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COMPENDIUM OF ABSTRACTS

Regulatory Agility Navigating Winds of Change

2023 National Regulatory Conference

15 – 17 August 2023

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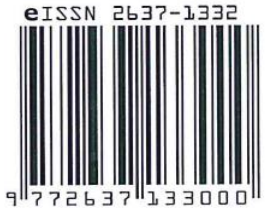

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EDITORIAL BOARD

2023 National Regulatory Conference

Background

The National Regulatory Conference is a biennial event jointly organised by National Pharmaceutical Regulatory Agency (NPRA) and the Malaysian Pharmacists Society (MPS). The conference provides a platform for local and international experts from both the regulatory authorities and the industries to share research findings, latest updates and current issues in regulatory. The theme for this year's conference, "Regulatory Agility, Navigating Winds of Change" aptly represents NPRA's effort to fulfil the demands for timely access to medicines and vaccines needed during the Covid-19 pandemic. A regulatory system that is agile yet fastidious is the key to ensure that only efficacious, safe and of quality products are granted approval amidst the limited availability of evidence.

Objectives of National Regulatory Conference 2023

1. To disseminate information on recent developments in the regulatory landscape
2. To share regulatory experience in navigating the challenges of the pandemic
3. To promote current best practices towards regulatory excellence

List of Poster Presentations

1. A Study to Identify the Common Deficiencies with Generic Product Applications Assessed by NPRA
2. Determination of Ethanol, Isopropyl Alcohol and Methanol in Alcohol-Based Hand Sanitiser to Ensure Product Quality, Safety and Efficacy
3. Cumulative Correspondence Time On Applicant Side for Registration of New Chemical Entity and Biological Products
4. Resilience in Malaysia Clinical Trial Approval During COVID's Pandemic
5. Local Quantitative Signal Detection (QSD): An Overview of Adverse Drug Reaction Signals Detected by National Pharmaceutical Regulatory Agency (NPRA)
6. An Evaluation of Customer-Related Services in The National Pharmaceutical Regulatory Agency (NPRA)

Abstracts

Abstract 1

A Study to Identify the Common Deficiencies with Generic Product Applications Assessed by NPRA

Seetha Ramasamy[1], Kobu Thiruvanackan[2], Wong Chui Shan[1], Fauziah Mohamed Kasim[1], Carol Ling Hui Ming[1], Muhammad Fariq Afifi Abdullah[2], Sim Bee Ai[3]

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Introduction: Even with the improvement of the online submission system and guidelines, a high number of generic product applications are rejected during screening.
Objective: This study aimed to identify common deficiencies with generic product applications that may delay the review process, identify areas for potential improvement and help future applications.
Method: A retrospective search of generic products rejected during screening was performed using NPRA's Quest 3+ database via MySQL system from January 2017 to May 2019. Information on the remarks made during screening was analysed and categorised according to ASEAN Common Technical Dossier (ACTD) and Quest 3+ sections. The number of remarks for each category was calculated to find the most common deficiencies during submission. A validated Google survey form was sent to generic product applicants from January to April 2020 to identify the sections perceived the most difficult to fill according to the ACTD and Quest 3+ sections.
Results: An average of 81% screening applications were rejected yearly from 2017 till 2019. From January 2017 to May 2019, 940 rejected screening applications were analysed from Quest 3+. A total of 96 respondents answered the survey. From the screening rejection, sections with the highest comments from evaluator were Specification of Finished Product; Packaging particulars; Drug Substance; Manufacturing Process & Process Validation; and Analysis Protocol & Method Validation. From the survey analysis, sections perceived as difficult by applicants were Analysis Protocol & Method Validation; Drug Substance; Bioequivalence Study; Manufacturing Process & Process Validation; and Stability Study. Based on the survey feedback, the common problems encountered in these sections were due to the Quest 3+ system, lack of knowledge and country specific requirements.
Conclusion: This study demonstrated a different understanding of common deficiencies between regulators and industry. Improvements on the Quest 3+ system, guidance documents, training, standardization of requirements, Good Submission and Review Practice have been implemented based on the feedback given.
Keywords: Generic, Drug, Product, Common Deficiencies, National Pharmaceutical Regulatory Agency (NPRA).

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Abstract 2

Quantitative Determination of Ethanol, Isopropyl Alcohol And Methanol In Alcohol Based Hand Sanitizer From The Malaysian Market

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Introduction: The World Health Organization recommends hand hygiene to minimize COVID-19 spread, using soap and water or alcohol-based hand sanitizer (ABHS). ABHSs reduce virus transmission via skin contact. Unfortunately, many competing ABHSs have uncertain quality, safety, and effectiveness, posing a risk to consumers.

