ALKYL SULFONATE ESTER IMPURITIES COM(21)39

Report from the Secretary and Scientific Director

Patient impact
Indirect (High) Appropriate controls of impurities in monographs assure APIs and finished products are of the expected quality. A focus on minimising potential exposure to toxic impurities reduces the potential risk to patients.

Redactions under section 40(2), personal information

Background

Members will recall that for several years, the European Pharmacopoeia has included production statements in monographs for mesilate, besilate and tosilate salts. The BP has also introduced its own production statements to ensure a consistent approach is taken across the publication (minutes 73 and 132.2 refer).

Whilst this proposal was being considered by the European Pharmacopoeia during the public consultation (Pharmeuropa) stage we received feedback and some critical correspondence from interested parties (Dr David Snodin, who was working with a BP Expert, [redacted] and a BP Commission member, [redacted] . They published a "reader's tribune" article arguing against the inclusion of the production statements at the time and submitted feedback on the proposals to the BP and direct to the Ph. Eur. A brief summary is provided as Annex 1.

Dr Snodin *et al*'s position was (and remains) that the production statements are unnecessary, are not supported by the available evidence and represent a regulatory burden on industry and drug developers.

The UK Delegation to the Ph. Eur. Commission carefully considered this feedback at the time and concluded that the inclusion of these statements was helpful to users and was a useful flag of a potential risk. The Delegation acknowledged the dissenting view, but felt that on balance, the BP should go with the consensus across Ph. Eur. and EMA that they were necessary. Since risk assessment is an established part of regulatory filings, and the production statements merely reiterated this for these substances and did not mandate testing, the inclusion of a production statement (rather than a test requirement) did not in fact add to the regulatory burden on applicants.

Recent correspondence

During the last few months, we have received some further correspondence and information and been made aware of recent publications on this subject matter. We have also received and answered several Freedom of Information requests and released relevant information in response to these.

The purpose of this paper is to do the following:

- Update Commission on recent correspondence received on this subject and recent information
- Share information that we have released in response to requests under the Freedom of Information Act 2000
- Propose some future actions that Commission may wish to agree to moving forward

Recent correspondence

A summary of the recent correspondence is below.

Date	Correspondence	Annex
9/8/20	Link to Dr Snodin's Chemistry World opinion article, critical of the regulatory approach taken toward alkyl sulfonate impurities	2
3/8/21	Comments received from Dr Snodin on the draft *Ph. Eur.* monograph for Dabagatrin Etexilate Mesilate (DEM)	3
20/8/21	Response to an FOI request regarding reports and draft production statements relating to alkyl sulfonate esters in sulfonate salts (ref 21/852)	4
20/8/21	Response to an FOI request regarding the production statement in the Co-Dergocrine Mesilate BP monograph (ref 21/867)	5
31/8/21	Dr Snodin replies with a critique of the minutes and documents released under FOI 21/852	6
2/9/21	Dr Snodin sends a follow-up to add to his critique of these documents some further comments on the draft *Ph. Eur.* DEM monograph	7
16/6/21	Response to two FOI requests about three BP monographs and four Ph. Eur. monographs (ref 21/967)	8
20/9/21	Dr Snodin provides some further comments on the draft *Ph. Eur.* Dabigatran Etexilate Mesilate monograph	9

Note: The cover letters/emails to each FOI response only have been attached to this paper. Where these refer to other documents which we released, these are available for review on the BP Commission forum thread but have not been included in the papers for brevity.

Summary of issues:

The main issues for consideration arising from these communications are summarised below:

Production statement wording

The current BP production statement wording is below:
"*Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern*."

Dr Snodin suggests that the use of the word "genotoxic" in the production statements is imprecise, and that the word "mutagenic" is more appropriate and would be consistent with the relevant ICH Guideline (this is M7(R1) on the "assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk").

This feedback has been passed to EDQM for their consideration, but this is also relevant to the BP production statements that we have agreed for our national API and product

monographs. A glossary of several terms is provided at the end of this paper to illustrate the (sometimes quite subtle) differences between them.

The Secretariat has discussed this feedback with a senior non-clinical assessor in MHRA Licensing division, who has confirmed that mutagenic is a more precise term for alkylating agents.

- Commission is asked to consider whether the current term should be reviewed in light of these comments.

Need for the production statement at all

Dr Snodin maintains his previous view that the inclusion of the statements is not warranted because the risk of these impurities forming is negligible and that regulators have overreacted based on speculation and assertion rather than evidence. A copy of a presentation given by Dr Snodin to a technical seminar in 2016 is included as Annex 10.

In his recent communications Dr Snodin has provided further mechanistic and kinetic arguments that the risk of these impurities forming is low, and in some cases, impossible. It should be noted that he makes this argument against including a test for impurity D in the new Ph. Eur. monograph for Dabigatran Etexilate Mesilate in his *Pharmeuropa* comments; [redacted] As this data does not belong to, nor is held by, us we have not yet shared this or given any feedback on this point. The comments have been communicated to EDQM for consideration in the usual way and they will consider what level of feedback or additional information to share or publish as part of this process.

Redacted under section 27(2) of the FOIA - International Relations

Guidance on the content of risk assessments

Dr Snodin also criticises the lack of specific guidance issued by the BP, Ph. Eur. or EMA on what an acceptable risk assessment might look like. As part of our responses to the various FOI requests, we have referred him to an EMA letter to manufacturers which was published in 2008 (https://www.ema.europa.eu/en/documents/other/request-assess-risk-occurrence-contamination-mesilate-esters-related-compounds-pharmaceuticals_en.pdf) which provides guidance to manufacturers, including a list of considerations for assessing the risk of alkyl sulfonate ester formation. With reference to the first point, it may also be noted that this letter refers to mutagenic action of mesilate esters in preclinical studies.

Proposals

The current position of the BP Commission is as described above. In light of the continued interest in this matter, and the experience of the statements having been published for several years, members are invited to consider whether it is timely to revisit the previous decision and to confirm or rethink the continued use of this approach.

Members are also asked to consider the following proposals:

- It is proposed to review the wording used in the BP monograph production statements to refer to “mutagenic” rather than “genotoxic” impurities, in line with the ICH guideline M7
- It is proposed to ask the European Pharmacopoeia to carry out a similar review to consider the use of “mutagenic” instead of “genotoxic” in the production statements in Ph. Eur. monographs
- Commission is invited to revisit its’ previous decision and either confirm or review whether there is a continued need for these production statements long-term

Glossary: some molecular toxicology terms

Genotoxicity
In genetics, genotoxicity describes the property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer. While genotoxicity is often confused with mutagenicity, all mutagens are genotoxic, whereas not all genotoxic substances are mutagenic.

Genotoxicity is the capability of substances to damage DNA and/or cellular components regulating the conformity of the genome, such as the spindle apparatus, topoisomerases, DNA repair systems and DNA polymerases and includes all adverse effects on genetic information.

Mutagenicity
In genetics, a mutagen is a physical or chemical agent that permanently changes genetic material, usually DNA, in an organism and thus increases the frequency of mutations above the natural background level. As many mutations can cause cancer, such mutagens are therefore carcinogens, although not all necessarily are. All mutagens have characteristic mutational signatures with some chemicals becoming mutagenic through cellular processes.

Mutagenicity is specifically the capability of substances to cause DNA damage or mutations.

