FEEDBACK ON THE CONSOLIDATED COMMENTS

Virtual Public Consultation
05 August 2022 | 10AM – 11:30 AM
Proposed issuance "*Guidelines on the Filing and Submission of Acceptable Variations on Protocols and Non-standard Protocols for the Review and Pre-Approval by the Food and Drug Administration Prior to the Conduct of Bio-efficacy Test Studies of Household Pesticides for the Purposes of Securing a Certificate of Product Registration*"

Question / Comment no. 1

Is there still a need for a conducted foreign non-standard bio-efficacy test study to undergo the pre-approval process?

In the proposed guidelines, bio-efficacy test studies conducted or commenced before the end of the transitory period will not be required to undergo pre-approval as a precondition for product registration.

Question / Comment no. 2

Considering that most bio-efficacy test protocols for termiticide requires a long-time frame, with 1 year being the shortest, will a non-standard or modified bio-efficacy test which has already commenced but have not yet completed before the end of the transitory period be covered by the proposed Guidelines?

In the proposed guidelines, bio-efficacy test studies conducted or commenced before the end of the transitory period will not be required to undergo pre-approval as a precondition for product registration.

Question / Comment no. 3

I believe that DOH AO No. 2019-0008 includes the product registration for turf pesticides. Are there any currently available accepted test protocols for the said product? Will all the non-standard or modified test protocols for turf pesticides undergo the pre-approval process?

In the current draft of the proposed guidelines, standards for bio-efficacy test protocols for turf pesticides have yet to be identified. It should be noted that the Annex listing the standard test protocols will be subject for review and updating. Should there be recommendations or proposals coming from marketing authorization applicants, HUP establishments, researchers, etc. on standards for inclusion in the Annex, the Center is open to receive such for further review. On such recommendations or proposals, a copy of the standard and a letter-request from the proponent should be submitted to the FDA.

Question / Comment no. 4 (1/2)

Does the 20 WD cover the pre-assessment until the evaluation of the application?

The timeframe for the delivery of service, in this proposed guideline, is 20 working days which is consistent with the provisions of RA 11032 relative to the processing timeline for highly technical transactions. Given that the pre-assessment step is introduced into the registration process as a statutory requirement for government agencies under RA 11032 with the sole criteria of checking for the completeness of documentary requirements and that the processing timeline is defined under the same law as “the “time consumed by all government offices and agencies covered under Section 3 of this Act from the acceptance of an application or request with complete requirements,

Question / Comment no. 4 (2/2)

accompanying documents and payment of fees, up to the issuance of certification or such similar documents approving or disapproving an application or request", the 20 working days proposed timeline, by virtue of RA 11032, will only commence after a complete and paid application has been received by the FDA.

It is emphasized that the review of compliance to administrative and technical requirements, including the determination of the soundness of the protocol to achieve its intended outcome, is performed during the Center evaluation. 2/2

Question / Comment no. 5

Will there be a notice of deficiency (NOD) or will deficient applications be outrightly approved/disapproved?

No actual notice of deficiency(ies) is issued to deficient applications during pre-assessment. Following RA 11032, the result of an application will only either be approval or disapproval.

However, applicants will be informed of the deficiencies by providing a copy of the pre-assessment checklist indicating the missing documentary requirements.

Question / Comment no. 6

Can we be informed during the evaluation of application on the possible deficiencies rather than meriting an immediate disapproval?

For the purposes of the proposed Guidelines, the letters of disapproval will cite the reasons for the disapproval of the application. Following RA 11032, applications will only either be approved or disapproved. However, should there be a proposal from stakeholders to reinstate the issuance of Notice of Deficiencies, the Center is open to receive and review position papers, and make the appropriate representations with the Anti-Red Tape Authority on the implementation of RA 11032.

Question / Comment no. 7

Can the FDA, FPA and DOST have a standardized/harmonized bio-efficacy test protocols?

There are no existing joint undertakings between the FDA, FPA and DOST to harmonize/standardize bio-efficacy test protocols. However, it must be noted that through the proposed guidelines the FDA intends to ensure consistency with regional and international standards.

Should there be recommendations or proposals coming from marketing authorization applicants, HUP establishments, researchers, etc. on standards for inclusion in the Annex, including those previously-approved by FPA and DOST, the Center is open to receive such for further review. On such recommendations or proposals, a copy of the standard and a letter-request from the proponent should be submitted to the FDA.

Question / Comment no. 8 (1/3)

Did the FDA consult bio-efficacy test centers in regards to the feasibility/capability to conduct test protocols of pesticide products? We hope the FDA may address and recognize the limitations of testing centers in conducting bio-efficacy test protocols.

The proposed Guidelines has undergone a consultation period to receive comments from the public from 29 June to 29 July 2022, including a WTO-TBT notification from 6 July to 29 July 2022, and the virtual consultation held on 5 August 2022. Consultations were conducted through such platforms to cover various stakeholders including representatives from sectors covering local micro, small, medium enterprises, local and foreign large scale-private enterprises, research and development, pest control operators.

