Laporan Penutupan Seranta Awam

TAJUK CADANGAN:

MALAYSIAN GUIDELINE FOR BIOEQUIVALENCE INSPECTION
2ND EDITION

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KANDUNGAN

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1. PENGENALAN

1.1. Pihak Berkepentingan Terlibat

Seranta awam *Malaysian Guideline for Bioequivalence Inspection* Edisi Kedua dan soal selidik berhubung penerbitan hasil pemeriksaan melibatkan pihak berkepentingan yang berikut:

- Pusat kajian BE dalam negara
- Pusat kajian BE luar negara
- Pemohon tempatan bagi pemeriksaan pusat kajian BE luar negara
- Pemohon Penilaian Keperluan Pemeriksaan Kajian BE (BEDE)
- Industri farmaseutikal

1.2. Ringkasan Seranta Awam

Seranta awam ini telah diadakan selama 29 hari bermula 8 April 2024 hingga 6 Mei 2024. Seranta awam ini melibatkan dua (2) soal selidik yang bertujuan untuk mendapatkan maklumbalas pengemaskinian *Malaysian Guideline for Bioequivalence Inspection* Edisi Kedua dan pendapat berhubung penerbitan hasil pemeriksaan di laman sesawang NPRA.

Secara umum, seranta awam ini telah dilihat sebanyak 142 kali dan telah menerima 37 (26.06%) maklumbalas. Daripada 37 maklumbalas yang diterima, 5 (13.51%) maklumbalas didapati tidak berkaitan dengan kandungan seranta awam. Daripada maklumbalas yang berkaitan, 5/32 (15.62%) menyokong penuh pengemaskinian garis panduan tersebut manakala 27/32 (84.38%) menyokong dengan pindaan. Tiada bantahan diterima untuk kedua-dua soal selidik yang terkandung dalam seranta awam ini.

2. SOAL SELIDIK PERTAMA: MAKLUMBALAS *MALAYSIAN GUIDELINE FOR BIOEQUIVALENCE INSPECTION* EDISI KEDUA

2.1. Soal selidik ini bertujuan untuk mendapatkan pandangan serta cadangan penambahbaikan dalam edisi kedua *Malaysian Guideline for Bioequivalence Inspection*.

2.2. Pengemaskinian garis panduan ini bertujuan untuk memberi lebih penjelasan dan maklumat tambahan yang lebih komprehensif berkaitan proses permohonan pemeriksaan serta prosedur dan skop pemeriksaan BE.

2.3. Pengemaskinian garis panduan ini tidak melibatkan polisi baru. Penambahbaikan dan maklumat baru yang ditambah merupakan proses kerja yang telah dilaksanakan sejak penerbitan edisi pertama garis panduan ini untuk meningkatkan ketelusan prosedur berkaitan pemeriksaan BE.

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3. SOAL SELIDAK KEDUA: DATA DEMOGRAFI DAN PANDANGAN TERHADAP PENERBITAN HASIL PEMERIKSAAN

3.1. Soal selidik kedua ini bertujuan untuk mengumpul maklumat demografik responden seranta awam ini dan mendapatkan pendapat mereka terhadap cadangan penerbitan hasil pemeriksaan di laman sesawang NPRA.

3.2. Maklumat yang dicadangkan untuk diterbitkan adalah seperti berikut:

- Nama fasiliti (nama tapak klinikal dan/atau tapak bioanalitikal)
- Tarikh pemeriksaan
- Hasil pemeriksaan (*compliant / non-compliant*)

3.3. Secara keseluruhan, semua responden bersetuju dengan cadangan untuk menerbitkan hasil pemeriksaan BE di laman sesawang NPRA untuk tujuan ketelusan.

4. KOMEN UMUM

4.1. Ringkasan

Secara umumnya, semua pihak berkepentingan menyambut baik pengemaskinian *Malaysian Guideline for Bioequivalence Inspection* dan penerbitan hasil pemeriksaan. Tiada bantahan diterima untuk kedua-dua soal selidik dalam seranta awam ini.

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Table 1. Comments, suggestions and enquiries received for Malaysian Guideline for Bioequivalence Inspection, 2nd Edition

