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CONFERENCE ABSTRACTS

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Regulatory sciences and quality

Unlocking possibilities in pharmacy practice: The nexus between practice, policy, and education

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Background: Pharmacy profession keeps changing with advances into new frontiers requiring versatile and hands-on professionals. Demand for practical hands-on skills is higher than ever. According the International Pharmaceutical Federation (FIP) Pharmacy Workforce Transformation Programme, there is a need to invest in the development of adaptable, flexible and competent pharmaceutical workforce to realize Universal Health Coverage (UHC), Sustainable Development Goals (SGDs) and to strengthen health systems. A study by the Ministry of Health on Kenya's Pharmaceutical Industry Index established that pharmacy courses offered by local universities were theoretical devoid of practical skills. These give basis to need for practical and pragmatic training in line with emerging practice and policy transformations.

Solution: To bridge the gap between practice, policy, and education – African Pharmaceutical Network in 2022 conceptualized the Pharmacy Academy, an institute that focuses on pharmaceutical sciences and practice with an aim of training market ready, fit for purpose professionals for Africa's pharmaceutical future. Targeting pharmacists and pharmaceutical scientists, courses are delivered by practicing professionals. Started in April 2023 with Regulatory Affairs training, the courses are accredited by the FIP and Pharmacy and Poisons Board (PPB). To infuse industry trends and foster learning, guest lectures are included in the program coupled with case discussions & presentations. The Academy has three programs on offer i.e., Regulatory Affairs, Pharmacovigilance & Patient Safety and Pharmaceutical Supply Chain Management. Cognizant of the regulatory frameworks and role of policy in practice, each course has a policy module to mainstream policy-minded practice. The courses are delivered over a period of three (3) months with enrolment on a rolling basis in cohorts at a fee of USD. 300 for non-members and USD. 250 for members.

Impact: We have trained 123 pharmacists in Regulatory Affairs with over 20 having secured roles since graduation. The other programs in their second cohort of offering have 47 learners enrolled. We have our alumni engaged in ongoing policy projects e.g., the African Medicines Agency (AMA) ratification advocacy. Beyond employment, we measure impact based on the level of engagement of our alumni in industry forums to shape policy priorities & practice.

Conclusion: Fit-for-purpose education and training programmes that equip pharmacists & pharmaceutical scientists are critical in driving industry transformations. The Pharmacy Academy delivers programs to bridge this gap through various short courses. To support this, there is need for continued investment and structured collaboration in untouched domains where the value of such programs will contribute to the furtherance of the profession of pharmacy.

Pharmaceutical track and trace (E-Pedigree) technology: Challenges and opportunities for pharmacists

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Introduction: Healthcare has become one of the crucial industries in the World. All countries experience similar challenges such as increasing healthcare expenditure, proliferation of counterfeit medicines, and aging population. These challenges force policymakers to adapt strategies for the protection of public safety and for ensuring cost-

containment of healthcare products and services. In parallel, the regulatory environment is continuously changing in response to the effects of globalization and harmonization, outsourcing of emerging markets, the increasing complexity of disease targets, the introduction of new technologies, and the rising sophistication and demands of both patients and healthcare systems. The use of technology is an important enabler of business transformation encouraging and facilitating closer relationships between regulators, payers, healthcare providers and patients as well as tackling the menace of counterfeit and parallel trade The track and trace system (TTS) provides policymakers with valuable data through dashboards and reports to make strategic decisions and ensure the traceability of pharmaceutical products from the manufacturer throughout the supply chain network. This will ultimately improve product handling and recall processes and prevent the sale of expired products while preventing counterfeit drugs from entering a national supply chain. The objectives of TTS are to monitor drug availability, prevent counterfeit drugs and ensure drug safety. Purpose: To identify the opportunities and challenges for pharmacists that will enable them to lead the development and implementation of TTS in different healthcare settings.

Method: As TTS is a relatively new and complex system, a scoping literature review will be conducted to identify the most recent development for TTS and to propose a model for pharmacists' role in the development and implementation of TTS.

Results: Recently, traceability systems and mechanisms have been identified by the National/Regional Regulatory Authorities (NRRA), as a useful and efficient tool to fight against the falsification and illicit distribution of medical products. The following challenges can be considered as opportunities for pharmacists to excel and provide valuable contributions to the TTS:
•Operational problems are likely to occur during system implementation, which NRRA and pharmacists should be prepared to face and solve.
•Pharmacists may effectively contribute to the redesign of product packaging, because the application of the data carrier will require product packaging with contrasted colors that may ultimately impact on the mandatory text required by regulations.
•Consideration should be given to the integrity and security of the data carrier; pharmacists should ensure that the appropriate materials are used so that the data carrier cannot be tampered with or altered throughout the whole chain. As the volume of serialized products increases, receipt and dispatch time delays may occur at wholesale distributors.
•Access to safe, quality, efficacious and affordable medical products need to be taken into account when developing and implementing the appropriate TTS.

Conclusion: As initiatives from well reputed organizations such as the WHO and US-FDA have taken place to develop and implement TTS, pharmacists are in a unique position to lead this technology transformation which improves drug supply chain counterfeit prevention and promotes patient safety.

CT-Luso – Ethics and regulatory capacity building partnership for clinical trials in Portuguese-speaking African countries

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Introduction: Africa offers excellent opportunities for conducting Clinical Trials (CT), particularly due to its epidemiological and genetic diversity. However, only 3,3% of global clinical trials take place on the continent. Several barriers hinder the conduct of CTs and the attraction of international investment, including ethical and legal gaps, and the need for enhanced training for professionals involved.

CT-Luso is an ethical and regulatory capacity building project focused on CTs in the Portuguese-speaking African Countries (PSAC): Angola, Cape Verde, Guinea-Bissau, Mozambique, and São Tomé and Príncipe, partnering with Portugal. This initiative involves 24 institutions engaged in biomedical research across six countries, including National Regulatory Authorities, Ethics Committees, Research Centers, and Universities. The project is funded by the Global Health EDCTP3, with support from the European Union, and will run for 40 months, beginning in September 2024.

CT-Luso aims to strengthen and harmonize the ethical and legal framework for conducting CTs and to enhance the functioning of competent institutions. It focuses on training professionals to effectively manage these processes in pursuit of international validation for research. Ultimately, it seeks to create a community of practice that ensures the continuous development of the project beyond its term, thus, building a strong foundation for establishing a Portuguese-speaking network for CTs. This network will facilitate the submission of research protocols across the five PSAC.

Methods: The Project is structured into eight work packages (WP): coordination and management (WP1), scientific leadership (WP2), analysis of legislative gaps and recommendations (WP3), training programs (covering WP 4, 5, 6, and 7), and communication (WP8).

Within the scope of WP3, CT-Luso has conducted a comprehensive study of existing biomedical research legislation and the regulatory frameworks of the competent bodies in the PSAC.

Results: The survey reveals a diverse and complex scenario regarding the regulation of biomedical research in the countries involved. Some countries, such as Guinea-Bissau and São Tomé and Príncipe, still lack a formal legal framework or have draft legislation that is not yet approved, like Cape Verde; others, namely Angola and Mozambique have established and regulated legal frameworks for biomedical research, including clinical trials. Nevertheless, all the countries surveyed show increasing awareness of the fundamental ethical principles essential for ensuring the quality and safety of research.

The analysis indicates that several key ethical aspects, aligned with international best practices, have already been incorporated into the legislation and/or draft legislation of all the countries. These include the primacy of human dignity and the protection of human beings, which underpin the ethical standards governing clinical trials, as well as the requirement for ethical approval before conducting studies. In addition, other requirements, such as obtaining informed consent in a clear and transparent manner, the confidentiality of participants' personal data and a rigorous assessment of the risks and benefits involved in trials, are also covered by current or draft legislation in all the countries analysed.

Conclusion: This survey provides a solid basis for the formulation of recommendations aimed at closing regulatory gaps and promoting the harmonization of ethical and regulatory practices.

Assessment of therapeutic equivalence of levothyroxine sodium in pharmaceutical tablets in Lebanon via novel analytical techniques: Quantitative analysis, in vitro release and tablet mapping

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Introduction: Levothyroxine sodium – classified as a narrow therapeutic index drug- is one of the most prescribed medications in the world, administered orally as a thyroid hormone replacement therapy in cases of hypothyroidism. However, from literature and clinical practice, its bioavailability has been questioned and drug recalls have been issued for some formulations in sense of impaired potency and therapeutic failure. In Lebanon, due to limited availability of doses, some patients were required to split tablets to achieve the required therapeutic dose. Also, in some cases of drug shortages, some patients switched between levothyroxine formulations whether brands or generics. Both cases, when monitored showed cases of hormonal imbalance suggesting inaccurate dose administration and inadequate bioequivalence.