Question / Comment no. 8 (2/3)

Nevertheless, the Center notes that the proposed guidelines does not intend to disallow or prohibit the modification of standard test protocols or the use of nonstandard test protocols which may be due to limited capabilities on the end of the bio-efficacy test centers. Instead, it is a means to promote the regulatory compliance of market authorization applicants by ensuring household pesticide registration applications submitted are accompanied by bio-efficacy studies that meet the Agency's technical requirements. This minimizes the disapproval of household pesticide registration applications caused by bio-efficacy studies that are found to be deficient in terms of generating reliable data or proving a product's claimed benefit. The proposed guidelines also allows efficient use of companies' resources.

Question / Comment no. 8 (3/3)

Should there be recommendations or proposals to recognize protocols which are less resource intensive than those already reflected in Annex A, the Center is open to receive such for further review. On such recommendations or proposals, a copy of the standard and a letter-request from the proponent should be submitted to the FDA.

Question / Comment no. 9

Will the processing time be similar to the previous regulation that takes around 6 months? Can this be shortened?

The proposed processing for the review and pre-approval of innovative and modified bio-efficacy test protocols is 20 working days, which can be extended for the same number of days provided that the applicant is given prior notice following RA 11032.

Question / Comment no. 10 (1/3)

Will an approval for the non-standard or modified test protocols be secured prior the conduct of bio-efficacy test? Or can we submit a conducted non-standard or modified test protocol for review and approval?

In the proposed guidelines, bio-efficacy test studies conducted or commenced before the end of the transitory period will not be required to undergo pre-approval as a precondition for product registration.

Question / Comment no. 10 (2/3)

The objective of the proposed policy is to assist market authorization applicants minimize wastage of resources from performing bio-efficacy tests which are not up-to standard or are not reasonably expected to yield reliable results for the purposes of product registration. Upon full implementation of the proposed guidelines, the Center strongly advises all market authorization applicants to secure a pre-approval of their modified/non-standard test protocols before conducting the bio-efficacy test to ensure that resources are only expended on performing modified/non-standard bio-efficacy test studies that meet the technical standards of the Center.

Question / Comment no. 10 (3/3)

Nevertheless, it will be within the discretion of the market authorization applicant if they desire to proceed with the conduct of their modified/ nonstandard bio-efficacy test study before securing the pre-approval under the condition that a pre-approval of the modified/ nonstandard protocol is secured prior to the submission of the product registration application as the pre-approval will, by then, be a mandatory requirement for the registration of household pesticide with bio-efficacy studies conducted using modified/ nonstandard protocol.

Question / Comment no. 11 (1/2)

Can the payment be settled after securing the approval of the non-standard or modified test protocols?

Payment of the appropriate fees and charges is a prerequisite for an application to be officially lodged with the Center for evaluation based on the definition of processing time in RA 11032, to wit: “time consumed by all government offices and agencies covered under Section 3 of this Act from the acceptance of an application or request with complete requirements, accompanying documents and payment of fees, up to the issuance of certification or such similar documents approving or disapproving an application or request”. It must be noted that pre-assessment, which only checks for the completeness of the documentary requirements, is a different step from evaluation and occurs prior to the payment of fees and charges.

Question / Comment no. 11 (2/2)

For the proposed guidelines, the fees and charges is based on DOH AO No. 50 s. 2001 - Php 500 + a minimum Legal Research Fee of Php 10.

Question / Comment no. 12 (1/2)

Most of the bio-efficacy trials especially for multinational companies are conducted abroad. In some cases, we already have foreign data from US, Europe and Australia. Whereas the aforementioned countries are classified as temperate zones, tropical areas can be found as well in the same countries, which is why we used those bio-efficacy trial results. In view of this, can the FDA provide a list of acceptable countries on bio-efficacy test study aside from ASEAN countries?

Such listing is not under consideration by FDA-CCHUHSRR, wherein the enquirer's proposed listing may be inappropriate. The comment itself acknowledges that specific sites in temperate countries may have a wide range of environmental and climatic conditions, including those similar to the Philippines.

Question / Comment no. 12 (2/2)

Prescribing a list may mean the exclusion of bio-efficacy data generated in suitable sites in temperate countries that are not included in the list. Instead of such a listing, the applicant may provide justifications on why data generated in the temperate zones may be acceptable.

For example: insecticides against *Periplaneta* roaches in homes. Even during winter, the insects inhabit conditions that allow them to thrive: e. g., heated homes, presence of food, etc. Data generated in these homes may be acceptable if temperature, humidity and other conditions of the roach habitat are relevant to the propose use in Philippine households.

Question / Comment no. 13

How will the processing of bio-efficacy test protocol pre-approval be managed by FDA in terms of review? What will you be looking for in the non-standard protocols? What are the expectations of your Center on submitted non-standard protocols?

The review will establish whether or not the non-standard protocols or modifications of a standard protocol can generate reliable bio-efficacy data under the proposed conditions of use, as specified in the label. As such, the applicant should provide sufficient details for the evaluator to determine scientific and statistical robustness of the proposed non-standard or modified procedures. The applicant should also articulate how and why the non-standard or modified protocol can generate data that compares favorably with the scientific and statistical rigor of the standard protocol. More information on these requirements are provided in Annex C.