No.	Level of Support	Topic	Comment	NPRA Response
1.	Support with Amendment	Line 27 -51	To update with the latest guideline such as ICH BMV Guideline M10, 2022	This reference has been added as per no. 11.
2.	Support with Amendment	Line 415	Propose to add in bracket "(exempted)" next to RM 0 for better clarity	The inspection fee table has been updated for better clarity.
3.	Support with Amendment	Line 432	1. "Description" column - Propose to specify if this processing fee also inclusive document review fee 2. "Additional Information" column. Propose to outline the procedures and timeline of refund request in the Guideline	1. The description column has been updated for better clarity in terms of the processing fee and document review fee. 2. The additional information column has been included with the information on refunds.
4.	Support with Amendment	Line 438	Propose to add word " contribution" for better clarity "The cost of inspection contribution will be prepared by NPRA based on…"	This part has been revised for better clarity. "The inspection cost estimate will be prepared by the NPRA based on the eligibility of the inspectors as outlined in the Pekeliling Perbendaharaan issued by the Ministry of Finance Malaysia and inputs from the applicant."
5.	Support with Amendment	Line 456	Propose to specify the minimum and maximum number of inspection days (if any) in Guideline. It would be very helpful for the applicant to allocate sufficient budget in their financial planning	Added sentence, "The inspection duration ranges from a minimum of three (3) days to a maximum of five (5) days."
6.	Support with Amendment	Line 488	We believe that sentence in Line 488 *to be submitted to* is typo instead it should be replace by *to be provided by*.	The sentence has been revised for better clarity. "The announcement letter will also list the names of inspectors, the inspection schedule, and the pre-inspection documents to be submitted to NPRA."
7.	Support with Amendment	Line 573	Please clarify if the NPRA technical meeting is after the closing meeting. If yes, is this NPRA technical meeting referring to the monthly JKPP meeting?	The NPRA technical meeting is an internal meeting among NPRA BE inspectors that is typically conducted once a month.

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8.	Support with Amendment	Line 576	In situations where 2 BE studies are inspected, is the same timeline applied?	Yes, if both studies are inspected on the same inspection visit.
9.	Support with Amendment	Line 577	Do NPRA allows extension request (with reasonable justifications) if BE centre requires more than 45 days to complete the CAPA? If this is allowed, propose to outline the procedure of extension request in the Guideline. Otherwise, propose to inform the impact if this timeline is not adhered.	BE centres should always strive to provide corrective & preventive action (CAPA) responses within the stipulated time frame. The BE centre should communicate with the inspectors to make arrangements for the relevant CAPAs to be submitted in the subsequent CAPA responses.
10.	Support with Amendment	Line 580	If exceeded 3 rounds of CAPA response, will the inspection deemed as void or still have opportunity to discuss with NPRA e.g. extension of correspondence rounds?	All observations should be addressed within acceptable timelines and within the time accorded for 3 CAPA submissions. Any concerns should be communicated with the inspectors during CAPA correspondences.
11.	Support with Amendment	Line 584	How long after the CAPA and responses provided would the BE Centre receive the certification?	After the inspectors have determined that no further CAPA is required, the inspection observations and CAPA responses will be tabled into the NPRA technical meeting, followed by a management meeting for a decision. The decision will be issued within 15 working days of the date of the meeting. For better clarity, a sentence has been added, “The issuance of the closing letter and certificate, as well as listing on the NPRA website, will be completed within 15 working days of the date of the management meeting.”
12.	Support with Amendment	Line 612	Failure to apply within this deadline may result in delay of the surveillance inspection. BE studies conducted after the expiry of the certificate’s validity date or during the gap in certificate validity may not be accepted for product registration purposes.	Failure to meet the deadline may cause a delay in the inspection, leading to a gap in the validity of the listing of a BE centre on the BE programme. Thus, all BE studies conducted during these gaps will not be accepted to support product registration

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			The term used here is 'may'. So, there is a possibility that it can be accepted? In what kind of situation would it be accepted?	evaluation unless the BE study has received a study-specific inspection exemption based on the outcome of the BEDE application or undergone a study-specific inspection with a satisfactory result.
13.	Support with Amendment	Line 627	Extraordinary inspection will be carried out by announcement. Please clarify what does 'carried out by announcement' mean? It this from time of inspection request? What is the timeline from announcement to actual inspection?	The sentence *"Extraordinary inspection will be carried out by announcement"* means that the respective inspectees will be informed beforehand about any extraordinary inspection. The timeline from the announcement to the actual inspection might vary depending on the availability of inspectors. However, the inspection dates should be agreed upon by both parties before the inspection is carried out.
14.	Support with Amendment	Line 656	1.Do NPRA allows inspection of 2 BE studies at the same BE centre from different Sponsor/Applicant? 2.In situations where NPRA has scheduled an inspection for Applicant A (for 1 BE study), and later receives an application from Applicant B (for 1 BE study) in the same BE Centre, is there any possibility for Applicant B to share the same schedule with Applicant A? Propose to address above queries in the Guideline or FAQ	Both scenarios will be decided during the inspection planning phase and based on the availability of inspectors. The NPRA does not share inspection plans between different applicants. However, the inspected BE centre may communicate with both applicants in the scenario mentioned. As such, the NPRA will leave it to the agreement between both applicants and the BE centre on the inspection dates.
15.	Support with Amendment	Line 663 - 684	It is stated that one of the decisions is "To determine the compliance of the BE study inspected". This could not be considered as a decision. A decision on whether the BE study is accepted or rejected should be reached and concluded.	The acceptance or rejection of the BE study will also be discussed in the NPRA technical meeting and management meeting, and the decision will be communicated in the inspection closing letter.
16.	Support with	Line 685 -	Section 5.0 states that only "Only BE studies	The paragraph has been revised for better clarity.