Objective: The study aims to test ABHS quality in Malaysia by developing and validating an analytical method using gas chromatography-mass spectrometry (GC-MS). This method identifies and measures ethanol or isopropyl alcohol as the active ingredient, and detects methanol as an impurity.

Method: A thorough and careful development process was carried out to optimize the chromatography method using GC-MS in Selective Ion Monitoring (SIM) mode. The method obtained from this process was then validated following the guidelines provided by the International Council for Harmonization (ICH) in their Harmonized Tripartite Guideline: Validation of Analytical Procedures: Text and Methodology Q2 (R1). Subsequently, the validated method was utilized to test ABHS products.

Results: Good linearity ($r2 > 0.999$ over the corresponding specification range), sensitivity (methanol limits of quantification, 1.15% v/v), accuracy (98–101%), and precision (RSD (%) < 5%) were achieved for the analysis. The method was effectively utilized to analyse 112 samples of ABHSs. Out of these, 13 samples were found to have inadequate levels of the active ingredients, accounting for less than 60%. Alarmingly, 6 samples were discovered to contain excessive methanol, surpassing the safety limit of 5%. The highest methanol content in these samples reached up to 24% in relation to the active alcohol percentage.

Conclusion: The findings of this study highlight the necessity of ongoing testing of ABHSs available in the Malaysian market. Furthermore, GC-MS has been proven to be a reliable and effective technique for carrying out this essential task.

Keywords: COVID-19, alcohol-based hand sanitiser, gas chromatography-mass spectrometry.

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Abstract 3

Cumulative Correspondence Time on Applicant's Side for Registration of New Drug Products and Biologics

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Introduction: The total time taken for a product, from submission to registration, includes NPRA's evaluation time and the time for the applicant to respond. In order to facilitate faster access, one of the steps initiated by NPRA is to limit the correspondence time on the applicant's side to a cumulative of 6 months. If the cumulative time on the applicant's side exceeds 6 months, the product can be rejected. This is applicable across all product categories. However, for new drug products (NDP) and biologics, the dossier is more complex and extensive. Therefore, the applicant may need a longer time to provide feedback to the questions raised.
Objective: The objective of this research is to collect and analyze the cumulative time on the applicant's side for products under evaluation from 1 April 2022 to 11 May 2023, in which the first correspondence has been issued.
Method: The total time was calculated using Microsoft Excel based on stop clock basis from the Quest 3+ system. Data were analyzed using Microsoft Excel and reported as average and percentage.
Results: Out of a total of 119 NDP, 37.8% exceeded the cumulative time of 6 months on the applicant's side while for biologics, 29% out of 62 products exceeded the 6months timeline. On average, applicants required approximately 60 days at each stage of correspondence. The main reasons for exceeding 6 months can generally be grouped into two: either the applicant needed more time to respond or NPRA requested for new data due to issues of quality/safety/efficacy/policy.
Conclusion: The findings from this study will be used to propose an extension to the cumulative correspondence time on the applicant's side for the registration of NDP and biologics so that these products, mostly without alternatives, can be made accessible in due time and not be rejected if they exceed 6 months.
Keywords: product registration, marketing authorization, timeline.

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Abstract 4

Navigating Regulatory Resilience: Clinical Trial Approvals Amidst the COVID-19 Pandemic in Malaysia

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Introduction: The COVID-19 pandemic has posed unprecedented challenges to global healthcare and the economy, but it has also created opportunities for process innovation. Despite the pandemic's impact, clinical research in Malaysia contributed RM 1.025 billion to the national income and 2688 skilled jobs in 2022. The National Pharmaceutical Regulatory Agency (NPRA) clinical trial approval, through issuance of Clinical Trial Import License/ Clinical Trial Exemption (CTIL/CTX), plays a crucial role in safeguarding public health by conducting scientific assessments of investigational products. Fast-track review for the CTIL/CTX application was introduced in August 2020 allowing faster access to COVID-19 therapies.
Objective: This study aims to compare the evaluation time of investigational products undergoing fast-track review versus standard review and the contributing factors associated with the differences in evaluation time.
Method: A retrospective database search was performed to identify CTIL/CTX applications approved between January 2020 and March 2023. STATA® and Microsoft Excel® were used to compare the evaluation days between the fast-track reviews versus standard reviews.
Results/Discussion: A total of 260 CTIL/CTX applications were analysed, with 242 undergoing standard review and 18 undergoing fast-track review. Unpaired t-test revealed a significant mean difference in evaluation days (14.55, $p<0.001$), with fast-track review (mean=7.33, 95%CI 5.83-8.84) significantly shorter than standard review (mean=21.88, 95%CI 20.70-23.06). In addition, strategic implementations of group evaluation, online screening and prompt Frequently Asked Question updates on NPRA website optimised the efficiency of clinical trial approval process without compromising the quality of review.
Conclusion: NPRA successfully utilised the fast-track review approach to reduce the evaluation timeline for CTIL/CTX applications during COVID-19 pandemic. This model could be implemented in future public health emergencies and also serve as references for other regulatory authorities.
Keywords: COVID-19, regulatory review, clinical trial approval, fast-track review, public health emergencies.

