FOI 23/643 - Alkyl-Sulfonate Impurities in Sulfonate-Salt Drug Substances and Drug Products

Dear

> *"Please find below the second part of my request with annotations. Hopefully, this will resolve your queries.*
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> *In addition, I wish to request release of any information/documents on the topic of alkyl-sulfonate (mesilate, besilate, tosylate) impurities arising from the work of the BP and/or in relation to the assessment of drug substances presented as sulfonate salts. Based on statements in EPARs and UKPARs, many assessors seem to perceive that such salts could contain alkyl-sulfonate impurities. But perception is not reality.*
>
> > Here I am seeking access to assessment reports, correspondence, meeting notes and emails concerning alkyl-sulfonate impurities in general in order to assess whether BP/MHRA accepts the belief, based on assertion and assumption, and propagated particularly by EDQM and EMA, that these impurities might be present in sulfonate-salt drug substances. For example, the following statement occurs in the EPAR for Leuprorelin mesilate: As the substance is a mesilate salt, limits have been set for acid content, ratio of methanesulfonic acid to peptide, and alkyl methanesulfonates as per ICH M7 guidance (https://www.ema.europa.eu/en/documents/assessment-report/camcevi-epar-public-assessment-report_en.pdf). The assessor clearly believes, without any explanation, that alkyl-mesilate impurities could be present in any mesilate-salt drug substance.
>
> *If MHRA is content to allow such perceptions to continue, what supportive evidence is available to the Agency regarding mechanism of formation? Information from case studies, internal policy or training documents would also be helpful.*
>
> > I would be most interested if an evaluation of MHRA assessment reports for sulfonate-salt APIs showed similar assumptions regarding the presence of alkyl-sulfonate impurities. For example, if an assessor demanded evidence on the absence of alkyl-sulfonate impurities, was this assumption questioned during internal or committee review?"

Having reviewed your request, we estimate that compliance with the request would exceed the appropriate costs limit under S.12 Freedom of Information Act 2000. Public authorities are not obliged to work past the appropriate costs limit under section 12(1) of the Freedom of Information Act 2000.

This is because your request in its present form covers:

- Assessment Reports, correspondence, meeting notes and emails concerning alkyl-sulfonate impurities for products that contain drug substances that are presented as sulfonate salts (mesilate, besilate, tosylate).

A search of our records has revealed that we hold over 300 Marketing Authorisations for products that contain drug substances that are sulfonate salts (mesilate, besilate, tosylate).
We would have to manually check our records for each of the Marketing Authorisations to locate the original assessment reports that were compiled at the time of authorisation and any related correspondence. For older products, we may not hold the information electronically and this would involve retrieving and searching our paper archives for the information.

The request for assessment reports, correspondence, meeting notes and emails could potentially cover a wide range of internal and external correspondence. It is unclear if you are referring to formal meetings between MHRA and the Marketing Authorisation Holders, such as scientific advice meetings, or Expert Committee meetings where particular products were discussed. The information presently requested would be difficult to identify and isolate.

We have reached our conclusion based on previous precedents set in relation to the location, retrieval, and extraction of information from our electronic and paper records.

Advice and Assistance

It would be advisable to significantly narrow the request to information for a small number (1-2) of Marketing Authorisations that you are interested in, we recommend one or two specific PL numbers. It is also advisable that you limit the scope of the request to a relevant time period. Availability of records is more likely for more recently authorised products for which the information is held electronically.

It would also be advisable to narrow the request in terms of the documents requested, to only the quality assessment report, as this is the document in which the assessment process and decisions for these impurities are captured.

Please note that detailed quality data and any details of the drug substance synthesis may be considered to be commercially confidential and so may be exempt from release under Section 43 (Commercial Interests) of the FOI act. We would, therefore, need to consider a refined request in relation to this Section of the Act. Please refer to Section 3.1.2 of the attached EMA guidance regarding commercial confidentiality which states in relation to the active substance:

Detailed information on the synthesis or manufacture of the active substance, including details on the by-products and degradation products of active ingredients and validation of the manufacturing / synthesis process, is commercially confidential.
and:
Concerning impurities and degradation products, qualitative and quantitative information is regarded as confidential unless disclosure is necessary for public health reasons. A general description of the types of test methods used and the appropriateness of the specification is not commercially confidential. However, detailed information on the test methods used and the specification and quantitative acceptance criteria established for the active substance is commercially confidential,

unless the tests meet specific monographs in the European Pharmacopoeia or another National Pharmacopeia.

https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

Please also note, that during assessment of a Marketing Authorisation Application (MAA) assessors should assess whether the Applicant has considered the potential for mutagenic impurities in the drug substance and the drug product in line with ICH M7 and other established guidance. To the best of our knowledge, this includes the risk for the presence of mutagenic alkyl-sulfonate impurities in sulfonate-salt drug substances. The process for assessment of potential alkyl-sulfonate impurities in the drug substance/drug product is the same as for other potential mutagens. The Applicant should consider the risks for potential mutagenic impurities, and if a risk is identified it is expected that the principles of ICH M7 should be followed to ensure appropriate controls are in place, if required. The Applicant would also be expected to demonstrate compliance with any relevant Ph. Eur. and BP monographs/chapters in the MAA.

If you do submit a refined request, then we will treat it as a substitute request to your original request and the 20 working day statutory time limit will begin from the date your refined request is received. In the absence of a refined request, we will send an official response to your original request, engaging the costs limit exemption under section 12(1) of the Freedom of Information Act 2000 within the 20 working day limit.

If you disagree with how we have interpreted the Freedom of Information Act 2000 in answering your request, you can ask for an internal review. Please reply to this email, within two months of this reply, specifying that you would like an Internal Review to be carried out.

Please remember to quote the reference number above in any future communications.

If you were to remain dissatisfied with the outcome of the internal review, you would have the right to apply directly to the Information Commissioner for a decision. Please bear in mind that the Information Commissioner will not normally review our handling of your request unless you have first contacted us to conduct an internal review.

The Information Commissioner can be contacted online via an electronic form: https://ico.org.uk/make-a-complaint/foi-and-eir-complaints/foi-and-eir-complaints/
Or by writing to:
Information Commissioner’s Office
Wycliffe House
Water Lane
Wilmslow
Cheshire
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Yours sincerely

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