

The GEONs API-fingerprint program: tackling falsifications of APIs

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Introduction

Falsification of active pharmaceutical ingredients (APIs) has been recognized as an important health issue since a series of health scares involving large numbers of casualties happened when altered APIs escaped detection in routine analytical testing. Any form of tampering the content or information about the content might affect the quality of the API, the finished product and therefore constitutes a direct threat to the health of patients (Position paper for OMCLs on API surveillance, EDQM). The conventional analytical approach often fails to detect falsification since the quality and quantity of the API might be within the current standards. Instead, methods that allow distinction of API samples, according to their source are needed.

Within the General European Official Medicines Control Laboratory (OMCL) Network (GEON) different initiatives were taken to augment the analysis and market surveillance of APIs used by the different manufacturers. Despite the efforts, API testing within the network is limited, compared to the surveillance of finished products. To tackle the issue of falsified API detection the API-working group (API-WG) of the GEON organizes atypical market surveillance studies (MSS), where an MSS (analysis according to the Ph. Eur.) is combined with a fingerprint study (MSSFP). An MSS, according to Ph. Eur. only gives an indication of the quality of the product on some distinct parameters, often chosen based on the manufacturing process. A MSSFP study allows to obtain a global image of the sample, to compare to batches of the (presumed) manufacturer and/or to data of

fingerprint studies performed in the past. (Deconinck et al., 2022, Rebiere et al., 2022).

The aim of the paper is to highlight the challenges and pitfalls in detecting falsified APIs and to give an insight in the work of the GEONs API-WG with a special focus on the MSSFP studies. A summary is given of the MSSFP study on sildenafil citrate and this for the set-up and the obtained results.

Materials and methods

Set-up of the study

Every MSSFP study focusses on one API, selected based on the risk of falsification or incidents that occurred in one of the member states. Sildenafil Citrate is the API of one of the worlds most falsified medicines.

The idea of an MSSFP study is to select analytical techniques that allow to differentiate API samples according to their manufacturer. The selection of the techniques starts with the Ph. Eur. From the monograph infrared spectroscopy, the method for related substances and the presence of residual solvents were selected as starting point. Further these techniques were complemented with fingerprinting techniques, proven valuable in the previous studies, i.e. Raman spectroscopy, X-ray powder diffraction (XRDP) and proton-Nuclear Magnetic Resonance (¹H-NMR).

All samples were analyzed in the same way for each method and the data was preprocessed, where necessary, followed by unsupervised chemometric analysis using principal component analysis (PCA) and hierarchical clustering (HCA). Also the combination of data through

mid-level data fusion was explored (Deconinck et al., 2022).

Sample collection

Every participating OMCL collected samples of the targeted API, available on their national markets following their own procedures. This resulted in the collection of 79 sildenafil citrate samples from 14 different manufacturers. Samples were then centralized and dispatched to the different testing OMCLs, where each OMCL performed one technique on all samples (Deconinck et al., 2022).

Results and discussion

Of the six analytical techniques, selected to obtain fingerprint data infrared and Raman spectroscopy, as well as the test on related substance were unable to distinguish between the manufacturers. This can be explained by the fact that all samples complied with the Ph. Eur. and these techniques are not sensitive enough to detect the small differences between the manufacturers. This could be different in the case of real falsified samples.

In contrast, the results of the test on residual solvents, XRPD and $^1\text{H-NMR}$ gave valuable fingerprint information and allowed to link the differences between the samples to the different manufacturers. Together the three techniques allowed the distinction of all manufacturers, except one. Therefore, these techniques are complementary and can be used together as fingerprint techniques for sildenafil citrate and so allow the detection/identification of falsified samples.

The combination of the data of different analytical techniques did not result in significant improvement of the results, except for the combination of the residual solvent data with XRPD. In fact the fused data allowed the distinction of the manufacturer, which was not possible to differentiate using only the individual techniques (Deconinck et al., 2022).

Conclusion

From a quality point of view all samples collected in this study complied with the Ph. Eur.

Three analytical techniques (residual solvents, XRPD and $^1\text{H-NMR}$) resulted in valuable fingerprint information, though none of the techniques allowed the distinction of all manufacturers. Therefore all three analyses are necessary, as well as three different chemometric models, i.e. the one based on residual solvents, the one on $^1\text{H-NMR}$ and the one based on the fused data of residual solvents and XRPD.

In general it can be concluded that in the case of a suspicious sildenafil citrate API sample, the GEON will proceed with analysis with each of the three techniques mentioned above in order to link the sample to a manufacturer or not. If this is not possible further analysis and research on origin and identity will be performed. In case the suspicious sample claims a manufacturer the analysis will be limited to the technique(s) able to characterize this manufacturer (Deconinck et al., 2022).

More general it should be emphasized that falsification of APIs is a real and underestimated threat, that manifests itself in the quality of finished products and health risks for the patients. Therefore it is the engagement of the GEON and the API-working group to promote API-surveillance throughout the network, to launch new MSSFP collaborative studies and to work with the European Medicine Agency to rationalize GMP inspections of API manufacturers at an international level. Further the GEON remains open for collaborative campaigns on combatting falsification, but also for cooperation with different regulatory authorities and active involvement in global campaigns in order to share the expertise and information gained during different project

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