Clastogenicity
A clastogen is a mutagenic agent giving rise to or inducing disruption or breakages of chromosomes, leading to sections of the chromosome being deleted, added, or rearranged. An example of this is mitotic loss of acentric chromosomal fragments.

Aneugenicity
This is mechanical problems from chromosomal breakage and exchange, mitotic loss of chromosomes.
An aneugen is a substance that causes a daughter cell to have an abnormal number of chromosomes (aneuploidy). A substance's aneugenicity reflects its ability to induce aneuploidy.

Aneuploidy
The occurrence of one or more extra or missing chromosomes leading to an unbalanced chromosome complement, or any chromosome number that is not an exact multiple of the haploid number (which is 23).

Redactions under section 40(2), personal information

COM(21)38; Annex 1

2000	European Pharmacopoeia Commission's (EPC) concerns over the (potential) genotoxicity of alkylsulfonate esters led to the insertion of Production Statements into the monographs for mesilate salts.
2007	The Guideline on the Limits of Genotoxic Impurities (CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006) came into effect. Subsequently the EPC published its Policy Statement, *Potentially Genotoxic Impurities and European Pharmacopoeia Monographs on Substances for Human Use* (Annex 2). The policy is consistent with that for impurities in general, Ph. Eur. General Chapter 5.10. Control of Impurities in Substances for Pharmaceutical Use and Ph. Eur. General Monograph 2034: Substances for Pharmaceutical Use.
2008	In 2008, following a GMP failure, ethyl methanesulfonate was found in Viracept® (Nelfinavir) and this triggered regulatory discussions. The EPC was asked to establish a Mesilates Working Party (MSL WP) with specific terms of reference.
April 2008	[redacted] agreed to be chair of a Ph. Eur. Working Party MSL alkyl mesilates. First meeting September 2008.
June 2010	[redacted] asked that Ph Eur production statements could be discussed at BPC and request for revision at EPC level and provided some technical articles in support of this request. PQRI article_sulfonate este op100118e_0000_proof_pkg.pdf PQRI article; "A detailed study of sulfonate ester formation and solvolysis reaction rates....." Teasdale et al OPRD article op100118e_ pdf; "Genotoxic impurities; from structural alerts to qualification", Snodin OPRD article The United Kingdom delegation to the EP Commission discussed these documents after they were sent to the Secretariat by [redacted] The UKD agreed that a request for revision of the production statement should be sent to Strasbourg.
June 2011	The MSL WP's proposals for modifying the Production statement (following the UK Delegation's request for revision) were endorsed (and enlarged somewhat) by both the QWP and the SWP. The proposed revised text was presented to *Ph. Eur.* Commission prior to publishing it in Pharmeuropa for public comment.
October 2011	[redacted] provided further views on the modified wording for the production statements: "This statement is not much better than its predecessor. There would have to be very specific chemical conditions (pH <0.5 with water and base such as an amine both absent) for methanesulphonate impurities to be formed. These conditions are not used in the manufacture of mesilate salts. The reference to the standard 'regulatory guidance documents' on toxicity is not helpful when we know that for example for ethyl methanesulphonate the permitted daily exposure was determined by Roche to be 2mg/kg/day - which is nearly 100,000 times the TTC which the CHMP toxicology guideline would suggest as the appropriate limit. The question is whether the new text would lead API reviewers for generic drug sources of any of the named monographs to ask for appropriate information and testing, or for

Redactions under section 40(2), personal information

	reviewers in a national agency reviewing a new mesilate salt to ask for appropriate information and testing. The monograph still lists all of the methanesulphonates as potential "baddies" which have to be shown to be absent to a defined low level regardless of how the drug substance is made, and then the reference to guidelines suggests that if present they must be limited to below the TTC."
January 2012	[redacted] *et al* submit a paper to EDQM for *Pharmeuropa* Readers' Tribune, formally requesting the support of the UK delegation to the European Pharmacopoeia Commission arguing that the need for a Production Statement should be reviewed based on the evidence outlined in the article. The UK Delegation consulted with [redacted] and concluded that it would not offer support to the article, since this represented the author's views not the views of the UK Delegation, on the basis that: • Pharmacopoeias are there to protect patients against the use of drug substances that are not made to GMP standards, including the use of poor-quality starting materials. • The Production Statement adequately flags up the possibility that alkyl mesilates may be present and that appropriate consideration by producers and assessors should be given to this. If producers can demonstrate that their systems are sufficiently robust so that there is no possibility of alkyl mesilates being produced, then that should be accepted by assessors. However, the Production Statement should remain for users, including independent analysts, who may not be aware of the possibility that residues of alkyl mesilates may be present in the API as a result of the use of impure methane sulfonic acid.
November 2012	Article was published in the journal GMP review, critical of the regulatory approach taken [redacted] article.pdf
February 2013	EDQM Received a further publication proposal from [redacted]. Since this concerned a public *Pharmeuropa* consultation on chapter 2.5.40, EDQM suggested this come through official communication pathway via the British Pharmacopoeia Commission, rather than by accepting the article for publication, in order to allow a technical discussion of the arguments provided in the respective Committees at the BPC and potentially in the MSL WP.
April 2014	Dr Snodin informed the BP that he was preparing a definitive publication on the issue of alkyl sulfonates, and reiterating his criticisms that in his view the "evidence" was merely speculation since no mechanism is proposed as to how alkyl sulfonates are formed during the synthesis of sulfonic acid salts, and no evidence has ever been published by Ph. Eur. or BP demonstrating the presence of alkyl sulfonates in a sulfonic acid salt, save for the highly atypical Viracept case that had a root cause of a massive GMP violation (combined with a spray-drying isolation procedure which precluded any solvent washing of the precipitated mesilate salt).
January 2015	Pharmeuropa changes. A draft revised production statement for all mesilate salts in the Ph. Eur. was published

"Alkyl mesilate impurities: a case study in regulation", Snodin et al, GMP review article

	in Pharmeuropa 23.4. [redacted] an expert on MC1, made some comments on the draft wording which changed the thinking of the Working Party. The WP discussed an alternative wording with the Quality Working Party and the production statement was revised to its' current form. The Chair of the Alkyl Mesilate Working Party, John Midgley, informed the UK Delegation that the same form of wording would be proposed for Besilate and Tosilate salts in the Ph. Eur. Diisetionate salts would not be amended at present because of their low usage in Europe.
September 2015	Dr Snodin submitted a request for revision to EDQM, with an accompanying article written by himself and Dr [redacted] which questioned the formation of these impurities. Alkyl sulfonates in sulfonic-acid salts_op_of_monograph_or_g request_for_revision This was submitted by the to the BP to consider by EDQM as the Ph. Eur. procedure requires revision requests to come from National Authorities The UKD passed on the request to suppress chapters 2.5.38, 2.5.40, 2.5.41 and to remove the production statements in monographs that referred to these chapters, but noted that this request did not reflect the opinion of the UK Delegation This request was not ultimately agreed by the Ph. Eur. Commission
January 2016	Dr Sam Atkinson, James Pound and Stephen Young met with Dr Snodin and Dr Teasdale to discuss the various points of view, and reiterated that the UK Delegation's position took into account the views of many stakeholders and needed to take a balanced approach and that, whilst respecting the scientific arguments being presented, since the consensus across the Ph. Eur. Commission was that the statements were useful, the position of the BP remained unchanged.