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	Amendment	709	conducted after the BE centre has been listed on the BE Programme shall be accepted for further evaluation by PPPK, NPRA. If the BE centre has been issued an exemption to conduct BE studies before the inspection by NPRA, the BE studies may also be accepted for further evaluation by PPPK, NPRA only after the BE centre has been listed on the programme. BE studies inspected during the inspection can also be accepted for further evaluation by PPPK, NPRA." The last sentence appears to conflict with the first sentence.	"All BE studies conducted at the BE centre listed on the BE Programme and within the listing validity period shall be accepted for further evaluation by the PPPK, NPRA. In addition, the BE study that was inspected by NPRA and found to be compliant with GCP, applicable principles of GLP and relevant regulatory requirements shall be accepted for further evaluation by the PPPK, NPRA."
17.	Support with Amendment	Line 699 - 702	To provide more clarity that the statement is only applicable to local BE center and not for foreign BE center to avoid confusion.	The paragraph has been revised for better clarity. "In addition, any local BE centre that is not listed on the BE Programme may be given an exemption to conduct a BE study to support product registration in Malaysia. The BE study will be inspected during the local BE centre's certification inspection. The BE study may only be accepted for further evaluation by the PPPK, NPRA after the local BE centre has been listed on the BE Programme."
18.	Support with Amendment	Line 699 - 702	For the statement "If the BE centre has been issued....listed on the programme", noted that it is applicable to local BE Center only. As such, appreciate it could be amend in a way to provide more clarity that it's applicable to local BE Center and not for foreign BE Center.	The paragraph has been revised for better clarity. "In addition, any local BE centre that is not listed on the BE Programme may be given an exemption to conduct a BE study to support product registration in Malaysia. The BE study will be inspected during the local BE centre's certification inspection. The BE

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				study may only be accepted for further evaluation by the PPPK, NPRA after the local BE centre has been listed on the BE Programme.”
19.	Support with Amendment	Line 741 - 748	Revision: 1. Listed ‘on’ the BE programme. Make it consistent in the whole document. 2. Suggest refer to section 4.4 only since the section title is the same as the box content ‘Conduct of Inspection’.	All relevant parts have been revised accordingly.
20.	Support with Amendment	Line 749 - 752	Revision: 1. Typically, the inspection cost and Terms and Conditions were issued 2 months prior to the MOH Malaysia Trust Fund Meeting, based on the inspection queue. 2. Inspection cost and terms and conditions. 3. Refer to section 4.4 only. 4. Listed ‘on’ the BE programme.	All relevant parts have been revised accordingly.
21.	Support with Amendment	Line 769 - 783	Total to be paid shown exclude application processing and document review fee. Propose to include those fees to reflect actual total amount.	This part has been revised as per suggestion.
22.	Support with Amendment	Line 775	The description “No charge will be imposed” is quite confusing for the situation in this example. Propose to update the description as “Not applicable. Hence, no charge will be imposed ” for better clarity.	This part has been revised as per suggestion.
23.	Support with Amendment	Line 1275	“Maintenance of blinding, if required by the protocol”. - Propose that maintenance of blinding of the analyst in the bioanalytical facility to be made compulsory.	The requirement for analysis of study samples to be conducted with the information on treatment has been specified in the latest ‘ASEAN GUIDELINE

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				FOR THE CONDUCT OF BIOEQUIVALENCE STUDIES'. Thus, we revised the sentence to "Maintenance of blinding until the end of the bioanalytical phase."
24.	Support with Amendment	Line 1013 - 1058	Management of The IMP. - Are the study sponsors allowed to designate the test and reference samples for each subject and preclude the BE site from randomly selecting representative retainment samples from the supplies received from study sponsor?	The IMP retention at the BE centre should be from the same batch that was supplied and used in the BE study. The BE centre is expected to retain all IMPs received before the dispensing activity.
25.	Support with Amendment	General comments /enquiries	Please clarify the circumstances where BE studies inspected DURING inspection can be accepted for further evaluation.	All BE studies inspected during inspection with satisfactory outcomes (GCP compliant) can be accepted for further evaluation. The outcomes will be specified in the closing letter. Section 5 has been revised for better clarity, "All BE studies conducted at the BE centre listed on the BE Programme and within the listing validity period shall be accepted for further evaluation by the PPPK, NPRA. In addition, the BE study that was inspected by NPRA and found to be compliant with GCP, applicable principles of GLP and relevant regulatory requirements shall be accepted for further evaluation by the PPPK, NPRA."
26.	Support with Amendment	General comments /enquiries	Archiving in clinical and bioanalytical site:– Suggest to elaborate on the expectations when the archiving service is being outsourced.	Additional information on Contract Archive Services is added under Appendix V and Appendix VI.
27.	Support with Amendment	General comments /enquiries	Currently, the BEDE assessment is indicated in the respective BE inspection types. Suggest indicating that BEDE assessment is a pre-requisite before	BEDE application is only required prior to study-specific Inspection. Thus, it is mentioned under sections 1 and 4.1. Further information with regard

