RESEARCH TO ASSESS **HEAVY METALS IN MEDICINES**

Research on an analytical technique to ensure compliance with recent regulations to control the levels of heavy metals in medicines was presented at the FIP congress. Lead author Fatima Carvalho, executive and technical director at LEF (the Laboratory of Pharmaceutical Studies), explains the work.

The International Conference of Harmonization (ICH) published a series of guidelines intended to control impurities in medicinal products for human use, one of them being ICHQ3D, initially published in December 2014, which is about the control of elemental impurities. Elemental impurities are metal element traces that can be present in a medicine and do not contribute to the medicine's therapeutic effect but can pose a risk for human health. As such, ICH Q3D on Elemental Impurities aims to limit the presence of potentially toxic elemental impurities, by establishing a new approach on the calculation of acceptable concentration limits based on the permitted daily exposure (PDE). This parameter is determined by considering relevant toxicological and pharmacological information for each one of the 24 elemental impurities, for oral, parenteral and inhaled administration.. This guideline is intrinsically associated with the changes in the European Pharmacopeia and the US Pharmacopeia, with the implementation of more efficient and specific analytical methods that provide better results.

What work has been done?

LEF has been working on two important strands of the elemental impurities' topic: first the elaboration of holistic-based risk assessments which enable the identification of higher-risk products and, secondly, the laboratory evaluation with the development and implementation of analytical technology, for testing both raw materials and finished products. Concerning this second strand, LEF set up a new laboratory totally dedicated to these types of analyses. After performing benchmarking, inductively coupled plasma mass spectrometry (ICP-MS) was the chosen technology because it offers extremely high sensitivity, (i.e. low detection limits), achieving high quality data in a range of 70 elements that can be measured in a single analysis.

Following the challenge of choosing the best analytical instrument, a new demanding phase was initiated with infrastructures and utilities installation and qualification, as well as a complete training programme for all laboratory staff. LEF has a new full good manufacturing practice compliant laboratory in operation generating analytical data to support risk assessment evaluation or drug product/raw material control.

From 83 risk assessments on elemental impurities performed by LEF, it was concluded that around 66% were compliant, with the concentration limits outlined by ICH Q3D considering the product's intended route of administration. Of the remaining portion, 21% were below the PDE limit but above the control limit (30% of PDE), and 13% were above the PDE limit, and it was necessary to perform additional analytical studies. Most times, after performing this analytical testing on raw materials and/or drug products, we could demonstrate that there was no evidence of the presence of elemental impurities contaminants in the medicine.

Significance

Regulations have established admissible concentration limits to control 24 elemental impurities potentially present in pharmaceutical products. These metal elements can enhance toxicity and induce toxic effects in patients. As such, the 24 elements were grouped considering their toxicity and abundance in the environment: Class 1 – significantly toxic and abundant; Class 2A – significantly abundant; Class 2B – moderately toxic and less abundant; Class 3 – toxicity dependent on the administration route and low abundance. The risk of having a significant concentration of one of these elemental impurities in a drug product is that these metal elements have the ability to induce significant health problems through genotoxic and carcinogenic effects (arsenic, cadmium); neurologic, reproductive and developmental toxicity, cardiovascular and renal adverse effects (lead); neurological and renal toxicity (mercury).

"Metal elements can enhance toxicity and induce toxic effects in patients."

LEF's experience indicates that the risk of encountering a significant level of elemental impurities in drug products is low. However, due to the significance of the adverse effects posed by these metals, it is important to establish appropriate methodologies to assess the risk, accompanied by appropriate risk management. Pharmaceutical sciences play an extremely important role in ensuring the quality and safety of medicines, giving patients the guarantee that a medicine has the correct strength and composition, and is free from microbiological and chemical contamination. The implementation of ICH Q3D is a good example of this.