Question / Comment no. 14

What will be the treatment to an application where the standard (reference product) is either unavailable in the market, not yet registered with FDA, or contains a different percentage?

As per DOH AO 2019-0008, the positive control must be an FDA-registered product with the same active ingredient/s as the product for registration and formulated into a similar product type. However, in case this is not possible, an FDA-registered household pesticide with active ingredient/s from the same chemical family as the one in the product for registration is allowed under DOH AO 2019-0008 as the former will have the same mode of action, similar toxicity pathway, similar biochemical or physiological targets, or similar toxicity mechanism as the product for registration. In this instance, the applicant should provide ample justification on the use of the surrogate positive control.

Question / Comment no. 15 (1/4)

Request FDA to accept non-standard protocols that have been accepted globally. The move to Standardize protocol is a step towards better accountability for organizations. Being an innovator with new formats, often standard protocols do not suffice the needs for efficacy results. Certain deviations are made based upon technical justifications. Such protocols and the studies generated have been accepted by regulators across Australia, SE Asian countries, Africa etc. FDA is requested to review this aspect of the efficacy study as well.

Question / Comment no. 15 (2/4)

Efficacy studies for household pest control products are carried out in laboratories under controlled conditions. These are maintained in accordance to the WHO guidelines. Company A [1] has been generating studies in globally certified lab based out of Australia and India. These studies have been accepted by the Regulatory Authorities across countries. Besides, it has been observed that often labs in the specified country are not equipped as per the need to the experiment. Accepting overseas lab studies for efficacy by FDA will be a welcome step as it will avoid unnecessary duplication of studies.

[1] The name of the company has been intentionally changed.

Question / Comment no. 15 (3/4)

The Proposed guidelines do not disallow or prohibit the use of modified or non-standard protocols, but instead provides pathways for the more efficient evaluation of product registration applications and at the same time, minimize the inefficient use of company resources on bio-efficacy test studies that do not meet the FDA's technical requirements. This means that FDA will still accept modified/non-standard bio-efficacy test protocols, provided that they are determined to be scientifically sound and is deemed appropriate to substantiate product claims and performance.

Question / Comment no. 15 (4/4)

On this note, the following arrangements and their corresponding timelines under the proposed guidelines must be taken note of:

1. Bio-efficacy test studies conducted following modified/non-standard protocols before the end of the transitory period will not be required to undergo pre-approval as a precondition for product registration

2. Bio-efficacy test studies conducted following modified/non-standard protocols after the transitory period will be required to undergo pre-approval as a precondition for product registration.

In both cases, though it is not part of the documentary requirements for the review and pre-approval of modified/non-standardized test protocols, companies are welcome to provide supporting documents such as the quality of the performing laboratory (globally certified etc) and proof that the protocol/study has already been accepted by other regulatory agencies.

Question / Comment no. 16 (1/4)

Is the no. of replicate equivalent to the number of respondents?

Is there a maximum no. of replicate/respondents? What is the basis of the minimum of 3 replicate?

The number of replicates and respondents depends on the statistical design. Usually, respondents are grouped into cohorts and the cohorts are used as replicates.

Question / Comment no. 16 (2/4)

The number of replicates is a statistical question. To illustrate using the simplified discussion provided in [https://www.ndsu.edu/faculty/horsley/ExptSize.pdf], the calculation of the number of replicates depends on:

1. An estimate of σ2 obtained from previous experiments.
2. The size of the difference (δ) to be detected.
3. The assurance with which it is desired to detect the difference

(i.e., Power of the test = 1-β).

4. The level of significance to be used in the actual experiment

(i.e., Type I error).

5. The test required, whether a one-tail or two-tail test

Further note: In the reference used, the example came up with 3 as the number of replicates.

Question / Comment no. 16 (3/4)

On the minimum number of replicates which is 3, this is the standard used for scientific researches/studies. However, the researcher may opt to compute for the number of replicates the company will use in your proposed modified/non-standardized test protocol.

To calculate for the number of replicates that need to be used, the following are considered:

1. An estimate of variance or σ2 obtained from previous experiments.
2. The size of the difference (δ) to be detected.
3. The assurance with which it is desired to detect the difference

(i.e. Power of the test = 1 - Type II error or β).

4. The level of significance to be used in the actual experiment

(i.e. Type I error which is usually α=0.05).

5. The test required, whether a one-tail or two-tail test.

Question / Comment no. 16 (4/4)

The formula to calculate the number of replicates required based on the selected parameters (see previous slide) is as follows:

$$\#reps = 2\left(Z_{\alpha/2} + Z_{\beta}\right)\left(\frac{\sigma}{\delta}\right)^2$$

where: $Z_{\alpha/2}$ is associated with the Type I error
Z_{β} is associated with the Type II error
δ is the true difference to be detected, and
σ is obtained from previous experiments

END

THANK YOU!

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Food and Drug Administration
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