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			applying for any BE inspections e.g. a section on its own.It will be good to have references on BEDE resources to help PRH understand this sequential process.	to the BEDE application is explained at the end of section 4.1. “Note: For further information with regards to the BEDE application, the applicant may refer to the application form for the *Evaluation on the Need for BE Study Inspection* and *Frequently Asked Questions (FAQs) for Desktop Evaluation of the Need for BE Study Inspection (BEDE)* available on the NPRA website.”
28.	Support with Amendment	General comments /enquiries	As a recommendation, we would like to suggest NPRA to add in another alternative for mode of inspection i.e. Virtual audit. We believe it will safe time and more cost effective Pre-requisite for a virtual audit (Example: Stable connection, OCR documents) can be separately spelled out to meet authority requirement to be having similar effective as physcial audit	BEEC had conducted virtual/remote inspections during the trailing end of the pandemic. From our internal assessment, we found that remote inspections on BE centres do not provide inspectors with the granularity and resolution required to assess the overall quality management system of a facility. However, BEEC does consider virtual/remote inspections as a potential tool to support the objective of the programme. If virtual/remote inspections gain more traction, it will be added into the next guideline update.
29.	Support with Amendment	General comments /enquiries	As we have been confirmed by NPRA verbally, for study specific inspection, it is confirmed that the outcome will be accepted for both BEEC and generic unit and applicant shall upload the cover letter from BEEC in the system whenever they would like to submit for product registration later on. Hence, we would like to get NPRA acknowledgement by formalize this information in the guideline 2nd Edition.	The acceptance of BE studies is stated under section 5. The acceptance of supporting documents during product registration should be checked against the latest guidance related to product registration applications that are relevant at the point of submission.

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30.	Fully Support	General comments /enquiries	In general, the draft guideline is well written as it provide more clarity and transparency.	Not Applicable
31.	Insignificant		I wanted to bring to your attention some important points regarding bioequivalence inspections that are relevant to our work. Here are the key takeaways:1. The National Pharmaceutical Regulatory Agency (NPRA) is responsible for conducting inspections and investigations of bioequivalence studies in Malaysia.2. The Bioequivalence (BE) Programme is a voluntary scheme that assesses whether BE centers comply with the necessary requirements outlined in the guideline and the Malaysian legal framework.3. Different types of inspections are conducted by the NPRA, including Certification Inspections, Surveillance Inspections, and Extraordinary Inspections.4. Study Specific Inspections are conducted for BE studies that require further evaluation and verification, covering various phases and analyses.5. The number of inspection days and fees depend on the type of inspection and study scope.6. The inspection process includes an opening meeting, conduct of the inspection, closing meeting, and reporting. BE centers must respond to inspection observations with Corrective and Preventive Actions (CAPAs) within a specified timeframe.7. The final decision on the BE inspection is made by NPRA management based on the inspection report, CAPAs, and recommendations from the lead inspector.Additionally, compliance with Good	Not Applicable

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			Clinical Practice (GCP) and Good Laboratory Practice (GLP) is crucial for BE centers. Non-compliance may result in non-acceptance or de-listing from the BE Programme. BE centers must also notify NPRA of any major changes to their listed sites.It is important for us to understand these regulatory requirements and procedures for conducting BE studies in Malaysia. If you have any further questions or would like more information, please let me know.Thank you for your attention to this matter.Best regards,ASYRAF	

