission Case and Challenges Identified

Policy Gaps and Key Takeaways

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EFSA BMD Tool Updates and Their Impact on Regulatory Submissions

- **EFSA online tool is available for the BMD derivation**
- The EFSA BMD online tool is a critical component for deriving BMD values in pesticide RA.
- Issues
  - Resource demanding, expertise needed
  - Issues with reproducibility and reliability of results
  - Not tested → Many bugs
  - Not user friendly or with practical issues
  - Regular updates, not transparent, versions are difficult to track, **no version control**

- ***Impact management needed:***
- Regular updates to this tool aim to improve accuracy and methodology. However, these updates can create challenges for regulatory submissions

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EFSA BMD Tool Updates and Their Impact on Regulatory Submissions

- EFSA invited CLE stats experts and other CLE members for a 3-hour online meeting (8th Nov 2024)
- **Key topics discussed:**
- It was highlighted the need for a stable regulatory version control to avoid disruptions in the process
  - Challenges with BMD Tool Updates: Explained the challenges faced when the BMD tool is updated, e.g. significant resource investment
  - Case Studies on BMD Tool Usage: CropLife presented case studies on the use of the BMD tool. Discussed issues such as new versions producing different results and the reliability of statistical results
  - Practical Issues with BMD Tool: CropLife discussed practical issues and emphasized of making the tool user-friendly for non-experts
  - Version Control and Documentation: Emphasized the need for clear version control and documentation for the BMD tool suggested having validation for version control process to ensure consistency in regulatory submissions
  - Collaborative Testing and Development: CropLife suggested involving multi-stakeholder testing groups and emphasized importance of thorough testing before releasing regulatory version
  - Feedback and Communication: **EFSA discussed the importance of providing feedback on the BMD tool. It was also emphasized the need for clear communication and collaboration to improve the tool**

- The post announcement related to the meeting is now available online at https://www.efsa.europa.eu/en/events/ad-hoc-stakeholder-meeting-croplife-europe

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EFSA BMD Tool Updates and Their Impact on Regulatory Submissions

- **EFSA outlined potential next steps**

- Clarify Regulatory Status: Discuss with the pesticide unit and DG SANTE to clarify the current status of the BMD tool's regulatory implementation
- Establish Regulatory Version: **Develop a clear framework for establishing regulatory versions of the BMD tool**
- Set Up Testing Framework: Explore the establishment of a framework for testing the BMD tool
- Enhance Communication: Improve communication methods to ensure clarity on the regulatory version and provide guidance for non-expert users
- Share Data for Testing: Provide data sets used in the presentation to EFSA for testing and validation purposes

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EFSA BMD Tool Updates and Their Impact on Regulatory Submissions
Case scenario

- **Submission Case:** A company submits an AIR pesticide dossier in 2025, using BMD values derived from the EFSA online tool version 0.0.0.9063
- **Evaluation Timeline:** The RMS evaluates the dossier in 2026, when the EFSA online version 0.0.0.9065 is the standard - the new BMD10=1.9x
- In addition, the current guidance does not clearly specify which parameters should be assessed using BMD and which should not, leaving room for back-and-forth discussions and potentially unharmonized approaches

- **Impact:** The updated tool generates **different** BMD values, leading to potential discrepancies between the submitted data and the RMS evaluation

CLE member examples

Version	BMD10
0.0.0.9063	x
0.0.0.9065	1.9x

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EFSA BMD Tool Updates and Their Impact on Regulatory Submissions
Case scenario

- **Policy Gap:**
  - ***Stakeholder collaboration:***
  - *How can we advocate for harmonized guidance across MS on managing BMD tool updates?*
  - *How can we ensure a more consistent interpretation and application of the BMD guidance and tools?*

- **Key Takeaways**
  - The EFSA online BMD tool is important to work effectively for regulatory purposes. Consistency in calculations is needed
  - Regular updates to tools like EFSA's BMD Tool are essential but can create regulatory challenges. Clear guidance and proactive communication between applicants and RMS can minimize disruptions
  - Stakeholder collaboration is critical to ensure consistent and fair evaluations

- **Mitigation Strategies**
  - Propose a standardized approach and a version control for handling BMD tool updates during evaluations

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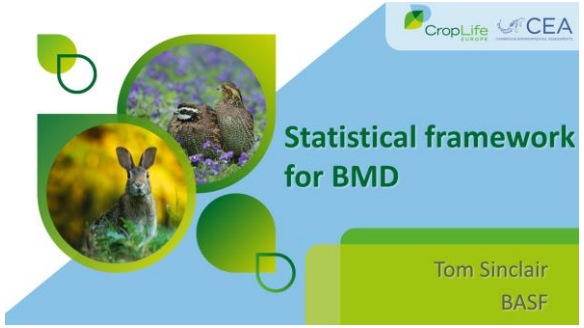
EFSA BMD Tool Updates and Their Impact on Regulatory Submissions
Case scenario

- **Policy Gap:**
  - ***Key topic for alignment: Is this EFSA version tool currently fit for purpose for regulatory submissions?***

- **Key Takeaways**
- EFSAs BMD calculator has not yet completed sufficient testing and is therefore not yet ready for regulatory use
- BMD tox values can not be used for regulatory purposes before

a regulatory acceptable version is available that satisfies user expectation

For more technical information refer to



- A regulatory version procedure is urgently needed to ensure clarity and consistency. Propose establishing a standardized approach for handling updates during evaluations

- ***A fully tested and validated regulatory version EFSA tool needed for submissions!***

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Conclusions

BMD process is currently missing

Streamlined processes, e.g. pre-submission meetings, efficient communication process including in depth discussion and BMD confirmation and clear timelines for feedback.

Early stakeholder engagement is critical to clarify varying requirements & avoid back-and-forth discussions

Seek agreement on tox endpoint for zonal submissions

Until the renewal of the approval of the active substance using the new B&M guidance significant confusion is expected unless further guidance provided. In the absence of clear direction zRMS, cMS might proceed based on their own interpretations and decisions

A regulatory EFSA tool version needed for submissions

EFSAs BMD calculator has not yet completed sufficient testing and is therefore not yet ready for regulatory use. A regulatory version procedure is urgently needed to ensure clarity and consistency. Propose establishing a standardized approach aligned with EFSA-CLE proposal for handling updates during evaluations

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THANK YOU

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