Purpose: In light of that, this study aimed to develop novel analytical techniques for the quantification of levothyroxine, its distribution amongst the excipients and bio-waiver studies as a guide towards bio-in-equivalence risk and to better predict its bioavailability.

Method: In this work, content of each part of the split tablets were quantified using UV-spectrophotometric method. Moreover, four different advanced techniques were used to quantify levothyroxine in its pharmaceutical formulations including the High-performance liquid chromatography (HPLC), Fourier transform infrared (FTIR) spectroscopy, Particle Induced X-ray Emission (PIXE) and Time of Flight-Secondary Ion Mass Spectrometry (ToF-SIMS). Additionally, the dissolution apparatus was used to conduct in vitro biowaiver study. Besides, Tof-SIMS was used as an imaging technique to check levothyroxine's distribution amongst the excipients.

Results: This study successfully developed and validated new methods for levothyroxine's determination with high accuracy and precision. Tablets were found to comply with the labelled amount. However, the tablet splitting practice did not always give the accurate required dose as different employed splitting techniques resulted in non-uniformity of half tablet weight relating to different drug content. The sensitivity of the different proposed methods can be confirmed by the low limit of detection and quantitation values, 0.953 and 3.18 g/mL, and 8.121 and 24.545 µg/ pellet for the HPLC and FTIR respectively. A detection limit of 2.70 µg/tablet was achieved using the PIXE technique demonstrating high sensitivity and accuracy in the detection. The HPLC method was used to analyze the dissolution samples in the three dissolution media for different levothyroxine pharmaceutical formulations. Results revealed dissimilar dissolution profiles suggesting bio-in-equivalence. It was found that the best fit model for levothyroxine release kinetics was the Higuchi model. Key findings from the ToF-SIMS technique was chemical characterization and behavior of levothyroxine under the experimental conditions. Results revealed the ability to quantify levothyroxine in a specific matrix. Also, chemical distribution of levothyroxine was mapped, showing a dot-like cluster distribution of the drug in the present tablet.

Conclusion: Overall, due to the variation in the dissolution profiles and in the split tablets, a recommendation should be addressed to endocrinologists and pharmacist to limit such practices of switching and asking the patients to split tablets.

To ensure product efficacy, stability and patient safety, not only the content of levothyroxine sodium should be considered, but also therapeutic efficacy by hormonal monitoring is highly advised.

Comparison of treatment effects between ACR response criteria and target-based outcomes for contemporary rheumatoid arthritis drug approval trials: A meta-epidemiological study

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Introduction: Regulatory priorities diverge between agencies - the FDA maintained ACR20 response as primary endpoint in rheumatoid arthritis (RA) trials, whereas the EMA emphasized target-based outcomes centered on remission and low disease activity (LDA). To systematically compare treatment effect estimates between American College of Rheumatology (ACR) response criteria (ACR20/50/70) and target-based outcomes in placebo-controlled trials of approved RA therapies.

Methods: A meta-epidemiological study was performed on randomized placebo-controlled trials investigating approved biological and targeted DMARDs (bioDMARDs and tsDMARDs) in patients with RA. Trials reporting at least one ACR response criterion and one target-based outcome were included. Odds ratios (ORs) for each outcome were computed, followed by calculation of a risk of odds ratio (ROR) to quantify differences in treatment effects between ACR and target-based outcomes. The primary outcome was the treatment effect differences between ACR20 and target-based efficacy estimates, and the second outcome was to explore which alternative ACR response criteria was concordance with target-based outcomes.

Results: A total of 53 RCTs (392 study arms) involving 30,778 RA patients were analyzed. Trials using ACR20 demonstrated significantly greater treatment effect estimates compared to those using remission outcomes (ROR = 0.65, 95% CI 0.52–0.81) and LDA outcomes (ROR = 0.78, 95% CI 0.69–0.89). Higher ACR thresholds (ACR50 and ACR70) showed closer agreement with target-based outcomes, with ACR70 aligning with remission (ROR = 0.88, 95% CI 0.76–1.01) and ACR50 aligning with LDA (ROR = 0.95, 95% CI 0.81–1.11). Subgroup analyses indicated that the discordance between ACR20 and target-based outcomes persisted across different intervention drugs, comparison types, and previous treatments.

Conclusion: ACR20 overestimates treatment effects relative to target-based outcomes, while ACR50/70 demonstrate better concordance. Harmonizing endpoints by integrating more stringent ACR response or co-primary endpoints (ACR response criteria + target-based outcomes) could bridge regulatory discrepancies and enhance clinical relevance in RA drug development.

Qualification of MFDS Reference Standards (RS): Confirmation of quality suitability and assignment of characteristic values

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Reference standards (RS) are highly purified and characterized specimens of drug substances, excipients, reportable impurities, degradation products, compendial reagents, and performance calibrators. In order to support product development and quality control in the pharmaceutical industry, we have been establishing and providing RS since 1991. In 2024, twenty new RS were prepared for national essential medicines whose stable supply is difficult through market functions alone, medical narcotics that have high unit prices and complicated import procedures that take a long time to secure, and pharmaceuticals listed in the Korean Pharmacopoeia monographs. In this study, candidate substances were selected to reflect industry demand (6 candidates for national essential drugs, 2 candidates for medical narcotics, 10 candidates for KP listed drugs and etc), and then the determination of quality suitability as RS was conducted. After identifying the candidate substances, including structure and molecular weight, using such as NMR and HRMS, in order to determine the content value of the candidates, a total of four institutions were participated, including ISO 17025-accredited institutions and GMP-certified pharmaceutical company-affiliated laboratories. After measuring the amount of impurities, volatile impurities (loss on drying test, or water determination and residual solvents test), inorganic impurities (residue on ignition test), and organic impurities (gas or liquid chromatography), in each candidate at four institutions, the content value was calculated using the mass balance method. As a result, the content values were 94.94~99.91% (as is) and the uncertainty were ± 0.018~0.222, which meet the internal compliance criteria of the Ministry of Food and Drug Safety(MFDS). These candidates are being supplied to the pharmaceutical industry as MFDS RS from 2025.

On-line and off-line SPE in drug analysis from biological material: A comparison based on green analytical chemistry approach

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Background: Large molecules and interfering species should be eliminated from biological material like blood, plasma, urine, breast milk, etc. prior to analysis because of the complex matrices containing proteins, salts, and other organic compounds. Conventional methods typically require large sample volumes, incur high consumable costs, involve exposure to toxic chemicals, and demand long sample preparation steps. In contrast, on-line sample preparation techniques eliminate these drawbacks, offering faster analysis, reduced waste, and more accurate results. Green analytical chemistry focuses on specific practices, including minimizing material and energy use, reducing waste, lowering occupational risks for analysts, decreasing or eliminating solvent disposal, and shortening analysis time. On-line sample preparation techniques meet several of these requirements. In order to specify Analytical GREEnness (AGREE) assessment criteria, twelve principles of green analytical chemistry were converted into a single 0–1 scale, where 1 represents the greenest score. Green Analytical Procedure Index (GAPI) is a tool used to value the environmental impact of a complete analytical process. It symbolize different phases of the methodology through colored pentagrams. Each pentagram centers on a specific view: sampling, analytical technique, sample preparation, the type of solvents and reagents used, and the energy required for the procedure.

Purpose: In the present study, determination of cefuroxime (CEF), a broad-spectrum antibiotic that combats bacterial strains and exhibit lactamase activity, in breast milk was performed by a newly developed and validated on-line SPE-LC method. The greenness profile of the on-line SPE procedure was compared with a hypothetical off-line SPE procedure developed by existing studies.

Method: On-line SPE-LC was performed by a system equipped with a DAD detector, a 10-port switching valve and a dual gradient pump. A C18 column was used and the SPE column was in-house packed with strong anion exchange sorbent. Acetonitrile and aqueous 10 mM o-phosphoric acid solution made up the mobile phase of the dual gradient program. AGREE and modified GAPI (moGAPI) tools were used to assess the greenness profile of the on-line and off-line procedures.