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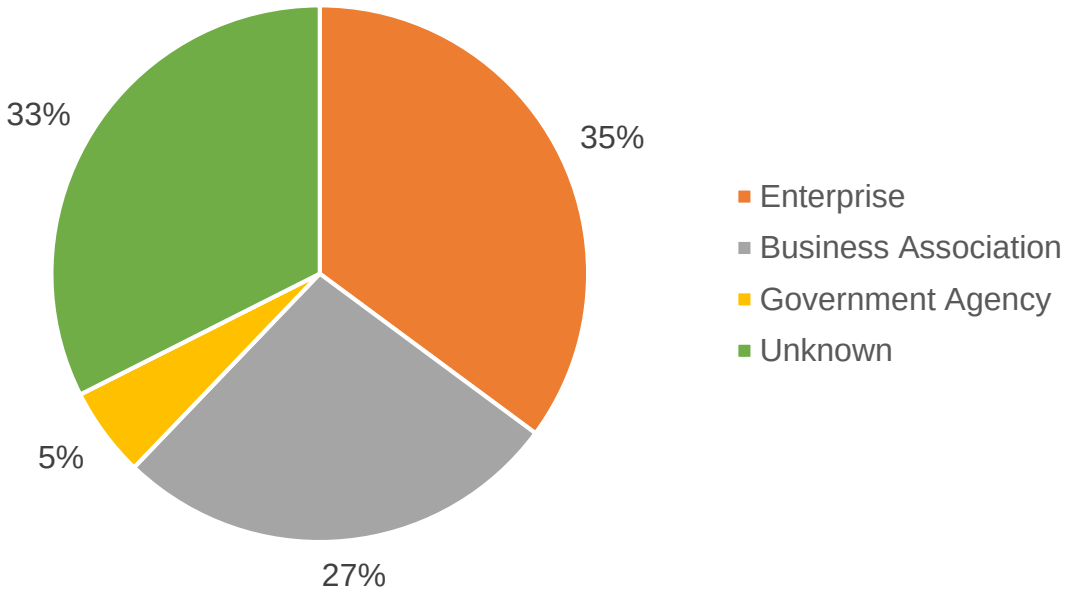
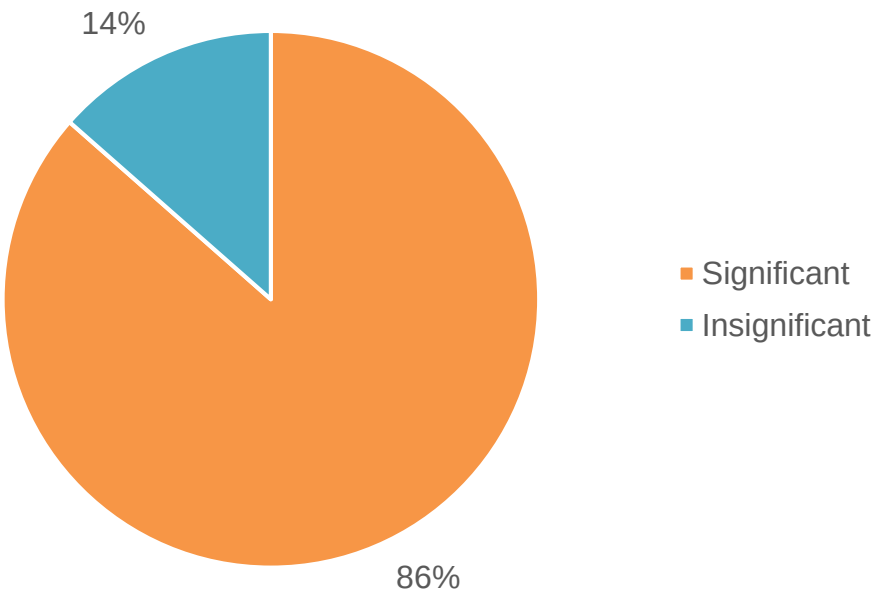
5. MAKLUMBALAS YANG DITERIMA

5.1. *Dashboard* Seranta Awam

5.1.1. *Respondents' demography* (n: 37)



5.1.2. *Significance of comments/feedback* (n: 37)



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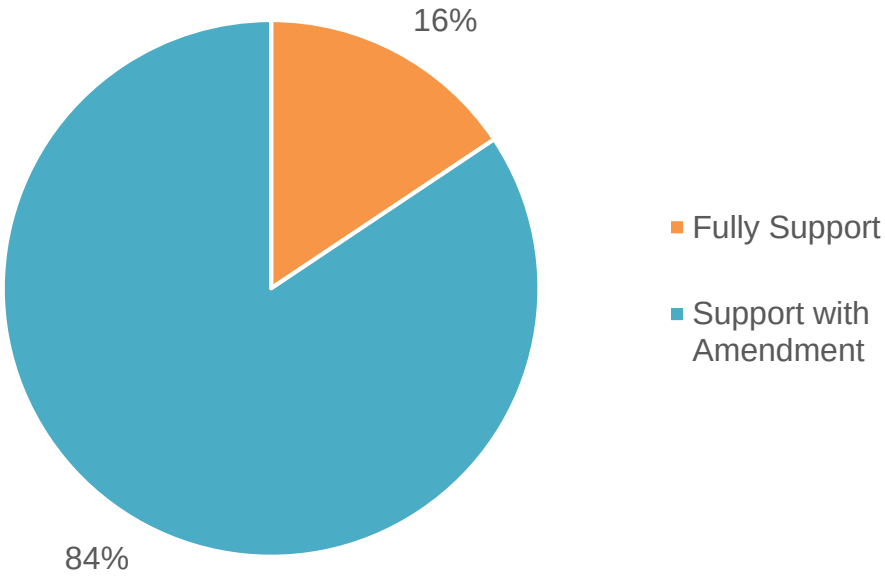
5.1.3. *Level of support for significant comments/feedback* (n: 32)



5.2. Maklumbalas Soal Selidik Pertama

5.2.1. Appendix 1: Summary of comments, suggestions and enquiries received for Malaysian Guideline for Bioequivalence Inspection, 2nd Edition.