Annex 2

Young, Stephen

From: snodind@xiphora.com
Sent: 17 August 2020 17:22
To: Young, Stephen
Cc: Pound, James; Atkinson, Samantha
Subject: RE: New article on alkyl sulfonates in sulfonic-acid salts

Dear Stephen

Thanks for the response.

I've very curious about whether the BP secretariat and advisors actually believe that the current policy on sulfonate esters is based on the scientific evidence. Would you be willing to comment?

I have an upcoming article in OPRD which touches on sulfonate-ester impurities in which I query the EP wording adopted in 2016. The previous wording that strongly hinted to the existence of the side-reaction hypothesis was ditched – presumably because the kinetic and mechanistic evidence made this no longer tenable. So can you explain the justification for tagging sulfonate esters as "potential impurities"? The only possibility I can think of is by read-across to the Viracept incident. As explained in the Chemistry World article this is also false. [I'm sure EDQM was well aware of the fact that no sulfonate-ester impurities were picked up in the 2008 EMA post-Viracept survey, but, like on many other occasions, decided to conceal this information.

Kind regards

David

EP monographs on mesylate-, besylate- and tosylate-salt drug substances contain the following guidance: "It is considered that [XXX esters] are genotoxic and are potential impurities in [name of the API]. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method [2.5.XX] is available to assist manufacturers." "Potential impurity" is defined in the EP section on Control of Impurities in Substances for Pharmaceutical Use as follows: "An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the substance." Despite multiple requests, the EP has over many years failed to set out a clear mechanism (with supporting evidence) explaining how alkyl-sulfonate impurities can arise. Nor have any (anonymised) data been released on assay results submitted by applicants under the Certification Procedure.

From: Young, Stephen <Stephen.Young@mhra.gov.uk>
Sent: 11 August 2020 11:34
To: snodind@xiphora.com
Cc: Pound, James <James.Pound@mhra.gov.uk>; Atkinson, Samantha <samantha.atkinson@mhra.gov.uk>
Subject: RE: New article on alkyl sulfonates in sulfonic-acid salts

Dear Dr Snodin,

Just a short email to acknowledge receipt and say thank you for your good wishes. Happily we have continued to operate throughout the pandemic, supporting the healthcare system response.

Thank you for making us aware of your Chemistry article and for sharing both the comments from EDQM and also your personal views.

With kind regards,

Stephen

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 09 August 2020 16:40
To: Young, Stephen <Stephen.Young@mhra.gov.uk>
Cc: Pound, James <James.Pound@mhra.gov.uk>; Atkinson, Samantha <samantha.atkinson@mhra.gov.uk>
Subject: New article on alkyl sulfonates in sulfonic-acid salts

Dear BP Secretariat

Hope this mail finds you well and Covid-free.

You may or may not be aware of my recent piece in Chemistry World? Just in case, here is a link: https://www.chemistryworld.com/opinion/questioning-european-policy-on-alkyl-mesylate-impurities/4012169.article

The article went through several iterations and EDQM was given the opportunity to comment on a couple of occasions. EDQM's comments on the first round are shown below.

I think the line that "EDQM has not received any complaints" is particularly egregious since it implies that Industry was gullible and should have been much more suspicious of guidance based solely on speculation.

EDQM withdrew all of their comments on receipt of the finalised version of the article. Surely EDQM would have cited any available evidence supportive of their policy. But no – which to my mind demonstrates unequivocally that avoiding admitting to a mistake is more important to EDQM than following scientific evidence.

A final point regarding the non-transparent QWP review in 2015. Based on our discussions in 2017 and on communications from EDQM, it is the case that the EPC has consistently voted to maintain the policy alkyl-sulfonate impurities. Therefore, it seems highly likely that Dr J-L Robert as chair of the EPC at the time was explicitly or implicitly mandated to ensure continuation of the policy. And sure enough he did this by taking a leaf from the big-tobacco/big-oil playbook by using the "uncertainty-remains" argument, in spite of crystal-clear evidence to the contrary. So, to my mind, it seems that the QWP review was effectively a sham.

Kind regards

David

EDQM's response on alkyl mesylate (for Chemistry World)

We would like to draw your attention to the fact that the article not only contains a number of misinterpretations concerning the approach taken by the European Pharmacopoeia (Ph. Eur.), but is also factually incorrect. As Secretariat of the Ph. Eur. Commission, the EDQM would therefore like to clarify the following points:

- The decision to include a production statement in monographs was taken by the Ph. Eur. Commission by unanimous vote, after a request was received from a member state authority. The statement itself was drafted by experts from member states and, like all Ph. Eur. texts, the draft was published for public consultation prior to adoption, at which time no comments were received. In addition, to date, the EDQM has not received any complaints from manufacturers about the Ph. Eur.'s control strategy for potentially genotoxic alkyl sulfonates in APIs.

- As Mr Snodin himself says, there is publically available evidence showing that elevated levels of the impurity ethyl methanesulfonate have been found in nelfinavir (the active substance in Viracept®).
- The control strategy for potentially genotoxic alkyl sulfonates in APIs was re-evaluated by the Ph. Eur. Commission some years ago, at which time the opinion of the EMA Joint CHMP/CVMP Quality Working Party was sought. While the EDQM has observer status to this group, it is chaired not by an EDQM staff member, but by an expert from an EU member state elected by the CHMP. The "EDQM technical director" role mentioned in Mr Snodin's paper does not exist. The response received from the Joint CHMP/CVMP Quality Working Party prompted the Commission to confirm its approach in March 2016.

The production statement in its current version does not make routine testing mandatory but emphasises that the manufacturing process is to be developed taking into consideration the principles of quality risk management, together with the quality of starting materials, process capability and validation.

These points have already been made clear to users in the past (see also the press-release "*Potential presence of mutagenic alkyl sulfonates in active substances*", published on 25 February 2016 on the EDQM website and available here).

Where's the evidence?

BY DAVID SNODIN | 30 JULY 2020

Policies based on false hypotheses can persist in spite of overwhelming contradictory data

Source: © John Holcroft/Ikon Images

Are toxic alkyl mesylates present in mesylate salt drugs?

Creating policies on scientific and medical issues is not an easy task. Often, decisions must be made when scientific knowledge is uncertain, and so a policy may be based on false hypotheses. Ideally, any dubious hypothesis is disproved by emerging evidence, but situations can occur where institutional inertia and dogma allow the policy to remain in place. An example of this can be seen in the suggestion that sulfonic acid salt drugs may be unsafe.

Over half of the top prescription drugs are presented as salts in order to optimise their pharmaceutical properties. Sulfonic acid salts such as mesylate (methanesulfonate) often provide the best technical solution, although hypothetical safety concerns were raised nearly 20 years ago.

In late 2000, the European Department for the Quality of Medicines (EDQM), secretariat to the European Pharmacopoeia, suggested that an ester-forming side-reaction could occur during the synthesis of a mesylate salt by addition of methanesulfonic acid to a pharmaceutical base dissolved in an alcoholic solvent such as ethanol. Thus, a toxic alkyl mesylate (ethyl methanesulfonate; EMS) might be present as an impurity in the mesylate-salt drug substance.