Results: On-line SPE-LC method provided good recovery (≥96.52%) and precision (RSD ≤1.18%) within the linear range. The AGREE and moGAPI scores of on-line and off-line SPE procedures were calculated as 0.59 and 76%, and 0.43 and 68%, respectively. Direct injection of the breast milk sample, complete automation, lower use of chemicals and a higher number of analyses per hour provided a better AGREE score for on-line SPE. The higher greenness of on-line SPE moGAPI chart was caused by no additional pre-treatment requirements.

Conclusion: On-line systems serve green analytical chemistry, reducing all the drawbacks of traditional off-line techniques. Green and sustainable analytical chemistry are significant new trends by means of 5 rules: reduce, reuse, recycle, repurpose, and replace. In this study, a model study was proposed serving four of these rules as reduce/replace/repurpose/reuse by using on-line SPE-LC method for the determination of CEF in human breast milk.

The contribution of signal detection in promoting safety, quality and efficacy of medical devices

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Introduction: The safety, quality, and efficacy of medical devices are paramount in advancing patient care and public health. Signal detection serves as a fundamental component of post-market surveillance, facilitating the identification and management of potential safety concerns. Existing methodologies face critical limitations, including inconsistencies in data collection, lack of standardisation, and inherent biases in reporting practices. This research aims to assess the contribution of signal detection in medical device vigilance, focusing on its impact on regulatory decision-making and its role in improving safety, quality, and efficacy while optimising benefit-risk assessments.

Method: The research employs a multi-phase, systematic methodology, commencing with a comprehensive scenario analysis of existing signal detection and management practices, including a comprehensive review of regulatory frameworks and global vigilance systems to identify gaps and harmonisation methodologies. Standardised definitions of signal detection will be established through expert focus groups comprising economic operators, healthcare professionals, and pharmacovigilance specialists. Incident reports from a local hospital will be analysed to identify key reporting triggers, with expert validation of guidance documents. A training program will be developed for regulatory authorities and healthcare professionals, enhancing expertise in signal detection and incident reporting. This structured approach aims to improve vigilance practices, regulatory policies, and patient safety in medical device surveillance.

Results: This framework is designed to standardise incident reporting and enhance regulatory oversight through a scientifically validated approach. Expected findings include identifying gaps in data collection and underreporting trends that impact vigilance efforts, reinforcing the need for harmonised signal detection strategies. Integrating artificial intelligence into signal detection is anticipated to enhance the ability to identify emerging risks efficiently, minimising delays in regulatory action. Stakeholder engagement through expert validation is expected to improve the reliability of incident reporting. The research will assess the influence of the European Medical Device Regulation (EU 2017/745) on vigilance strategies, promoting a proactive approach to post-market surveillance. The targeted training program for regulatory authorities and healthcare professionals will improve expertise in signal detection, ensuring better compliance and enhanced patient safety outcomes.

Conclusion: The research addresses critical knowledge gaps, including the underreporting of incidents and the lack of harmonisation across regulatory authorities. The research will strengthen regulatory policies and guide industry stakeholders in adopting best practices for addressing safety concerns. Expected outcomes include strengthening signal detection and management practices through evidence-based approaches, improved medical device regulations, and innovative courses on signal detection and management will be presented. By establishing a robust, scientifically validated framework for signal detection, this research seeks to mitigate risks associated with medical devices, ensuring their safe and effective use while enhancing patient outcomes. This research contributes to the field of regulatory sciences by addressing the challenges of medical device surveillance, offering innovative solutions to foster a safer and more effective healthcare system.

Antihypertensive activity of ethyl acetate fraction of Hydrocotyle javanica Thunb. in anaesthetised spontaneously hypertensive rats

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Introduction: Hypertension is a major risk factor for cardiovascular mortality. Hydrocotyle javanica Thunb (H. javanica), a tropical herb widely found in Malaysia, is traditionally claimed to have antihypertensive properties, but its effects remain scientifically unverified. This study aimed to determine the antihypertensive effects of the H. javanica fraction on vascular responsiveness in vivo using anaesthetised spontaneously hypertensive rats (SHRs).

Method: The petroleum ether, chloroform, ethyl acetate, methanol, and water extracts of H. javanica whole plants were screened for antihypertensive effects using non-invasive blood pressure measurements in SHRs. The methanol extract, identified as the most active, was further fractionated using liquid-liquid separation technique to obtain hexane, ethyl acetate, and water fractions. The ethyl acetate fraction of methanol H. javanica (EFHJ) extract exhibited the most potent antihypertensive activity and was selected for the mechanism study. For this study, 72 male SHRs (body weight 250 g – 280 g) were anaesthetised with urethane, and tracheotomy was performed. The left jugular vein and right carotid artery were cannulated for drugs/extract administration and direct measurement of mean arterial pressure (MAP) and heart rate, respectively. Only SHRs with a baseline MAP above 130 mmHg were included. After a stabilisation period of 30 minutes, agonists, antagonists, and EFHJ were administered accordingly. The antihypertensive mechanisms of EFHJ were investigated in the absence or presence of L-NAME (nitric oxide synthase inhibitor), indomethacin (cyclooxygenase pathway inhibitor), atropine (muscarinic cholinergic receptor blocker), hexamethonium (ganglionic nicotinic receptor blocker), prazosin (α1-adrenergic receptor blocker), and propranolol (β-adrenergic receptor blocker). The bioactive compounds associated with antihypertensive effect of H. javanica were identified using RP-HPLC.

Results: EFHJ reduced the mean arterial pressure of SHRs in a dose-dependent manner. EFHJ's blood pressure-lowering effects were significantly attenuated by atropine, L-NAME, indomethacin, hexamethonium, and prazosin. RP-HPLC analysis identified catechin, rutin, and quercetin as bioactive compounds present in EFHJ.

Conclusion: The findings collectively indicate that H. javanica possesses antihypertensive properties. EFHJ exerts its antihypertensive effects potentially through muscarinic cholinergic receptor activation, nitric oxide and cyclooxygenase pathways, α1-adrenergic receptor inhibition, and nicotinic ganglionic receptor blockade. Catechin, rutin, and quercetin may contribute to its antihypertensive properties.

Regulatory oversight of patient safety in medical devices

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Introduction: The progressively growing number of patients who depend on medical devices and in vitro diagnostic technologies to improve, maintain, and sustain health, results

not only in enhanced benefits in healthcare, but also in a great need for market regulation to safeguard patients. The aims of this study were to identify weaknesses in medical device patient-centred regulatory sciences, and to develop a post-market surveillance framework that would provide a strategic oversight approach to ensure long-term patient safety.

Method: The methodology design consisted of three phases. Phase I focused on identifying procedures that EU and non-EU countries have in place for the oversight of post-market surveillance and vigilance, coupled with a review of global standards and guidelines. Weaknesses identified from this review were captured in a data collection tool to be disseminated to European regulatory experts involved in surveillance and vigilance activities. Observations collated and evaluated from Phase I informed the development of a regulatory framework in Phase II. Phase III consisted of a SWOT analysis of the framework through pilot testing it on a sample of incident reports identified from a regulatory database.

Results: Phase I identified 5 key areas where patient-centric regulatory weaknesses exist. These areas formed the 5 domains of the data collection tool: (a) resources in regulatory authorities, (b) information on incident reporting, (c) legal requirements on legacy and custom-made devices, (d) the recall process, and (e) the integration of artificial intelligence in surveillance and vigilance regulation. Twelve regulatory experts from different European competent authorities completed the data collection tool. All agreed on the need for training of economic operators on responsibilities of post-market surveillance. The lack of AI integration in post-market surveillance and vigilance was underlined, with only 2 experts confirming its current use. The framework developed in Phase II consists of mapping the processes involved in ensuring safety and performance of medical devices across risk classes, including specific niches such as custom-made devices. It outlines responsibilities of stakeholders involved in post-market surveillance and vigilance to enhance collaboration and inform training modules. Guidelines on integrating AI into regulatory processes are provided. In Phase III, the SWOT analysis of the framework highlighted threats such as outpacing of regulation by rapid advancements in technology, and opportunities such as training and capacity building needs. Vigilance measures, such as field safety corrective actions and trend analysis, that could be taken as risk mitigation strategies throughout the lifecycle of the device, were defined after pilot-testing the framework.

Conclusion: The developed regulatory framework is intended to serve as a proactive resource for regulatory authorities to enhance post-market surveillance and vigilance in medical device regulatory sciences. By addressing key weaknesses and supporting integration of AI-driven solutions, the framework aims to provide a structured approach to mitigate risks while still fostering innovation, to maintain patient safety.