5.2.2. Table 1: Comments, suggestions and enquiries received for Malaysian Guideline for Bioequivalence Inspection, 2nd Edition

5.3. Maklumblas Soal Selidik Kedua

5.3.1. Appendix 2: Demographic data and opinion on publication of inspection outcomes

6. KESIMPULAN DAN CADANGAN

6.1. Kesimpulan

Berdasarkan kepada seranta awam yang dijalankan dari 8 April sehingga 6 Mei 2024 secara atas talian bagi pengemaskinian *Malaysian Guideline for Bioequivalence Inspection* Edisi Kedua, tiada bantahan diterima dan cadangan penambahbaikan garis panduan juga diterima. Soal selidik berhubung penerbitan hasil pemeriksaan juga tidak menerima sebarang bantahan dan majoriti responden bersetuju dengan cadangan penerbitan hasil pemeriksaan di laman sesawang NPRA.

6.2. Cadangan

Komen yang berkaitan akan dikemaskini dalam versi akhir garis panduan. Berdasarkan kepada komen yang diterima juga, penambahbaikan editorial juga akan dilakukan dalam versi akhir garis panduan ini. Penambahbaikan editorial ini bertujuan untuk menambahbaik susunan garis panduan dan memberikan penjelasan tambahan tehadap

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kandungan garis panduan. Maklumat hasil pemeriksaan akan dipaparkan di laman sesawang NPRA.

Disediakan oleh:
Nama: Nabila Mohd Shaffie
Jawatan: Ketua Penolong Pengarah Kanan UF52
Tarikh: 3 Julai 2024

Disemak oleh:
Nama: Nicholas Leow Chun Wei
Jawatan: Ketua Penolong Pengarah Kanan UF54
Tarikh: 26 Julai 2024

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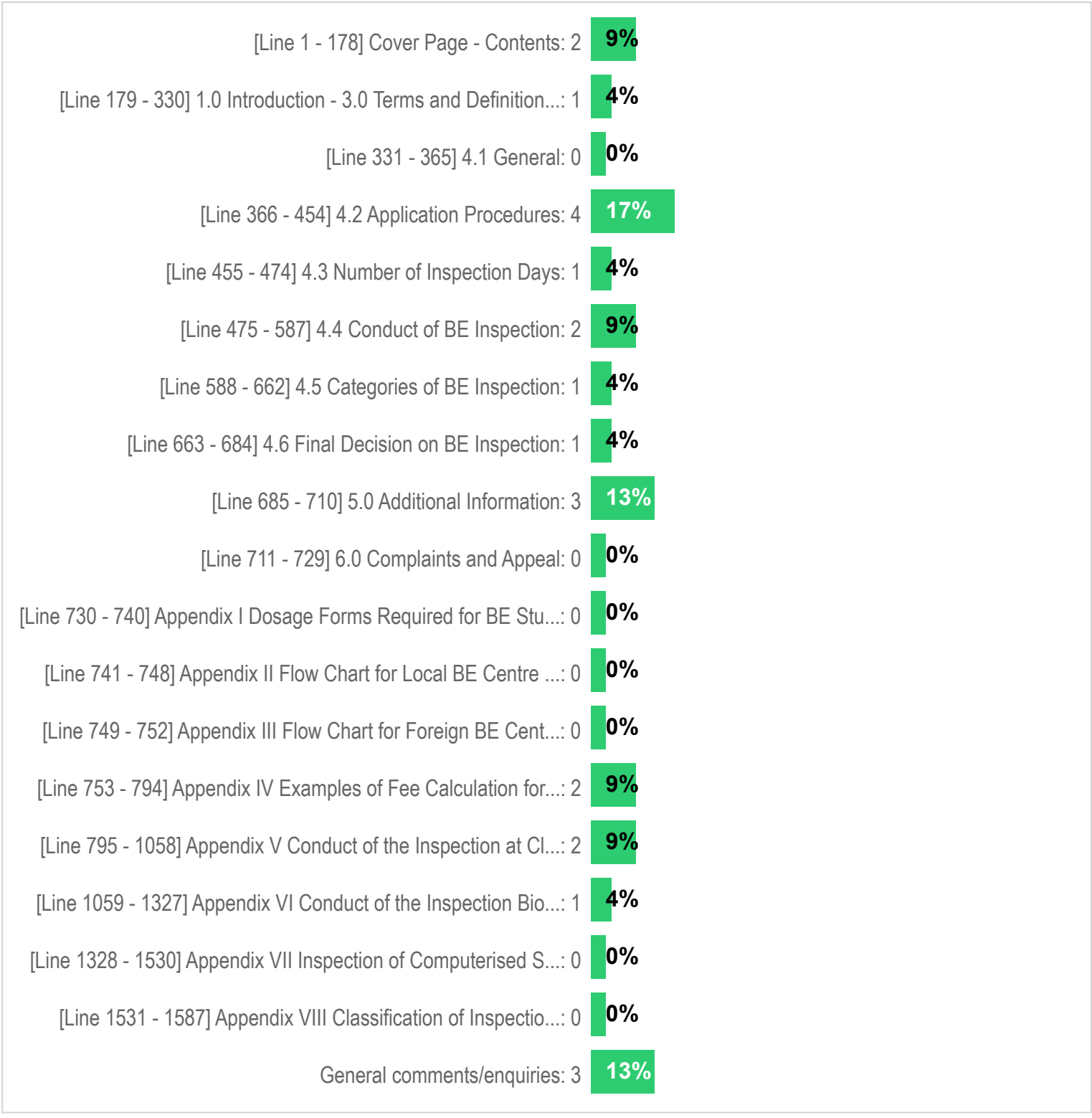
Results