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Abstract 5

Local Quantitative Signal Detection (QSD): An Exploratory Study of Adverse Drug Reaction Signals Detected by National Pharmaceutical Regulatory Agency (NPRA)

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Introduction: Quantitative signal detection (QSD) is used to identify drug-reaction pairs that are disproportionately reported from the database. In Malaysia, Adverse Drug Reaction (ADR)/Adverse Event Following Immunisation (AEFI) reports received by National Pharmaceutical Regulatory Agency (NPRA) are assessed by the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) before submission to the World Health Organisation global database (VigiBase). As of December 2022, the Malaysian database contains approximately 250,000 ADR reports. Therefore, QSD methods are needed for further drug safety monitoring.

Objective: To present drug- reaction pairs identified using local QSD based on VigiBase.

Method: The signal detection process consists of Signal triage; Signal validation and prioritisation; Signal assessment and Signal endorsement. Using Information Component (IC), disproportionality was periodically assessed from the Malaysian data in the VigiBase from June 2020 to February 2023. Criteria set to identify potential signals were drug-reaction pairs with: $N_{observed} \geq 3$; $IC_{025} \geq 0$; reports received within the past 3 years ≥ 50%; reaction that is not related to medication error, abuse, misuse, drug ineffectiveness, disease progression, and death; and reaction that is unlisted in the package insert. Reports for validated signals were then prepared and presented to MADRAC for endorsement.

Results: A total of 2,678 drug-reaction pairs have been triaged and 579 potential signals have been identified, 144 validated, 44 assessed and 13 endorsed by the MADRAC. Out of these, seven (7) signals are recommended for local risk minimisation actions and six (6) for continuous monitoring. As clinical trials usually provide limited information, some ADRs can only be detected after long-term use and based on local epidemiology data.

Conclusion: In this feasibility initiative, Malaysian signal detection activities have the potential to identify drug-reaction pairs for assessment to further strengthen pharmacovigilance and drug safety monitoring.

Keywords: Quantitative signal detection, pharmacovigilance, signal, adverse drug reaction, database.

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Abstract 6

An Evaluation of Customer-Related Services in the National Pharmaceutical Regulatory Agency (NPRA)

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Introduction: As the only regulatory body that regulates medicinal products, traditional medicines, health supplements, and cosmetics in Malaysia, NPRA provides services to cater to the needs of customers in areas such as product registration, cosmetics notification, and post-marketing activities.
Objective: The objective of this study is to evaluate the perceptions of customers towards the customer-related services provided by NPRA.
Method: This cross-sectional, questionnaire-based study was carried out among related industry players, government staff (non-NPRA staff), public and healthcare providers from 1st February until 30th April 2022, using an online self-administered questionnaire. The online form was distributed through email and also by announcement on the NPRA's official website. The perceptions of respondents were evaluated through 12 service-related questions. A 5-point Likert scale, where 1 = strongly disagree, while 5 = strongly agree, was used to indicate the level of agreement.
Results: Of 384 responses targeted, 251 were received, giving a response rate of 65%. Among the services provided in NPRA, a higher percentage of industry agreed that the payment process in NPRA was fast and easy while the government staff (non-NPRA staff) perceived that NPRA employees were professional and able to communicate well. Percentages of disagreement were observed to be higher in the areas of application processes related to regulatory activities and the telecommunication system at NPRA.
Conclusion: The majority of customers who have experienced customer-related services in NPRA have a good perception towards the services provided. However, there is still improvement needed in the services provided in order to deliver a better customer experience.
Keywords: Customer service, customer's perception, customer's experience, service quality, regulatory agency.

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