In 2004, the European Pharmacopoeia (EP), introduced a new requirement for any EP-compliant mesylate salt drug substance: the potential for alkyl mesylate formation should be determined, and is ‘particularly likely to occur if the reaction medium contains lower alcohol’. Although supportive evidence was not provided, at the time no objections were raised by industry scientists given the perceived expertise of the EP. Introduction of the policy would have been considerably more problematic if EDQM had released analytical data, obtained as part of a 2002 MSc project, demonstrating the absence of alkyl mesylates in a range of mesylate salt drug substances. Nevertheless, the concept was rapidly taken up by other regulatory bodies including the European Medicines Agency (EMA).

The EP’s policy appeared to be justified three years later, when patients using certain batches of Viracept (a protease inhibitor whose active ingredient is nelfinavir mesylate) complained of a strange taste attributed to the presence of around 0.1% EMS. However, the contamination was caused by a gross failure of good manufacturing practice (GMP): methanesulfonic acid reagent was stored in a tank containing residues of ethanol, leading to production of EMS. In addition, the isolation procedure for the drug substance involved spray drying, which prevented the possibility of impurity purging.

Despite the exceptional circumstances behind the Viracept incident, in early 2008 the EMA launched a survey of all sulfonic acid salt drug substances approved in EU countries along with a range of assumptions that alkyl sulfonate impurities would be found. A report on the outcome of this survey has never been published, but several years later a Freedom of Information request revealed that such impurities were consistently absent. Thus, it is inappropriate and misleading to read across from the unique event of Viracept contamination to the routine GMP synthesis of sulfonic acid salts.

Many process chemists and others in the pharmaceutical industry were concerned that policy (later extended to tosylate (toluenesulfonate) and besylate (benzenesulfonate) salts) was being driven solely by speculation, and so a consortium was formed to investigate the mechanisms and kinetics of sulfonate ester formation. These studies, undertaken at the independent Product

Quality Research Institute (PQRI), quickly established that ester formation is extremely slow, even under forcing conditions, and no ester is detected when an equimolar amount of base is present.

In response to the consortium's findings and several critical publications, the EDQM requested an assessment by an EMA expert group. This review was chaired by a European scientist who was also chair of the European Pharmacopoeia Commission (the decision-making body of the EP) which, on several occasions, has voted unanimously in favour of retaining controls on alkyl sulfonates. The review's conclusion that 'the presence and formation of these alkyl sulfonates cannot be totally excluded' is in stark contrast to the outcome of the PQRI investigations.

Today, manufacturers are required to either analyse drug substances for levels of alkyl sulfonates or to argue on the basis of scientific evidence that they will not be formed. But there is a catch with the latter approach in that both EDQM and EMA have not responded to requests to clarify the parameters supporting such an evidence-based explanation, thus maintaining false perceptions that these impurities might be present. Overall, regulatory policy has perpetuated unjustified concerns about the safety of sulfonic acid salts, possibly leading some drug developers to use suboptimal counterions.

While this is a problem in itself, the history of sulfonic acid salt policy illustrates a wider issue: that it can be incredibly difficult to change direction once a policy has been accepted as the status quo. In an ideal world, chemists should be able to bring pressure to bear on policymakers to 'follow the evidence'. However, this will not occur until there are significant changes in administrative procedures that increase the openness and transparency of the policy development process. Such changes are unlikely to occur quickly (if at all) in this particular case. In the meantime, individual chemists must continue to alert the broader professional community to policies that are not supported by evidence.

References

D J Snodin, *Org. Process Res. Dev.,* 2019, **23**, 695 (DOI: 10.1021/acs.oprd.8b00397)

Young, Stephen

From: Whaley, Michael
Sent: 04 August 2021 10:30
To: [redacted]
Cc: Young, Stephen
Subject: FW: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate
Attachments: Comments on Pharmeuropa Proposal for a Monograph on Dabigatran Etexilate Mesilate_DJS_Updated_03.08.21.docx

Hi All,

Steve and I have received some comments from David Snodin regarding a Pharmeuropa monograph.

Will you be able to review and provide David any feedback you may have.

Michael

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 03 August 2021 21:34
To: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Cc: Young, Stephen <Stephen.Young@mhra.gov.uk>
Subject: RE: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Dear Michael

As promised, here is an updated version of my comments on the proposed Ph.Eur Monograph for Dabigatran Etexilate Mesilate.

By all means get back to me if anything is unclear.

Kind regards

David Snodin

From: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Sent: 03 August 2021 14:18
To: snodind@xiphora.com; Young, Stephen <Stephen.Young@mhra.gov.uk>
Subject: RE: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Dear David,

Many thanks for your comments on the Dabigatran Etexilate Mesilate monograph published in Pharmeuropa.

Unfortunately I'm unable to open the word document you attached. I'm not entirely sure why. Would you be able to reattach and send again?

Many thanks,

Michael

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 30 July 2021 07:19
To: Young, Stephen <Stephen.Young@mhra.gov.uk>
Cc: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Subject: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Dear Stephen and Michael

Please use this updated version of my comments on Dabigatran Etexilate Mesilate rather than the one sent yesterday.

Kind regards

David

From: Young, Stephen <Stephen.Young@mhra.gov.uk>
Sent: 29 July 2021 18:10
To: snodind@xiphora.com
Subject: Automatic reply: Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Thank you for your email

I am out of office on leave until Monday 9th August.

Michael Whaley (michael.whaley@mhra.gov.uk) is deputising

Mobile numbers for myself and team are below
Steve – 07584362157
Michael – 07766602258
Graziella – 07471359107

Many thanks
Steve

Comments on Pharmeuropa Proposal for a Monograph on Dabigatran Etexilate Mesilate (Text no 3095; Direct link)

I have several objections regarding impurity aspects in relation to the above proposed monograph; in particular, various lines of evidence show that there is no possibility of generating any alkyl mesilate impurities. Relevant information is provided below.

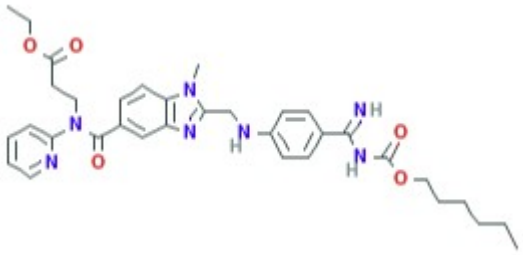
Mechanism of Alkyl-Sulfonate Formation

- Sulfonate-ester formation between an acid and an alcohol requires highly acidic conditions sufficient to protonate the alcohol and provide an hydroxonium-ion leaving group;
- Even under these conditions, ester formation is extremely slow because sulfonate anion is a poor nucleophile. [This was recently demonstrated indirectly by the facile synthesis of stable arenediazonium tosylate salts (Mihelač et al, 2021[1]). Previously, only non-nucleophilic counterions such as BF_4^- or PF_6^- were known to stabilise arenediazonium salts.]
- In a typical synthesis of a sulfonate salt, addition of a molar equivalent amount of sulfonic acid to the base form of the drug substance (normally dissolved in a protic solvent such as ethanol) will not produce any alkyl sulfonate by-product. This is because all of the added sulfonic acid will be neutralized (by an instantaneous diffusion-controlled proton-transfer reaction from sulfonic acid to base), thus leaving no free acid to protonate the ethanol solvent.