Pharmacy practice research leads to patients **LOST TO FOLLOW UP RESTARTING HIV TREATMENT**

Documenting telephone numbers at the first clinic appointment for HIV patients and updating contact records at every subsequent clinic visit is a simple but important aid in ensuring patients are not "lost to follow up", according to Frempomaa Nelson, principal pharmacist and head of medical pharmacy at Korle Bu Teaching Hospital, Accra, Ghana. Her poster at the FIP congress in Abu Dhabi, presented a retrospective review of patient records at her hospital between 2013 and 2018 and the findings of interviews using a standardised questionnaire.

The success of any antiretroviral therapy is highly dependent on the retention of patients in care. High rates of loss to follow up of these patients threatens treatment success, Ms Nelson explained. Her study revealed a large drop-out number among patients in HIV care, documented some of the reasons for this loss to follow up, and suggested solutions to avoid failure of antiretroviral therapy.

The results revealed that of 648 adult patients initiated on antiretroviral therapy in 2013, 31% had been lost to follow up within five years. Reasons included undocumented death (35.4%), undocumented transfer to another care facility (21.5%), being in denial (16.9%) and travel (10.8%). Interestingly, 1.5% of those lost to follow up had chosen to seek alternative (herbal) medicine.

Lost to follow up occurred most greatly within one year. The study also found younger patients and those with a low CD4 cell count at the time of initiating therapy were more likely to be lost to follow up.

The patients found to be in denial were invited to the clinic for counselling and some returned to treatment. "Luckily, after [the counselling] some of them resumed [treatment] because they felt we cared for them. If it had not been for this research they would have still been at home [not receiving treatment]", she said.

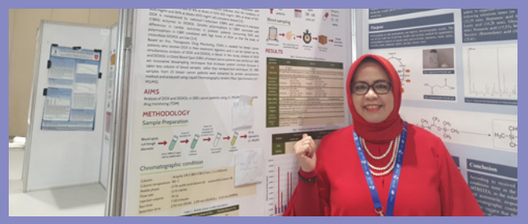
Ms Nelson also noted that another reason for lost to follow up was "clinic frustrations". Although this percentage is relatively low, as a result, her team has taken action to make the clinic more comfortable for patients and to provide an electronic appointment system. — *Bilal Alkubaisi*

PHARMACEUTICAL SCIENTISTS DEVELOP METHODS TO MAKE BREAST CANCER TREATMENTS **MORE EFFECTIVE AND LESS TOXIC**

More effective and less toxic treatment for breast cancer patients could be on its way, led by the work of Indonesian scientists presented at the FIP world congress. Researchers from the Faculty of Pharmacy at the University of Indonesia developed and validated a combined liquid chromatography-mass spectrometry (LC-MS/MS) method to analyse levels of metabolites of two cancer drugs tamoxifen and doxorubicin. In the case of tamoxifen, reduction of cancer recurrence occurs via the presence of the metabolites endoxifen (END) and 4-hydroxytamoxifen, with the presence of END depending on a patient's CYP2D6 genetic status.

"Tamoxifen is effective if a threshold blood concentration of END of 3.3ng/ml is achieved. This study showed that we can use LC-MS/MS to determine if therapy is effective and, therefore, we would know when adjustment of a dose is needed to make this treatment effective. This could be an improvement over current practice, which depends on checking oestrogen and progesterone receptor status and the stage of cancer, which is more diagnostic than therapeutic," said lead researcher Yahdiana Harahap. "In previous research the analysis used plasma. In this study, dried spot blood was used, which is more comfortable for patients," Professor Harahap added.

In the case of doxorubicin, the accumulation of the main metabolite doxorubicinol is responsible for damaging the heart. The researchers performed fingerprick tests on 25 patients and were able to show that LC-MS/MS can rapidly and accurately determine levels of the metabolite 40 minutes after a dose of doxorubicin. "The doxorubicin metabolite is not currently used as a predictor of whether or not doxorubicin can be used daily by breast cancer patients, but there is potential in therapeutic drug monitoring. Prospective research could also be conducted to assess whether this doxorubicin metabolite affects the response rate of breast cancer chemotherapy," said co-author Ramadhan Ramadhan, of the functional medical staff of surgical oncology, Dharmais Cancer Hospital, Jakarta, Indonesia. — *Lin-Nam Wang*



Yahdiana Harahap: Potential improvements to practice