Close

1. Kindly select the section / subsection relevant to your comment. If you have enquiries or comments that are not related to any section / subsection, please choose "General comments/enquiries".

Each comment submission will be for only 1 section / subsection. If you have comments / suggestions for other sections / subsections, kindly repeat the survey submission process. *



2. Kindly specify the Line No. of the relevant section / subsection. For general comments/enquiries, please indicate 'Not applicable' in the designated space.*

Total Answered	Total Bucketed	Total Pending	
23	0	23	Click to bucket!

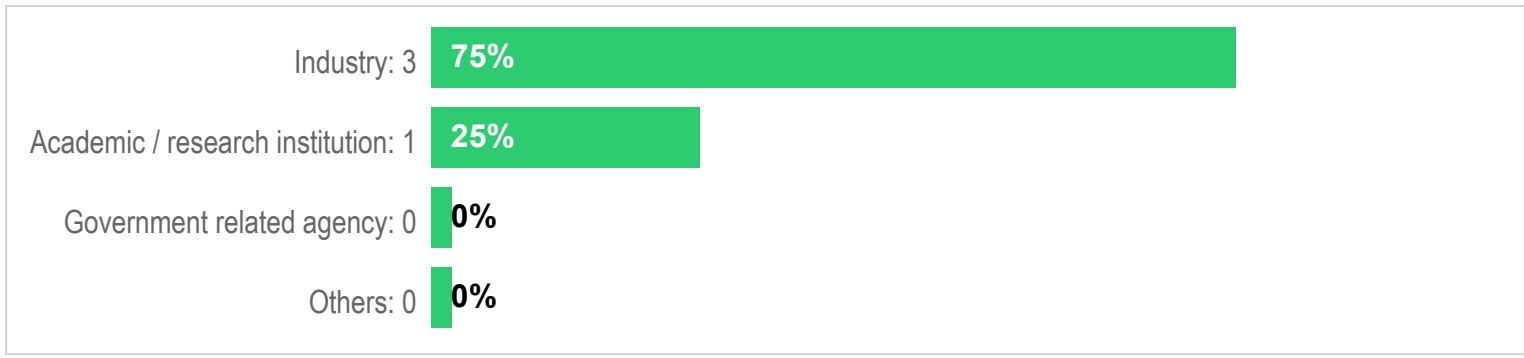
3. Kindly specify the proposed change / comment / enquiries.*

Total Answered	Total Bucketed	Total Pending	
23	0	23	Click to bucket!