Lack of Potential for Alkyl-Sulfonate Formation During Synthesis of Dabigatran Etexilate Mesilate

In the case of Dabigatran Etexilate Mesilate (trade name Pradaxa), the structure of the base form (Dabigatran Etexilate – see Figure 1) ensures that it is *impossible* for the addition of one molar equivalent of methanesulfonic acid (MSA) to create reaction conditions of sufficient acidity to catalyse sulfonate-ester formation between any free *n*-hexanol and MSA.

Figure 1: Dabigatran Etexilate (Base Form)



The dabigatran etexilate molecule contains 7 nitrogen atoms and PubChem lists four pKa values: 1.82, 3.18, 4.28 and 11.52[2]. The most basic nitrogen atom (pKa 11.52) will be the first to be neutralised by MSA and even if an excess of MSA were incorrectly added, protonation of the nitrogen atom with pKa 4.28 would be the next step, thus ensuring that the reaction medium never achieves a pH capable of catalysing sulfonate-ester formation from

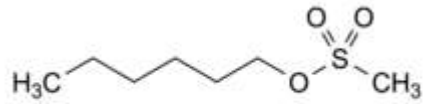
[1] https://www.sciencedirect.com/science/article/pii/S0143720820314236?via%3Dihub.
[2] Dabigatran | C25H25N7O3 - PubChem (nih.gov)

any alcohol including free *n*-hexanol. In any case, the latter is unlikely to be formed by carbamate ester hydrolysis owing to the buffering effect of the various nitrogen atoms present in the molecule.

Thus, there is no possibility for formation of Impurity D, *n*-hexyl mesilate (Figure 2).

An independent chromatographic analysis of impurities in Dabigatran Etexilate Mesilate[3] found no evidence for the presence of *n*-hexyl mesilate.

Figure 2: *n*-Hexyl Mesilate



D. hexyl methanesulfonate, 172

Impact of Reaction Conditions Required to Generate Residues of n-Hexyl Mesilate on the Drug Substance.

In anhydrous ethanol held at 40°C for 12 hours in the presence of 1M MSA around 0.1% conversion to EMS (ethyl methanesulfonate) is achieved[4]. In other words, there will be 1000 ppm *in solution*. In the presence of a drug substance very little EMS will be retained as impurity, a purge factor of nearly 5000 having been determined (Snodin, 2019[5]).

Purge factor$_{\text{alkyl sulfonate}}$ = Concentration in solution/Concentration in API

Rate constants for formation MMS (methyl methanesulfonate), EMS and IMS (isopropyl methanesulfonate) in anhydrous alcohol-MSA systems are essentially similar (Teasdale et al, 2010[6]), and so a comparable rate of formation of *n*-hexyl mesilate in an *n*-hexanol-MSA system is expected to occur. Thus, assuming a lower purge factor of say 1000, generation of 1000 ppm *n*-hexyl mesilate in solution in the presence of 1 M MSA (pH = 0) at 40°C for 12 hours, would produce, at least in theory, an impurity content of 1 ppm *n*-hexyl mesilate in Dabigatran Etexilate Mesilate. [In fact, the conversion would be much lower since, at most, only traces of *n*-hexanol would be expected to be present during mesilate-salt formation.]

What effect would these reaction conditions have on Dabigatran Etexilate Mesilate? Mutha et al, 2018[7] studied its acid hydrolysis in the presence of excess 0.5N HCl (pH = 0.3) for 24 h (temperature not mentioned, probably room temperature of 25°C). Under these conditions around 8% of the API was degraded, the main degradant (DP-1; *ca* 5.3%) being the carboxylic acid resulting from hydrolysis of the ethyl-ester substituent (Ph.Eur Impurity E). This is considered support the notion that, under these conditions, the *n*-hexyl carbamate ester moiety is more resistant to hydrolysis that the carboxylic-acid ethyl ester. If the acid

[3] Gradient RP-HPLC method for the determination of potential impurities in dabigatran etexilate in bulk drug and capsule formulations - ScienceDirect
[4] https://pubs.acs.org/doi/abs/10.1021/op500397h
[5] https://pubs.acs.org/doi/abs/10.1021/acs.oprd.8b00397
[6] https://pubs.acs.org/doi/abs/10.1021/op900301n
[7] https://www.researchgate.net/publication/326322161_Hydrolytic_Degradation_Study_of_Dabigatran_Etexilate_Mesylate_Isolation_and_Structural_Elucidation_of_New_Degradants

hydrolysis had employed excess 1M MSA at 40°C for 12 hours, no doubt degradation would have been significantly greater possibly resulting in cleavage of the carbamate ester moiety. The latter is supported by remarks in the 2010 EPAR for Dabigatran Etexilate Mesilate[8]:

In aqueous solution at 40 °C, dabigatran etexilate mesilate undergoes considerable hydrolytic degradation. The results of the stress stability studies show that dabigatran etexilate mesilate predominately undergoes degradation by hydrolytic pathways.

The active substance is susceptible to hydrolysis in presence of humidity under acidic conditions, which is why a manufacturing process limiting water and acidic conditions is chosen.

In conclusion, using worst-case assumptions, the reaction conditions necessary to generate around 1 ppm *n*-hexyl mesilate impurity in Dabigatran Etexilate Mesilate, would cause marked hydrolytic breakdown of the drug substance and produce a range of additional degradation products.

Ph.Eur Purity Criteria for Methanesulfonic Acid

In addition, any requirements in relation to the general provisions relating to mesilate-salt impurities (methyl, ethyl and isopropyl mesilates) should be waived for the reasons mentioned above plus the fact that MSA reagent would need to be of high purity compliant with Ph.Eur 2.5.37 and 2.5.39.

Regulatory Reviews

The Annex to this document contains excerpts from the initial reviews of Pradaxa by EMA, FDA and PMDA, and it is clear that the only concern on alkyl-mesilate impurities related to the quality of the MSA reagent. [The developer, Boehringer Ingelheim International GmbH, demonstrated that alkyl methanesulfonates are not generated during the synthesis of the drug substance – consistent with the mechanistic arguments presented above.] Consequently, since strict controls on MSA impurities are mandated via Ph.Eur 2.5.37 and 2.5.39, there should be absolutely no need to include *any* alkyl-mesilate impurities in the Ph.Eur monograph for Dabigatran Etexilate Mesilate.

Imprecise and Potentially Confusing Production Statement

Finally, a comment on the Production Statement: “It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in dabigatran etexilate mesilate.” The wording is considered imprecise because genotoxicity relates to mutagenicity, clastogenicity and aneugenicity, and only the first endpoint, mutagenicity, is relevant to ICH M7 (R1)[9].The Q&A supplement to ICH M7 (R1)[10] is explicit on this point:

The terms “mutagenic potential” and “genotoxic potential” are not interchangeable. Mutagenic potential refers to the ability of a compound to induce point mutations (i.e.,

[8] https://www.ema.europa.eu/en/documents/assessment-report/pradaxa-epar-public-assessment-report_en.pdf
[9] M7 (R1) Step 5 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (europa.eu)
[10] questions-answers-ich-guideline-m7-assessment-control-dna-reactive-mutagenic-impurities_en.pdf (europa.eu)

bacterial reverse mutation assay), while genotoxic potential refers to both mutagenic and clastogenic potential. ICH M7 focuses specifically on mutagenicity.

An impurity exhibiting only clastogenic or aneugenic potential would be outside the scope of ICH M7 (R1).