An evaluation of a systematic quality signal extraction framework in medicinal products regulatory sciences

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Introduction: The concept of signals is evolving, particularly in today's increasingly fast-paced and globally interconnected world, where continuous adaptation to change is essential. Pharmaceutical professionals encounter increasing demands to acquire new knowledge, and skill sets whilst leveraging opportunities to construct innovative frameworks and research tools to enhance multidisciplinary learning on a broader scale. Effective quality assurance (QA) in pharmaceutical regulatory sciences necessitates a systematic approach for the identification and management of quality-related signals. Given the absence of a standardised framework, this study introduces a Systematic Quality Signal Extraction Framework (SQSEF) to facilitate consistent signal recognition, categorisation and correlation with key thematic QA principles. The signal framework ultimately aims to contribute to the quality, safety and efficacy of medicines.

Method: This study deals with the SQSEF component of a Quality Assurance Signal Analytics Framework (QASAF). The SQSEF was devised through a retrospective analysis of eleven case studies focusing on Quality Improvement Forms (QIFs) submitted at the Quality, Continuous Improvement and Internal Audits Unit at the Malta Medicines Authority. The SQSEF was validated through a structured expert focus group consultation. The criteria of the SQSEF were evaluated using the Content Validity Method. The suggestions and recommendations made during the validation process led to the development of the template which facilitates the analyses of the identified signals.

Results: The SQSEF incorporates data analysis as a key element, serving as a structured tool to facilitate the recognition of quality assurance signals through the systematic analyses of quality records. The SQSEF is presented in a tabular format comprising four criteria (i) Record Description, a brief explanation of the fundamental rationale for the QIF submission, (ii) Proposed Action Plan, a description of the proposed actionable strategy designed to attain a specific objective within a specified period, (iii) the identification of Positive and Negative Signal(s) and Associated Principle(s), and (iv) the Signal Classification Grading System (SCGS). The SCGS captures each identified signal along its assigned Likert scale value, in accordance with the criteria and threshold outlined in the classification grading system. The criteria and threshold are derived and adapted from the Pharmacovigilance Audits Module, as specified in the EU Guideline on Good Pharmacovigilance

Practices. A formula was devised which assigns a sequential number to an identified signal for each case study, S(x). The identified signals were represented by the notation [S(x)]n, indicating the 'x'-th signal identified in a case study, and 'n' indicating the cumulative number of identified signals, which is not subject to a fixed limit.

Conclusion: A multicriteria evaluation framework was structured and applied as a support for informed strategic decision-making and enhanced regulatory practice in the context of the management of signals for quality assurance in medicinal products regulatory sciences. The framework holds significant application potential, as it encourages an empirical evaluation of signals and associated principles concerning the implications and contributions to the organisational quality management system, process optimisation, regulatory compliance, continual improvement and broader quality assurance factors. It is aspired that the framework serves as a visual and analytical tool for researchers and regulatory professionals.

Cost-effectiveness analysis of neoadjuvant chemotherapy regimens EC-T vs. FAC for breast cancer in Indonesia

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Breast cancer poses a significant global health concern. In Indonesia, it has a high incidence rate, resulting in a substantial financial burden on the national health insurance system. Neoadjuvant chemotherapy (NACT) is an alternative breast cancer treatment, and taxane-based regimens have demonstrated strong clinical efficacy. However, research on taxane-based vs non-taxane regimens for NACT in Indonesia is scarce. This study fills this gap by comparing the cost-effectiveness of EC-T (epirubicin, cyclophosphamide, docetaxel/paclitaxel) and FAC (5-fluorouracil, doxorubicin, cyclophosphamide) regimens.

Method: This cross-sectional study was conducted at Dr M. Yunus Regional Public Hospital and received ethics approval from the Medical and Health Research Ethics Committee (MHREC) at the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr Sardjito General Hospital (reference number KE/FK/0831/EC/2024). It involved adult women (≥18 years) with stage I-III B breast cancer who underwent neoadjuvant chemotherapy using either the EC-T or FAC regimen in an outpatient setting. Exclusion criteria comprised patients with metastatic disease or those who died during treatment. Patients in the EC-T group received four cycles of cyclophosphamide (600 mg/m²) and epirubicin (90 mg/m²), followed by four cycles of either docetaxel (75 mg/m²) or paclitaxel (175 mg/m²). In contrast, the FAC group underwent a six-cycle chemotherapy regimen consisting of cyclophosphamide (500 mg/m²), 5-fluorouracil (500 mg/m²), and doxorubicin (50 mg/m²). A retrospective data of financial and outpatient medical records from January to August 2024 was collected, and subsequent analysis was performed using R Studio.

Results: The study found no significant differences in patient characteristics between the two treatment groups (30 patients in EC-T and 24 in FAC), indicating their suitability for cost-effectiveness analysis. Clinical results revealed that 56.67% of EC-T patients experienced a partial response (PR), whilst 20% experienced a complete response (CR). By comparison, the FAC group's PR rate was 16.67%, and their CR rate was 8.33%. With a 76.67% efficacy rate, EC-T outperformed the FAC group by a substantial margin ($p = 0.000$). Multivariate regression analysis identified the chemotherapy regimen as the primary factor influencing therapy response ($p = 0.001$), while the cancer stage had no significant effect ($p = 0.206$). Direct medical costs of EC-T incurred were higher (IDR 26,221,346 ± 1,626,589) compared to FAC (IDR 17,714,861 ± 2,404,445). Nevertheless, EC-T had a lower Average Cost-Effectiveness Ratio (ACER) (IDR 34,200,268) than FAC (IDR 70,859,443). The Incremental Cost-Effectiveness Ratio (ICER) analysis revealed that FAC required an additional IDR 16,469,917 to achieve a mere 1% increase in effectiveness, thereby confirming EC-T's superior cost-effectiveness despite its higher direct medical costs. A one-way sensitivity analysis confirmed that EC-T's cost-effectiveness held up across most scenarios, bolstering the findings' credibility.

Conclusions: This study indicates that EC-T is a more cost-effective neoadjuvant chemotherapy (NACT) option, with an incremental cost-effectiveness ratio (ICER) below Indonesia's 2023 gross domestic product (GDP) per capita (IDR 73,894,500). Furthermore, the results highlight the potential benefits of taxane-based regimens in neoadjuvant chemotherapy and provide valuable insights for healthcare policymakers to optimise treatment strategies for breast cancer care.

Challenges in accessibility to CE marked medical devices within the European Union

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Introduction: The European Union (EU) has introduced the 2017/745 Medical Device Regulation (MDR), and the 2017/746 In Vitro Diagnostic Regulation (IVDR) to address the safety, quality and efficacy of medical devices available in the

EU market. These regulations introduced challenges to pharmacists and stakeholders, such as medical device manufacturers and importers, involved in the pharmaceutical processes which make use of medical devices. The need for competence building, through pharmacy education and specialisation in taking a leadership role in the assessment of medical devices, was identified. The aim of the study was to identify challenges faced by stakeholders, brought about by the implementation of current EU MDR and IVDR.

Method: A literature analysis was carried out, for the period 2017-2025 to determine the impact of the regulation on all stakeholders involved, using the databases, Hydi – Hybrid Discovery search gateway of the University of Malta, Google Scholar library, and PubMed. The impact of the introduced regulations was also addressed through the review of the published evaluation initiated by the European Commission in 2024, entitled 'EU rules on medical devices and in vitro diagnostics.' Feedback provided by manufacturers and academic and research institutions during online consultations was thematically analysed.

Results: A total of 46 articles were selected for the study. Eleven articles (24%) stated that some medical devices are at risk of market withdrawal, mostly paediatric and orphan medical devices, as a consequence of the need for exceptional market approvals. Reasons expressed for this potential disruption in availability of medical devices are administrative and increased certification expenses (n=16, 35%), followed by expanded requirements for clinical evidence (n=9, 20%), and lack of innovation of new medical devices (n=6, 13%). A sample of 46 responses provided during online consultations was analysed. Twenty-two stakeholders (48%) highlighted increased costs to be the most common challenge faced. Types of costs identified as being challenging included, increased production cost (n=10), qualified human resources (n=2), support for clinical evidence (n=4) and increased requirements for technical documentation (n=6). Additional challenges stemming from the implementation of the regulation, include increased bureaucracy (n=19, 41%), which led to the delayed processing time of notified bodies and comprehensive MDR certification causing a barrier to entry of medical devices on the EU market. Five (11%) are due to increased support for clinical evidence (n=1), qualified human resources (n=2), and lack of guidance and clarity of the MDR regulation (n=3).