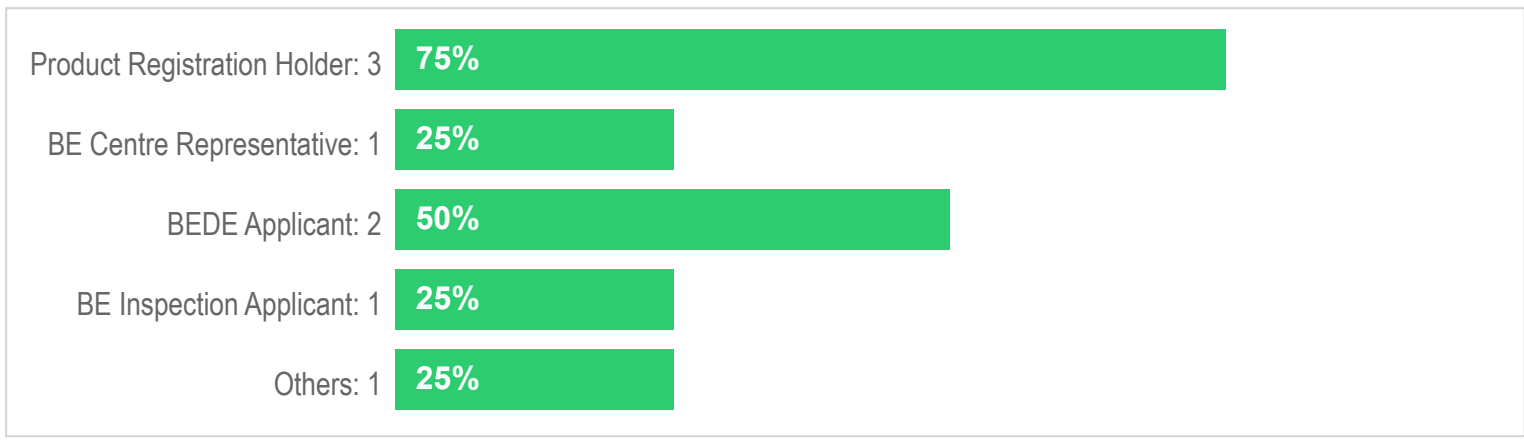
Results

Close

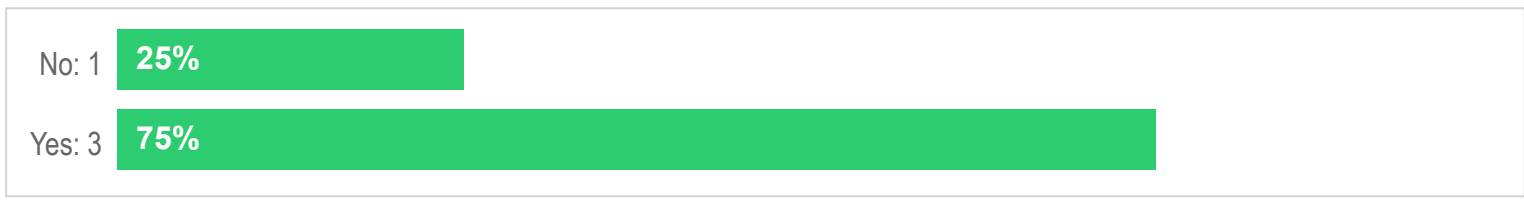
1. Affiliation*



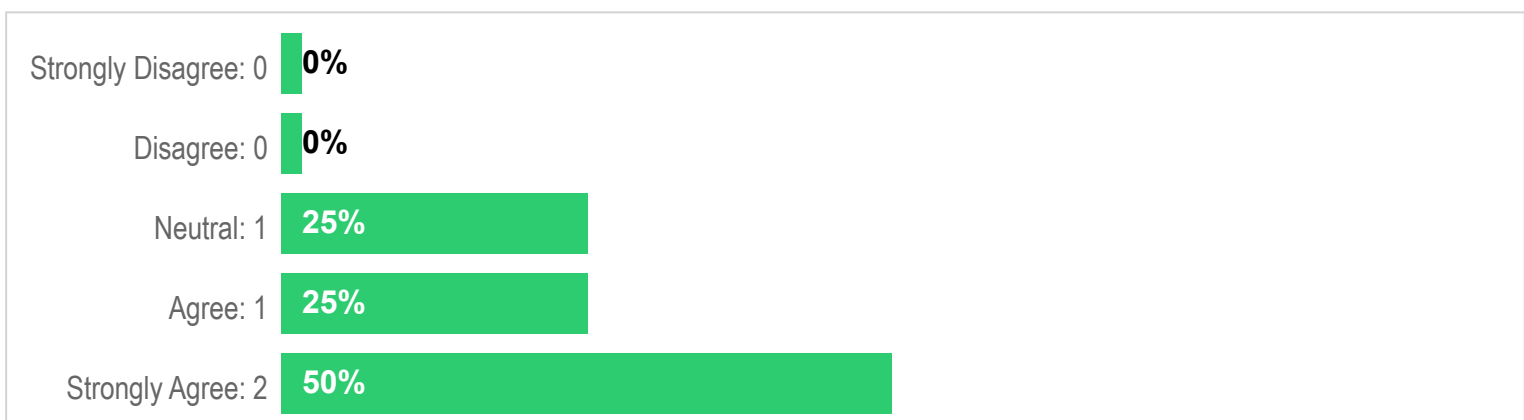
2. Role in bioequivalence study*



3. Have you read the previous edition of this guideline?*



4. Do you agree if the name of bioequivalence centre (clinical site / bioanalytical site) and its inspection outcome (compliant / non-compliant) published to the public via NPRA website for transparency purposes?*



5. If the answer for question 4 is Disagree or Strongly Disagree kindly specify the reason.*

Total Answered	Total Bucketed	Total Pending	Click to bucket!
4	0	4	