Likely Biological Activity of n-Hexyl Mesilate

The general assumption that all sulfonate esters are mutagenic (in relation to testing positive in the Ames assay) is not necessarily the case. For example, Glowienke et al, 2005[11], showed that ethyl and isobutyl tosilate gave negative results in the Ames reverse bacterial mutation assay (TA100 ±S9). Although no literature reports of an Ames evaluation of hexyl mesilate could be found, Ueno et al[12] investigated whether bulky alkylated bases can induce point mutations or chromosome aberrations. Points mutations were not induced by *n*-alkyl methanesulfonates having *n*-alkyl group with five or more carbons (including *n*-hexyl mesilate), suggesting that bulky base adducts produce chromosome aberrations rather than point mutations. The Ueno et al data strongly suggest that *n*-hexyl mesilate, being clastogenic rather than mutagenic, would be out of scope according to ICH M7 (R1) and so the proposed limit is considered inappropriate (for an impurity that will not be formed).

Summary of Key Points

Impurity D (*n*-hexyl mesilate) should be deleted from the proposed monograph, and the provisions of the production statement on alkyl-mesilate impurities should be waived, for the following reasons.

1. Published kinetic and mechanistic data (see Snodin & Teasdale, 2014[13], and references cited therein) indicate that sulfonate-ester formation between a sulfonic acid and an alcohol is highly unfavoured thermodynamically owing to:
    a. the need for strongly acidic conditions to protonate the alcohol (to product a hydroxonium-ion leaving group);
    b. the extremely feeble nucleophilicity of the sulfonate anion.
2. The base form of dabigatran etexilate is highly buffered in that addition of one molar equivalent of MSA will merely neutralise the most basic nitrogen atom, leaving several additional nitrogen atoms to be neutralised before acidic reaction conditions would be produced.
3. In these circumstance, no alkyl mesilates would be produced from any alcohols present in the reaction mixture.
4. Under the experimental conditions required for formation of alkyl mesilates, there would be marked degradation of the drug substance.
5. The developer, Boehringer Ingelheim International GmbH, demonstrated that alkyl methanesulfonates are not generated during the synthesis of the drug substance – consistent with the kinetic and mechanistic arguments presented above.

[11] Structure–activity considerations and in vitro approaches to assess the genotoxicity of 19 methane-, benzene- and toluenesulfonic acid esters - ScienceDirect
[12] http://people-x.co.kr/past_homepage/2017/ICEM2017/data/ICEM2017_Abstracts.pdf
[13] Mutagenic Alkyl-Sulfonate Impurities in Sulfonic Acid Salts: Reviewing the Evidence and Challenging Regulatory Perceptions | Organic Process Research & Development (acs.org)

6. The only concerns raised in the initial quality reviews of dabigatran etexilate mesilate related to the presence of pre-existing alkyl mesylates in the MSA reagent. However, this issue can be considered resolved in owing to the strict purity criteria for MSA set out in Ph.Eur monographs.
7. Finally, there is evidence that *n*-hexyl mesilate is likely to be clastogenic rather than mutagenic, thus out of scope for ICH M7 (R1).

David J Snodin, PhD

Bristol, 03.08.21

Annex

Notes on published assessments of Pradaxa impurities

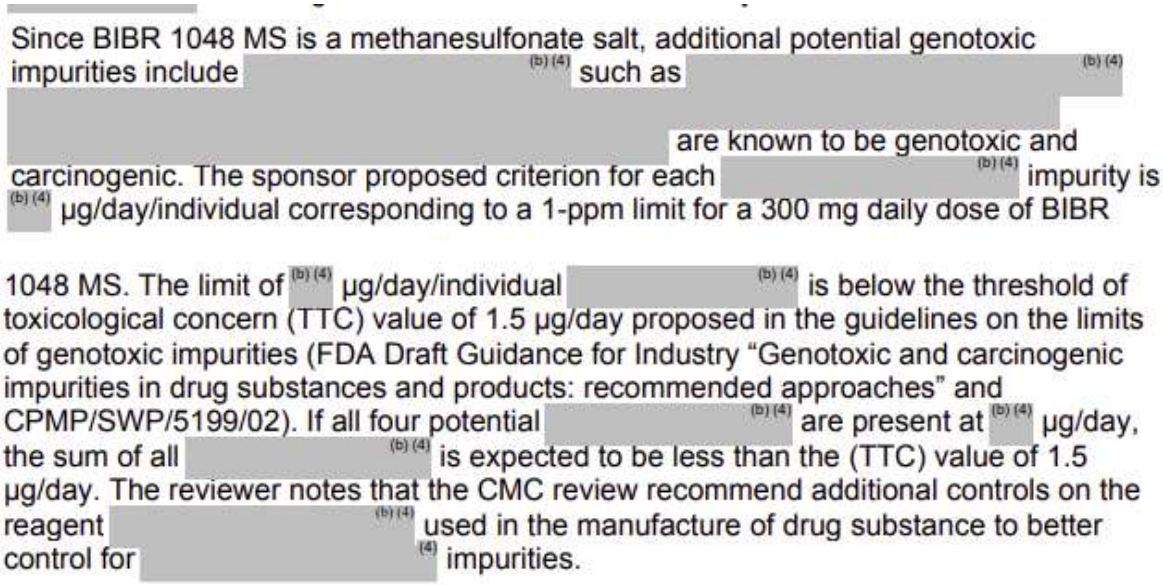
European Medicines Agency (EMA)

The 2008 EPAR for Pradaxa contains the following statement[8]:

Data showing that alkyl methane sulfonates compounds are not formed during drug substance production have been presented which justify why quality controls in the last step of the synthesis are not necessary.

Food and Drug Administration (FDA)

A partially redacted comment in FDA's Pharmacology Review of Pradaxa clearly refers to potential alkyl mesylate impurities[14]:


Since BIBR 1048 MS is a methanesulfonate salt, additional potential genotoxic impurities include (b) (4) such as (b) (4) are known to be genotoxic and carcinogenic. The sponsor proposed criterion for each (b) (4) impurity is (b) (4) µg/day/individual corresponding to a 1-ppm limit for a 300 mg daily dose of BIBR

1048 MS. The limit of (b) (4) µg/day/individual (b) (4) is below the threshold of toxicological concern (TTC) value of 1.5 µg/day proposed in the guidelines on the limits of genotoxic impurities (FDA Draft Guidance for Industry "Genotoxic and carcinogenic impurities in drug substances and products: recommended approaches" and CPMP/SWP/5199/02). If all four potential (b) (4) are present at (b) (4) µg/day, the sum of all (b) (4) is expected to be less than the (TTC) value of 1.5 µg/day. The reviewer notes that the CMC review recommend additional controls on the reagent (b) (4) used in the manufacture of drug substance to better control for (4) impurities.

Pharmaceuticals and Medical Devices Agency (PMDA)

The Japanese PMDA assessment of Pradaxa also focuses on the potential for alkyl mesilate impurities and concludes that there is no need to include these in the drug substance specification[15]:

[14] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000PharmR_Corrrected%203.11.2011.pdf
[15] https://www.pmda.go.jp/files/000207341.pdf

2.B.(2) Alkyl ester of methanesulfonate, a genotoxic substance

[redacted] On the other hand, the strength of alkyl ester of each methanesulfonate in the proposed product is ≤ [redacted] ppm in the results of lot analysis as well as of the stability study for the drug substance and the drug product. [redacted] ppm for the daily dose of 300 mg of dabigatran etexilate amounts to [redacted] µg/day, and this is lower than the accepted toxicological threshold value of 1.5 µg/day. This leads to a conclusion that the exclusion of alkyl ester of methanesulfonate in the specification is appropriate.