Conclusion: The identified challenges highlight the need for the increased demand for competencies required to assist in ensuring the availability of medical devices which abide by the new requirements. An increase in costs for stakeholders, ranging from production to administrative expenses, envisages a more challenging approval mechanism for medical devices. Pharmacists can fill a number of the gaps that exist in this area through the application of their knowledge of regulatory compliance with medical devices research and development. The role of the provision of educational courses in this field is crucial to the success of this role of pharmacists in the regulatory sciences.

Capacity building in the medical device regulatory inspectorate

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Introduction: Harmonised inspections strategies of medical device economic operators are considered as one of the arms of market surveillance activities within the 2017 medical device regulations (EU MDR 2017/745), that enhance the use of safe medical devices on the European market. Cooperation between regulatory bodies and business market is essential to ensure utmost clarity and effectivity in regulation interpretation. Communication is strengthened through inspections of economic operators. Inspectors' capacity can be enhanced through training, resource usage, technical help, assessment, feedback and collaboration. Key competencies for regulatory inspectors can be categorised as (i) regulatory knowledge and technical expertise, (ii) inspection skills and (iii) ethical and professional conduct. The aim was to establish a capacity-building framework for medical device regulatory inspectors within European National Competent Authorities (EU NCAs), presented as a structured guidance document. This initiative focuses on enhancing inspector competencies to ensure robust regulatory surveillance of medical devices.

Method: A validated questionnaire was disseminated to medical device regulatory inspectors across EU NCAs to gather information on the framework implemented, including number and type of inspections carried out, expertise available and training plan of inspectors.The questionnaire included multiple choice, close and open ended questions. Respondents were requested to rate using a 5-point likert scale the challenges faced by the respective NCA and the areas for which inspectors require further training.Observation sessions of joint inspections of EU-based manufacturers (JIMs), as part of Work Package 6 of the Joint Action Market Surveillance (JAMS) Programme were conducted. Inspections of local distributors and importers were also performed. The data collected through the questionnaire and observation sessions was applied for the development of a validated capacity-building framework, serving as a tool for EU NCAs to provide guidance on the required competencies of medical device regulatory inspectors.

Results: Twelve European NCAs answered the questionnaire. Availability of inspectors (n=7) and integration of the IT system – European Database on Medical Devices (EUDAMED) (n=7), were the highest rated challenges faced by NCAs. Main areas in which inspectors require additional knowledge through training, include software as a medical device (n=7), followed by specialist processes (n=6), technical file review (n=4) and experience in design, manufacture and quality of

medical devices (n=5). During the JIMs (N=2) and local inspections (N=3), 'major' non-compliances in the quality management system, such as inadequate documentation control was identified in all of the inspections. Data obtained during phase II, contributed to the development of a framework, incorporating EU NCA's and economic operators' perspectives through questionnaire results and non-compliances observed during inspections respectively. The framework includes sections: (i) key competencies for medical device regulatory inspectors, (ii) training and development, and (iii) competency evaluation and assessment.

Conclusion: The developed framework can be applied as a guidance document, which supports workforce capacity building. Identification of expertise and essential inspector skills across EU NCAs strengthens inspectors' capacity to perform effective inspections and improve regulatory compliance.

Regulatory CMC submission challenges and recommendations for synthetic oligonucleotides and RNA therapies

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Introduction: Synthetic oligonucleotides and RNA-based therapies have emerged as transformative modalities in modern medicine. These therapies, including antisense oligonucleotides, siRNAs, aptamers, and mRNAs, offer highly targeted mechanisms of action. Despite their clinical promise, regulatory Chemistry, Manufacturing, and Controls (CMC) frameworks lag behind, posing significant submission and approval challenges.

Aim: Critical analysis of regulatory CMC submission challenges associated with synthetic oligonucleotides and RNA-based therapies, and to propose evidence-based recommendations to streamline regulatory compliance and approval.

Method: A retrospective qualitative and quantitative analysis was conducted on regulatory documents and dossiers submitted to the FDA and EMA. Four product case studies under regulatory review were assessed. Key areas evaluated included upstream/downstream manufacturing, specification setting, analytical development, impurity profiling, and responses to agency queries. The study utilized document management systems and regulatory literature databases.

Results: The study identified five major areas of regulatory concern:

1. Identity and Purity Specifications = Insufficient identity tests and inconsistent impurity profiling strategies.
2. Manufacturing Challenges = Variability in process control, especially for GalNAc-conjugated and modified backbones.
3. Assay Development = Lack of harmonized assay and potency requirements.
4. Comparability Requirements = Inadequate strategies for post-approval changes due to unclear guidelines.
5. Immunogenicity and Toxicity = Gaps in non-clinical and clinical evaluation expectations for novel modalities.

Agency feedback reflected divergent global standards, underscoring the absence of ICH-specific guidance for synthetic oligos.

Conclusions: CMC compliance for synthetic oligonucleotides and RNA therapies demands a tailored, risk-based regulatory approach. This study proposes:
- SOPs and checklists for oligo-specific CMC documentation.
- A harmonized global regulatory strategy for specification, stability, and impurity qualification.
- Proactive regulatory engagement to pre-empt data gaps.
- Collection of Objection & queries related to immunogenicity of the biological oligonucleotide (Protein Part) clinical safety & efficacy data.

These measures are essential to support dossier readiness, reduce approval timelines, and ultimately, accelerate patient access to innovative therapies across global markets.

Challenges of performing clinical trials

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Introduction: Trials performed in small communities pose challenges due to number of participants and facilities. The aim was to investigate the impact of new regulations, brought into effect in January 2022, for clinical trials in Malta and create a template for clinical trial planning, to outline the steps involved in setting up clinical trials. The new EU guidelines from 2022 outlines the new regulations to be followed when setting up clinical trials, including the use of CITS which is a system that must be used to upload all documentation needed for a clinical trial.

Method: A questionnaire for healthcare professionals was developed to identify experiences and perceptions about challenges in clinical trial participation and this was disseminated in March 2024. Qualitative interviews were held with the national economic development agency to discuss national strategies to attract and support investment and operations in the area of clinical trials, with private pharmaceutical companies and private clinics to establish interest in participating in clinical trials and with medical specialists with experience in clinical trials. Subsequently a

template to guide professionals through procedures was developed intended to address challenges identified.

Results: Forty-five questionnaires were completed by 43 specialist doctors and 2 pharmacists who reported time constraints, lack of funding and infrastructure as the main hurdles. Five private pharmaceutical companies were contacted but these did not show an interest in being involved in any clinical trials. The 3 private clinics contacted showed an interest and are willing to offer all their facilities for such trials. The national economic investment agency highlighted the lack of a Contract Research Organisation (CRO) in Malta as a challenge whilst an interest in strategic measures to attract CROs. Three specialist doctors from Mater Dei Hospital, involved in 3 different types of trials, were interviewed and their main concerns identified. The template developed highlights practical approach to application for approval, setting up a team of health professionals, finding premises and laboratory services, and recruiting volunteers in the context of small healthcare and pharmaceutical ecosystems.

Conclusion: This research identified challenges and opportunities at the level of the national economic development agency and in healthcare systems. The template developed addresses these challenges and serves to support healthcare professionals embarking on participating in clinical trials by serving as a resource that identifies stakeholders which are able to offer funding, facilities like medical clinics, and services like laboratory services. The rationale for aspects in the new EU legislation regulating clinical trials intended to ensure patient safety are highlighted so that healthcare professionals are empowered to navigate the process through proper management and good governance.

Assessment of niacinamide content in commercial skin care products

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Introduction: Niacinamide is frequently used in cosmetic products and has numerous positive effects on human skin such as anti-inflammatory, antimicrobial, photoprotective etc. Cosmetic products in the EU are governed by Regulation EC 1223/2009. However, regulation that applies to cosmetic products does not include control of the active substances. There are only recommendations and no restrictions regarding the concentration of niacinamide in cosmeceuticals. On the other hand, higher concentrations in the preparations without ensuring the stability of this vitamin can cause redness or irritation after applying these products.

Purpose: The purpose of this study was to assess niacinamide content in some cosmetic products available on the market.

Method: Four different cosmetic products for skin care, marked as serum, face cream, face mask and anti-dark circle eye mask were tested. Sample preparation included liquid-liquid extraction of niacinamide by using water, methanol or their mixture. Analysis was performed using HPLC method on Zorbax Eclipse XDB C18 column at 35°C. Phosphate buffer pH=4.0 (25mM) mixed with methanol in volume ratio 90:10 was used as mobile phase. The flow rate was 0.5 ml/min. Chromatographic peak of vitamin was detected at 260 nm.

Results: The average content of niacinamide was found to be 14.0±0.11% in serum, 9.5±0.14% in face cream, 5.0±0.15% in face mask and 7.4±0.12% in anti-dark circle eye mask. The niacinamide concentration found in the cream and face mask was in line with the declared values, while in the serum and eye mask it was significantly higher than declared.

Conclusion: The presence of niacinamide was confirmed in all analyzed cosmetic products, however its content varied depending on type of formulation and its purpose. The determined concentrations of niacinamide in the examined products ranged between 5.0% and 14.0% (w/w). Usually recommended concentrations in cosmeceuticals are 3.5-5.0%. It can be noted that the content of niacinamide in some cosmetic products is significantly higher than recommended values.

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Regulation of food supplements

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Introduction: Food supplements, which deliver essential nutrients like vitamins, minerals, and probiotics, face inconsistent global regulation. Jurisdictions classify them differently—some as pharmaceuticals (requiring rigorous safety evaluations) and others as food products (with laxer standards). These disparities in definitions, labeling, analytical methods, and oversight create challenges for market access, consumer trust, and safety. Harmonizing regulations is critical to address these gaps and ensure efficacy, safety, and transparency.

This study evaluates global regulatory frameworks for food supplements to identify inconsistencies and propose strategies for harmonization. It addresses the lack of a universal definition and examines how divergent approaches

(e.g. pharmaceutical-grade standards vs. flexible food regulations) impact safety assessments, labeling accuracy, and consumer confidence.

Method: A systematic review followed the PRISMA framework, analysing peer-reviewed literature, policy documents, and industry reports from PubMed and Google Scholar (2013–2023). Inclusion criteria focused on studies addressing regulations, safety, or harmonization. Thematic analysis identified trends in regional regulatory approaches.

Results: Key findings illustrate clear divides across jurisdictions EU and Canada prioritize safety via precautionary principles, enforcing strict manufacturing controls and pre-market approvals. US and Asia favour market accessibility, permitting supplements with minimal oversight if labeled correctly. While medicines and medical devices are regulated by established statutory bodies such as the European Medicines Agency in Europe, food supplements are regulated haphazardly. The Food Drug Agency in the US takes a more pragmatic approach. Community pharmacists are in a position to guide patients in rationale and appropriate informed selection of food supplements.

Conclusion: Global regulatory misalignment in food supplement oversight undermines equity. This study advocates for harmonized standards to balance precautionary safeguards with market flexibility. Collaboration among policymakers, industry leaders, and health authorities is critical to establish unified definitions, testing protocols, and labeling requirements. Such alignment would enhance consumer protection, reduce disparities, and support sustainable market growth. While challenges like jurisdictional resistance persist, cohesive international efforts can bridge gaps, ensuring supplements meet consistent safety benchmarks without stifling accessibility or innovation.

Extended stability evaluation of dexrazoxane solutions: implications for prolonged clinical administration

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Introduction: Dexrazoxane, a cardioprotective adjunct in oncology, is clinically employed to mitigate anthracycline-induced cardiotoxicity. Currently, five manufacturers have obtained regulatory approval for dexrazoxane injections in China. However, stringent usage window (≤4-hour, diluted in sodium lactate Ringer's solution or 0.9% NaCl) imposes significant operational constraints. This limitation persists despite centralized preparation through Pharmacy Intravenous Admixture Services (PIVAS), necessitating evidence-based protocol revisions. This study combines physicochemical properties with pharmacokinetic parameters to systematically evaluate the stability of dexrazoxane solution, and establish scientific rationale for extending clinical usage windows.

Methods: Dexrazoxane solutions were prepared according to manufacturer guidelines and stored in infusion bags under two conditions: ambient temperature (25 ±2 ℃) and refrigeration (4 ±2 ℃) for 24 hours. Throughout the observation period, solutions were monitored for changes in appearance, pH, particulate matter, and concentration using visual inspection, a pH meter, a particle analyzer, and high-performance liquid chromatography at various intervals. Triplicate samples were analyzed to ensure statistical robustness. A liquid chromatography-tandem mass spectrometry method was established to quantify dexrazoxane and doxorubicin in plasma. Pharmacokinetic parameters were compared in Sprague-Dawley rats (n=6) administered fresh versus 12-hour refrigerated dexrazoxane solutions, combined with doxorubicin at clinically translatable doses.

Results: Throughout the 24-hour observation period, refrigerated solutions maintained physicochemical stability with no visible precipitation or flocculation. There were no significant changes in pH or insoluble particle counts, and drug concentrations exceeding 95% of the initial value. In contrast, ambient-stored solutions demonstrated progressive degradation, with concentrations falling below 95% stability thresholds within 8 hours. Pharmacokinetic analyses revealed no statistically significant differences in key parameters between fresh and refrigerated solutions: AUC (0-∞) ($p = 0.19$), Cmax ($p = 0.42$), and elimination half-life ($p = 0.69$). Doxorubicin exposure profiles remained consistent across two groups, confirming unimpaired drug-drug interaction dynamics. The primary factors influencing the stability of the reconstituted solutions were storage time and environmental conditions, with minimal impact from the solvent choice.

Conclusion: Refrigerated dexrazoxane solutions retain full stability for up to 12 hours post-solvation. This evidence-based extension enables optimized PIVAS workflows without compromising therapeutic efficacy.

Risk management by the marketing authorisation holder in product quality review

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Introduction: Product Quality Reviews, forming part of current Good Manufacturing Practices, are periodic product

quality assessments of authorised pharmaceutical products in the EU, including those intended for export only. Product Quality Reviews are performed to ensure that current specifications for raw materials and final products are appropriate and reliable, to identify any trends and to determine ways to enhance both the product and the process. The Marketing Authorisation Holder is responsible for conducting routine product reviews and audits of the manufacturing processes in addition to adhering to Good Manufacturing Practice.

The aim was to carry out a risk assessment, using Failure Mode and Effect Analysis, on the Product Quality Reviews performed by the Marketing Authorisation Holder to identify the risk imposed if any of the current checks are not executed.

Method: Eighteen reviews done by the Marketing Authorisation Holder were identified from the Standard Operating Procedure effective at the time of the study, which are carried out within ninety days of receipt of the Product Quality Review of the manufacturer. For each identified review, the potential failure modes, their associated effects and their risk priority numbers were determined to derive a risk score for each component under review. The classification of the 'severity', 'occurrence' and 'detectability' was presented in the form of a five-point Likert Scale. Each factor was scored on a scale of 1 to 5, where a score of 1 denoted a low risk score. All three parameters were then multiplied to obtain the Risk Priority Number. Each review was ranked as 'low risk and should be considered for delegation' if the risk score fell between 1 and 12, 'moderate risk and may be considered for delegation' if the risk score fell between 13 and 35 and 'high risk and not to be delegated' if the risk score fell between 36 and 125. This risk assessment was compiled into a quality report, which was validated, reviewed and approved by managerial personnel and other relevant personnel within the Marketing Authorisation Holder. The areas for which the Marketing Authorisation Holder is directly responsible for were also taken into consideration.

Results: The outcome of the risk assessment resulted in one review which ranked as 'low risk' with a score of 10, ten reviews as 'moderate risk' with scores ranging between 18 and 32, and seven reviews as 'high risk' with scores ranging between 40 and 48. Examples of failure modes identified include lack of equipment qualification, delays in submissions and failure to initiate recalls in time. Three reviews were determined to be delegated by the Marketing Authorisation Holder to the batch release site. In case the batch release site and the manufacturer are the same, these reviews are to be reviewed by the Marketing Authorisation Holder during planned external audits.

Conclusion: By adopting this risk-based approach, resources can be more effectively allocated by the Marketing Authorisation Holder, allowing time previously spent on Product Quality Reviews to be redirected toward addressing other critical quality issues.