[redacted]

The applicant explained as follows:

Process parameters that could be involved in the generation of alkyl ester of methanesulfonate regarding the content and the capsule were investigated. [redacted]

Annex 4

FOI 21/852 - Freedom of Information request

20th August 2021

1. Introduction

Dear Dr Snodin,

I am writing to you in response to your request for information regarding alkyl sulfonate esters production statements. Although you did not specifically refer to the Freedom of Information Act in your email, we have treated the request as such [our **ref: 21/852**].

1. Your request

Your original request was received on 25th July 2021, which the MHRA decided to treat as an FOI request on the first working day after this date (26th July 2021). Under the FOI Act, the Agency has 20 working days to provide a response, which is 24th August 2021.

In your email you requested the follow information:

"*I wish to request copies of any reports/draft statements by EAG MC1 relating alkyl sulfonate esters in sulfonate salts.*"

2. Our response

In considering the response, we have included both EAG:MC1 and BP Commission meetings relevant to your request since we believe this provides a full and complete reply. Below is a timeline of the relevant meetings. The papers, reports and minutes of these meetings are included as annexes to this response as detailed in the table.

Date	Meeting	Note
Jul 2016	BP Commission meeting The Commission discussed production statements for alkyl sulfonate esters at the request of EAG: MC1.	The meeting paper is attached as annex 1. You referred to the publicly available summary minute of this discussion minute in your original request. The full minute of the discussion can be found within annex 2.
Dec 2016	EAG:MC1 meeting The issue of production statements for alkyl sulfonate esters was further discussed.	The meeting papers and minutes are attached as annex 2 and annex 3
Mar 2017	BP Commission meeting The Commission discussed the minutes of the MC1 meeting in Dec 2016 and the recommendation to develop a production statement.	The MC1 minutes from Dec 2016 attached as annex 3 above and the minutes of the BPC discussion are attached as annex 4.
Dec 2017	EAG:MC1 meeting The wording of the production statement was discussed, and a form of words agreed for endorsement by the BP Commission.	The meeting papers and minutes are attached as annex 5 and annex 6.
Mar 2018	BP Commission meeting The Commission discussed the proposed wording and agreed a final wording to be checked prior to publication.	The meeting paper is attached as annex 7. You referred to the publicly available summary minute in your original request. The full minute of the discussion is attached as annex 8.
Jun 2018	EAG MC1 meeting The revised wording from BP Commission was agreed by EAG:MC1 (discussed under Matters Arising)	Matters arising was a verbal update at this meeting so there is no meeting paper. The meeting minutes are available on our website at https://www.pharmacopoeia.com/file/MC1---June-2018.pdf
Jul 2018	BP Commission meeting The revised wording from BP Commission was agreed by	Matters arising was a verbal update at this meeting so there is no meeting paper.

	EAG:MC1 (discussed under Matters Arising)	The meeting minutes are available on our website at https://www.pharmacopoeia.com/file/BPC---July-2018.pdf

You will note that some personally identifying information has been redacted as exempt from disclosure, under section 40 of the FOI Act (personal information relating to a third party).

You will also note that some of the information is the intellectual property of third parties and is subject to copyright. Any copyright will still apply to the information once it has been disclosed and as the person who receives the information you are still obliged, by law, to respect the rights of the copyright owner(s).

3. Your right to review

If you disagree with how we have interpreted the Freedom of Information Act 2000 with regards to your request, you can ask for the decision to be reviewed. The review will be carried out by a senior member of the Agency who was not involved with the original decision.

If you have a query about the information provided, please reply to this email.

Yours sincerely,

Inspection, Enforcement and Standards Division

Medicines and Healthcare products Regulatory Agency

Annex: background correspondence

[Insert all relevant background correspondence

Annex 5

Young, Stephen

From: IE&SFOI
Sent: 20 August 2021 16:44
To: Young, Stephen
Subject: FW: FOI 21/867
Attachments: FoI Requests on BP Monographs for three mesilate salts_19.08.21.docx; FoI Request on 4 BP Monographs.docx

FYI

Regards

[redacted]

Redactions under section 40(2), personal information

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 20 August 2021 13:52
To: IE&SFOI <IEandSFOI@mhra.gov.uk>
Subject: RE: FOI 21/867

Dear IE&S FOI Team

I'm disappointed and surprised that MHRA holds no information justifying the requirements of the Co-dergocrine Mesilate BP monograph. You indicate that any Ph.Eur monograph will be elaborated with input from the BP secretariat. In that case, are there background documents relating to preparation of the Ph.Eur monograph for Co-dergocrine Mesilate.

You also state the following:

We will be happy to pass on your rationale for why a production statement should not be included in this specific monograph to the EP expert group and request that a revision to the monograph is considered based on this. You should be aware that you may be asked for experimental data to support the rationale for the revision going ahead. Please note that it may be the view of the expert group or EP Commission that the monograph need not be revised.

I think it's more than a bit much for me to be asked for experimental data when neither EP nor BP has ever published any kind of evidence-based rationale supporting the Production Statement. Moreover, all of the public-domain information negates the need for a Production Statement. If BP or EP disagrees, please ask them to set out the evidence.

But you may be interested in two additional FoI requests (attached) that I submitted today and the evidence contained therein. By all means supply this information to the appropriate EP and BP experts.

Kind regards

David Snodin

From: IE&SFOI <IEandSFOI@mhra.gov.uk>
Sent: 20 August 2021 12:16

To: snodind@xiphora.com
Cc: FOI_Policy <FOI_Policy@mhra.gov.uk>
Subject: FOI 21/867
Importance: High

20th August 2021

Dear Dr Snodin,

REF: FOI 21/867

1. Introduction

I am writing to you in response to your request for information regarding the inclusion of a production statement in the monograph for Co-dergocrine Mesilate included in the British Pharmacopoeia. Although you did not specifically refer to the Freedom of Information Act in your email, we have treated the request as such [our **ref: 21/867**].

2. Your request

Your original FOI request was received on 29th July 2021. Under the FOI Act, the Agency has 20 working days to provide a response, which is 27th August 2021.

In your email you requested the follow information:

- *Documents setting out the evidence-based justification for including a Production Statement on alkyl-mesilate impurities in the monograph noted above;*
- *If the monograph was deemed suitable to be replicated in the BP merely because it is listed in the Ph.Eur, documents showing due diligence carried out by the BP Secretariat regarding the validity of the Production Statement on alkyl-mesilate impurities.*

3. Our response

I can confirm we do not hold the information that you requested.

As you are aware, the UK participates in the development and implementation of the European Pharmacopoeia. The UK is a founding signatory to the "Convention on the Elaboration of a European Pharmacopoeia" (available at *https://rm.coe.int/168006ff4c*).

Article 1 (b) of the convention requires contracting parties "to take the necessary measures to ensure that the monographs which will be adopted by virtue of Articles 6 and 7 of the present Convention and which will constitute the European Pharmacopoeia shall become the official standards applicable within their respective countries." In the UK this is done by reproducing all European Pharmacopoeia content within the British Pharmacopoeia.

This process is described in the introduction section of the British Pharmacopoeia. For your convenience this text is reproduced below.