In-syringe polypropylene fiber-supported liquid-phase microextraction for determination of tyrosine kinase inhibitors by LC-MS

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Introduction: Tyrosine kinase inhibitors (TKIs) serve as targeted therapeutics for malignancies such as chronic myeloid leukemia and non-small cell lung cancer. However, their clinical application is challenged by narrow therapeutic windows, significant inter-individual metabolic variations, and potential hepatorenal toxicity. Therapeutic drug monitoring (TDM) proves essential for optimizing personalized regimens. Conventional TDM approaches face limitations including laborious sample preparation, substantial reagent consumption, and prolonged analytical workflows. Recent advances in liquid-phase microextraction (LPME) demonstrate superior performance through minimal solvent usage, rapid operation, and efficient analyte enrichment. This study aims to develop an in-syringe polypropylene fiber-supported liquid-phase microextraction (PPSLPME) method for plasma sample preparation. Coupled with liquid chromatograph mass spectrometer (LC-MS), the strategy seeks to establish a cost-effective analytical platform with enhanced sensitivity and selectivity for TKIs quantification.

Methods: First, a hypersensitized LC-MS method was established for through optimization of LC gradients, electrospray ionization conditions, precursor-product ion pairs, cone and collision energy. Stable isotope-labeled internal standards ([$^2H_4$]-Lenvatinib and [$^2H_6$]-Alectinib) were incorporated to improve quantitative accuracy and matrix effect correction. Subsequently, critical PPSLPME parameters, including extraction/desorption solvent types, volumes and durations, supporting medium mass, and sample volume were systematically optimized via single-factor experiments. Method reproducibility was evaluated by comparing polypropylene fibers from different commercial oil-absorbing cotton brands and melt-blown polypropylene layers sourced from disposable masks. Finally, comprehensive method validation was conducted in plasma matrices, including assessments of linearity, limit of quantification, limit of detection, precision, accuracy, and matrix effects.

Results: The developed methodology extracted TKIs from 1 mL of diluted plasma using optimized PPSLPME conditions: 3 mg fiber, 10 µL n-octanol as extractant, 150 µL methanol as desorption solution, with 10 extraction and 2 elution cycles. The protocol achieved complete sample preparation within 5 minutes at ~0.07 USD per test. Comparative analysis of polypropylene fibers from commercial oil-absorbing cotton and disposable masks demonstrated method reproducibility,

with recovery RSDs <15% across all target analytes. Validation demonstrated satisfactory linearity ($R^2 \geq 0.991$) across the following concentration ranges: 0.01-10 ng/mL for alectinib, 0.01-10 ng/mL for lenvatinib, 0.1-100 ng/mL for ibrutinib, 1-1000 ng/mL for gefitinib and dasatinib, and 3-3000 ng/mL for afatinib. Limits of quantification for the six TKIs were determined to be 0.01-3 ng/mL. The analytical procedure showed 65-85% extraction recovery and 85-110% relative matrix effect.

Conclusion: The PPSLPME-LC-MS method provides a rapid, economical, and reliable analytical platform for TKIs quantification in plasma samples. The proposed technique demonstrates potential for extending to hydrophobic drug monitoring in biological matrices.

SWOT analysis of the pharmaceutical supply chain in Saudi Arabia: challenges and opportunities in the era of vision 2030

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Introduction: The pharmaceutical supply chain in Saudi Arabia plays a vital role in the nation's healthcare system, especially as the country pursues the ambitious goals outlined in Vision 2030. This study presents a SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis of the pharmaceutical supply chain, examining its current state and the challenges and opportunities it faces.

Methods: Data was sourced from a range of academic articles, government reports, and industry analyses. The collected data were analyzed through thematic analysis to identify key themes and factors relevant to the pharmaceutical supply chain in Saudi Arabia. These factors were categorized into the SWOT framework, which consists of four categories: strengths, weaknesses, opportunities, and threats. Each factor was ranked based on its relative importance, determined by its frequency of mention and emphasis within the reviewed literature. The identified factors were then organized into the SWOT framework. Internal factors, including strengths and weaknesses, were distinguished from external factors, including opportunities and threats. This structured approach facilitated a thorough evaluation of the pharmaceutical supply chain in Saudi Arabia, allowing for the development of strategic recommendations aimed at enhancing the efficiency and resilience of the supply chain in alignment with the objectives of Vision 2030.

Results: The SWOT analysis of Saudi Arabia's pharmaceutical supply chain revealed several critical insights. These findings highlight the key strengths, weaknesses, opportunities, and threats that influence the performance of the supply chain. The analysis also uncovers opportunities in the integration of advanced IT solutions and regional collaborations that could bolster the supply chain's efficiency and resilience. Conversely, external threats, including geopolitical risks and global supply chain disruptions, pose substantial challenges.

Conclusion: The study concludes with recommendations for streamline regulatory processes to enhance supply chain responsiveness. This includes updating existing regulations to align with international best practices and developing more flexible regulatory frameworks that can adapt to changing market conditions. In addition, prioritize investments in cold chain infrastructure to ensure the safe and efficient distribution of temperature-sensitive pharmaceuticals. This could involve adopting advanced technologies and improving logistical processes to reduce reliance on imports. Also, the need to continue integrating IT solutions and automation into the supply chain to improve efficiency, accuracy, and resilience. Leveraging data analytics and IoT can provide real-time insights and enable better decision-making throughout the supply chain.

Content of hydroxyanthacene glycosides in the products of senna available on the market

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Introduction: The herbal preparations of senna (Senna alexandrina Mill.; Cassia senna L., C. angustifolia Vahl) are given for the short-term treatment of constipation (EMA/HMPC/228759/2016). According to German Commission E (1993), the administration of senna may only be used if the intended effect cannot be achieved by dietary adjustments or the administration of bulk-forming laxatives. Nevertheless, the preparations of senna are available not only for rational treatment but also for dietary supplementation. The active compounds of senna are related to certain adverse effects. Consequently, the daily exposure to hydroxyanthracenes has been limited at 0.35 mg/kg bw per day of sennoside B (EFSA, 2018). It is important to note that "stimulant laxatives should not be consumed continually for periods longer than one to two weeks" (EFSA, 2013), and use in children below 12 years of age, during pregnancy or lactation, is not recommended (EMA). Therefore, the ingestion of hydroxyanthracenes through food products is subject to limitations imposed by certain authorities. Consequently, it is essential to continuously monitor the quantities of hydroxyanthracenes in medicinal and non-medicinal products available on the market. The objective of this study was to explore products available on the Lithuanian market.

Method: The products were purchased from a local pharmacy in January of 2025. The percentage content of total hydroxyantracene glycosides expressed as sennoside B (THG) in the samples was evaluated using the methodology applied from Eur. Ph. monograph 04/2020:0206. The equipment was qualified, and the quality management system of the laboratory was approved under accreditation procedure (LA.184-01.). The estimated daily intake of THG was analysed based on recommendations provided by manufacturers or distributors.

Results: The percentage content of THG in the samples was found to be within a range from 0.04 to 3.10% (extended uncertainty ±0.00 and ±0.21, respectively) for non-medicinal products and from 0.80% (±0.06) to 2.05% (±0.14) for medicines. Two medicinal tablets were found to contain 4.02 and 7.05 mg of THG per single dosage unit, whereas the non-medical formulation units (tablets and sachets) contained between 2.57 and 46.5 mg of THG (mean: 27.96 mg; median: 29.70 mg) per unit.

A comparison of the maximum daily intake of THG demonstrated that the mean daily intake of adults (in accordance with the directions provided) from non-medicinal products may reach 63.92 mg/day (with a median of 45.00 mg/day). This is higher than for medicines with an average of 33.24 mg/day. It is important to note that non-medicinal products did not include any warnings about the duration of use, nor did many of them contain any information about exemptions for children on their labelling.

Conclusion: The mean quantities of hydroxyanthracenes found in the single-dose units and recommended daily doses of herbal medicines are lower than in the units and the maximum daily intake of non-medicinal products. It is important to review the regulatory coherence of herbal medicinal products and sub-medicinal products, as well as the adequacy of their labelling, to ensure rational treatment and positioning of herbal products on the market.

Good clinical practices in regulated and semi-regulated market: A comparative analysis

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Introduction: All drugs have safety concerns throughout their development. However, they are eventually approved for use by national health authorities on the basis that the benefits outweigh the risks through evidence provided by clinical trial research. The approval process and degree of regulation for clinical trial conduct differs across regions.

Aims: The primary aim of this study is to compare how clinical trials are regulated in a regulated and a semi-regulated market and to analyse the degree of regulatory implementation in each region in terms of clinical trial regulation.

Methodology: A comparative analysis between 3 regulatory environments existing in these regions was done via literature review, case studies and through interviews to capture the experiential perspectives of key individuals with good working knowledge. These markets are regulated by US-FDA, considered a stringent regulator and Botswana and India, considered semi-regulated.

Results/Discussion: Most of semi-regulated countries are developing. Countries. Considering a streamlined regulatory process and highly skilled workforce, India has experienced an increase in registered Clinical Trials. Implication of Clinical trials in semi-regulated markets include reduced costs and a larger pool of patients. There are still major hurdles that need to be overcome, like the capacitating of personnel and the availability of trained researchers.

Conclusion: The regulations exist and are in place, however they are not enforced to latter. Due to differing reasons like trying to attract more researchers, and trying to facilitate the availability of state of the art health care systems

The impact of global clinical trial harmonization initiatives in Botswana

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Global clinical trial harmonisation initiatives, such as the International Council for Harmonisation (ICH) guidelines, have been developed to streamline the regulatory requirements for clinical trials across countries. These initiatives aim to reduce duplication, improve efficiency, and ensure the safety and efficacy of new medical products. However, their implementation often poses challenges to local regulatory systems, particularly in low- and middle-income countries (LMICs) like Botswana, which must balance global standards with local needs and capabilities. Recently, the establishment of the African Medicines Agency (AMA) aims at facilitating harmonised guidelines for Africa, as well as the already WHO established African Vaccine Regulatory Forum (AVAREF) which has a scope of harmonised clinical trial application evaluations and providing clinical trial oversight in Africa. Some other initiatives include The Southern Africa Regulatory for Clinical Research (SEARCH) project which aims to enhance capacity building in member countries to provide clinical trial oversight.

This research explored how global harmonisation efforts influence the development of local regulatory policies and the extent to which they contribute to increased capacity, efficiency, and alignment with international standards. A comparative analysis of multiple regulatory environments was done to shed light on the successes, gaps, and opportunities created by these harmonisation initiatives.

Research Aims: 1. To evaluate how global harmonisation initiatives (e.g., ICH guidelines) have influenced local regulatory policies for clinical trials in Botswana and the African region.

2. To examine the impact of these harmonisation efforts on clinical trial timelines, regulatory review efficiency, and trial approval processes.

3. To propose policy recommendations that balance global harmonisation with local regulatory priorities.

A comparative analysis between 2 harmonised regulatory frameworks existing in these regions was done via literature review, case studies and through interviews to capture the experiential perspectives of key individuals with good working knowledge.

The study revealed that while global clinical trial harmonisation initiatives, such as ICH guidelines, AVAREF, Memorandum of Understandings between countries, etc, have positively influenced regulatory frameworks in Botswana and the broader African region, several challenges and gaps remain in their implementation. Challenges like resource constraints, limited technical expertise, and lack of appropriate legislation were found to continue to hinder full adoption. The need to balance global requirements with country-specific public health priorities emerged as a recurring challenge.

Overall, while harmonisation has led to notable improvements in clinical trial regulation, it was also discovered that capacity-building approach is essential for ensuring its success in LMICs like Botswana.

Risk management by the marketing authorisation holder in product quality review

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Introduction: Product Quality Reviews, forming part of current Good Manufacturing Practices, are periodic product quality assessments of authorised pharmaceutical products in the EU, including those intended for export only. Product Quality Reviews are performed to ensure that current specifications for raw materials and final products are appropriate and reliable, to identify any trends and to determine ways to enhance both the product and the process. The Marketing Authorisation Holder is responsible for conducting routine product reviews and audits of the manufacturing processes in addition to adhering to Good Manufacturing Practice.
The aim was to carry out a risk assessment, using Failure Mode and Effect Analysis, on the Product Quality Reviews performed by the Marketing Authorisation Holder to identify the risk imposed if any of the current checks are not executed.

Method: Eighteen reviews done by the Marketing Authorisation Holder were identified from the Standard Operating Procedure effective at the time of the study, which are carried out within ninety days of receipt of the Product Quality Review of the manufacturer. For each identified review, the potential failure modes, their associated effects and their risk priority numbers were determined to derive a risk score for each component under review. The classification of the 'severity', 'occurrence' and 'detectability' was presented in the form of a five-point Likert Scale. Each factor was scored on a scale of 1 to 5, where a score of 1 denoted a low risk score. All three parameters were then multiplied to obtain the Risk Priority Number. Each review was ranked as 'low risk and should be considered for delegation' if the risk score fell between 1 and 12, 'moderate risk and may be considered for delegation' if the risk score fell between 13 and 35 and 'high risk and not to be delegated' if the risk score fell between 36 and 125. This risk assessment was compiled into a quality report, which was validated, reviewed and approved by managerial personnel and other relevant personnel within the Marketing Authorisation Holder. The areas for which the Marketing Authorisation Holder is directly responsible for were also taken into consideration.

Results: The outcome of the risk assessment resulted in one review which ranked as 'low risk' with a score of 10, ten reviews as 'moderate risk' with scores ranging between 18 and 32, and seven reviews as 'high risk' with scores ranging between 40 and 48. Examples of failure modes identified include lack of equipment qualification, delays in submissions and failure to initiate recalls in time. Three reviews were determined to be delegated by the Marketing Authorisation Holder to the batch release site. In case the batch release site and the manufacturer are the same, these reviews are to be reviewed by the Marketing Authorisation Holder during planned external audits.

Conclusion: By adopting this risk-based approach, resources can be more effectively allocated by the Marketing Authorisation Holder, allowing time previously spent on Product Quality Reviews to be redirected toward addressing other critical quality issues

Healthcare professionals' and consumers' awareness and understanding of the Black Triangle Scheme and its influence on adverse drug event reporting in Australia: A mixed-methods study

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Background: In pharmacovigilance, it is considered important to report all adverse drug events (ADEs) to regulatory authorities. However, priority is given to several specific ADEs, including ADEs for medicines included in the Black Triangle Scheme. In Australia, the Black Triangle Scheme was introduced by the Therapeutic Goods Administration in 2018 to enhance the reporting of ADEs related to new medicines, or medicines used in new ways. Medicines in this Scheme are subject to additional monitoring as there is less information available for them compared to others. To remind people on the importance of reporting ADEs of these medicines, a black inverted triangle ("▼"), is in their product information. However, there are questions about public and healthcare professionals' (HCPs') awareness of the Scheme and about its effect on ADE reporting practices.

Purpose: We aimed to evaluate HCPs' and consumers' awareness of the Black Triangle Scheme and its influence on ADE reporting.

Methods: A mixed-methods study was conducted consisting of an online questionnaire followed by one-on-one interview with participants who indicated in the questionnaire that they were willing to participate. Participants were HCPs and medicine consumers in Australia recruited via advertisements on social media, in general practices and pharmacies, and through professional and consumer organisations. The questionnaire included questions related to awareness and understanding of the Scheme, and reporting behaviour towards medicines labelled with the black triangle. A semi-structured guide was used during the interviews. Descriptive and qualitative data analyses were conducted.

Results: 405 participants completed the questionnaire (138 HCPs, 267 consumers) of whom 21 participated in the interviews (11 HCPs, 10 consumers). About half of the HCPs (52%) and a tenth of the consumers (10%) were aware of the Scheme, with 63% of the HCPs and 11% of the consumers indicating that they had seen the black triangle. Among those aware of the Scheme (n=93), 42 reported an ADE related to a medicine with a Black Triangle symbol at least once, and 36 indicated they reported an ADE specifically because the medicine was part of the Scheme. After seeing the Black Triangle symbol and its description, 66% (n = 255 of 385) stated they would be very likely or likely to report any ADE associated with a medicine carrying the Black Triangle symbol. Qualitative analysis of the interview transcripts led to four themes: (i) awareness about the Black Triangle Scheme, (ii) noticeability and informativeness of the Black Triangle symbol and its description, (iii) perceived utility of the Scheme, and (iv) influence of the Scheme on future ADE reporting practices.

Conclusion: Awareness of the Black Triangle Scheme seems particularly low among consumers. Once aware, most participants indicated positive views on the Scheme and higher likelihood of reporting. However, issues related to the noticeability and informativeness of the Black Triangle symbol and its description were raised. Enhancing the reach and impact of the Scheme through better designed product information and communications could improve public and professional perceptions of the scheme and raise incidents of ADE reporting in Australia for medicines under its remit.