In accordance with previous practice, all monographs and requirements of the European Pharmacopoeia are reproduced in this edition of the British Pharmacopoeia or, where appropriate, within its companion edition, the British Pharmacopoeia (Veterinary) 2022.
Where a monograph has been reproduced from the European Pharmacopoeia, this is signified by the presence of a chaplet of stars alongside its title. Additionally, reference to the European Pharmacopoeia monograph number is included immediately below the title in italics in the form 'Ph. Eur. monograph xxxx'. Where the title in the British Pharmacopoeia is different from that in the European Pharmacopoeia, an approved synonym has been created (see Appendix XXI B) and the European Pharmacopoeia title is included before the monograph number. The entire European Pharmacopoeia text is delineated by two horizontal lines bearing the symbol 'Ph. Eur.'.
The European Pharmacopoeia texts have been reproduced in their entirety but, where deemed appropriate, additional statements of relevance to UK usage have been added (e.g. action and use statement, a list of British Pharmacopoeia

preparations). It should be noted, however, that in the event of doubt of interpretation in any text of the European Pharmacopoeia, the text published in English under the direction of the Council of Europe should be consulted. Correspondence between the general methods of the European Pharmacopoeia and the appendices of the British Pharmacopoeia is indicated in each appendix and by inclusion of a list at the beginning of the appendices section.

In the spirit of mutual recognition and work-sharing, technical review and diligence is done via our input into the European Pharmacopoeia expert groups, comments on draft text during the consultation periods and the UK Delegation's participation in the European Pharmacopoeia Commission. Once monographs are adopted by the EP Commission and published in the European Pharmacopoeia, they are reproduced in the British Pharmacopoeia without further review. We do not hold any additional documents prepared by the BP Secretariat relating to your specific requests.

We will be happy to pass on your rationale for why a production statement should not be included in this specific monograph to the EP expert group and request that a revision to the monograph is considered based on this. You should be aware that you may be asked for experimental data to support the rationale for the revision going ahead. Please note that it may be the view of the expert group or EP Commission that the monograph need not be revised.

Please advise if you would be content for us to do this, and/or if you have any further queries about the information provided, by reply to this email: IE&SFOI@mhra.gov.uk

If you are unhappy with our decision, you may ask for it to be reviewed. That review will be undertaken by a senior member of the Agency who has not previously been involved in your request. If you wish to pursue that option please email: info@mhra.gov.uk

Due to the ongoing Covid-19 situation, we are not able to accept delivery of any documents or correspondence by post or courier to any of our offices.

After that, if you remain dissatisfied, you may write to the Information Commissioner at;
The Information Commissioner's Office
Wycliffe House
Water Lane
Wilmslow
Cheshire
SK9 5AF
They will make a decision on whether or not we have interpreted the FOIA correctly in handling your request.

Yours sincerely

IE&S FOI Team
MHRA
Inspection, Enforcement and Standards
cc FOI_Policy

permanently delete what you have received. Incoming and outgoing email messages are routinely monitored for compliance with the Department of Health's policy on the use of electronic communications.

For more information on the Department of Health's email policy, click

DHTermsAndConditions

Annex 6

Young, Stephen

From: snodind@xiphora.com
Sent: 31 August 2021 21:32
To: Young, Stephen
Cc: Whaley, Michael
Subject: RE: Production Statement on Alkyl Mesilates in Mesilate-Salt Drug Substances
Attachments: Alkyl sulfonates in sulfonic acid salts_ fact or fiction.ppt; Comments on Minutes from Meetings of BP Commission and EAGs regarding alkyl mesilates_DS_ 31.08.21.docx

Dear Stephen

Please find my comments on the 8 documents provided under FoI relating to BPC and EAG minutes from 2016-2018.

Hopefully, the comments are self-explanatory if you have the various documents to hand. I felt it would overload the Word document if I were to embed 8 PDFs. However, I can send these PDFs in a separate email if necessary.

In addition, I can provide full-text copies of the cited articles.

Finally, I'm also attaching a copy of a presentation made a few years ago in Berlin which shows, *inter alia*, information on the consequences of using technical-grade MSA (containing 500 ppm MMS) to synthesise a mesilate salt – basically, none. This is because the purge factors are so enormous when standard isolation procedures are used (such as solvent-washing of precipitated mesilate salt). And recrystallisation is also a highly efficient technique for removing any MMS. [I'm not advocating the use of low-purity MSA or the need for recrystallisation; the salt-forming reaction is very straightforward and robust.]

Please get back to me if you have any queries. By the way, I should be most happy to attend a face-to-face or remote Q&A session with you and/or BPC/EAG members.

Kind regards

David

From: Young, Stephen <Stephen.Young@mhra.gov.uk>
Sent: 31 August 2021 15:15
To: snodind@xiphora.com
Cc: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Subject: RE: Production Statement on Alkyl Mesilates in Mesilate-Salt Drug Substances

Dear Dr Snodin,

Thank you for your email.

We are currently dealing with your two subsequent FoI requests as below

- Benzatropine Mesilate, Loprazolam Mesilate and Prochlorperazine Mesilate
- Betahistine Mesilate, Dihydroergocristine Mesilate, Saquinavir Mesilate and Ziprasidone Mesilate

Please send your thoughts on the minutes so myself and Michael and we will discuss with the relevant Chairs.

With kid regards

Stephen

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 24 August 2021 16:32
To: Young, Stephen <Stephen.Young@mhra.gov.uk>
Cc: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Subject: Production Statement on Alkyl Mesilates in Mesilate-Salt Drug Substances

Dear Stephen and Michael

I've recently acquired via FoI copies minutes from meetings of the BPC and relevant EAGs relating to discussions on introducing a Production Statement on potential alkyl-mesilate impurities into BP monographs for mesilate-salt drug substances.

I believe there are significant errors and omissions in the way that this issue has been approached by the BP, and so I have created a detailed commentary on various statements recorded in the minutes of meetings that took place between 2016 and 2018.

Can you advise me on whether it would be appropriate for me to send my document to you and/or to you and the chairs of the relevant EAGs?

Kind regards

David Snodin

Comments on Minutes from Meetings of BP Commission and EAGs regarding Alkyl Mesilates

BPC Meeting, July 2016

In 2000, the European Pharmacopoeia Commission's (EPC) concerns over the (potential) genotoxicity of alkylsulfonate esters led to the insertion of Production Statements into the monographs for mesilate salts.

Comment: The side-reaction hypothesis (a reaction between a solvent such as methanol, ethanol or isopropanol and methanesulfonic acid) for formation of alkyl mesilates was strongly implied by EDQM in Pharmeuropa in January 2000 (Annex 1A). In January 2004 a draft monograph for Doxazosin Mesilate was published in Pharmeuropa (Annex 1B). This monograph contained the original version of the Production statement which was more specific regarding the formation of alkyl mesilates:

> The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

No supportive evidence, mechanistic or otherwise, was provided in Pharmeuropa. However, it should have been clear that some kind of acid-catalysed esterification reaction between methanesulfonic acid (MSA) and a protic solvent would be involved (as is the case with carboxylic-acid esters). However, when a molar equivalent amount of MSA is added to the base form of a drug substance dissolved in ethanol:

(a) All added MSA will be neutralised with no residual acidity available to catalyse ester formation. [Later research established that extremely acidic conditions are require to effect a minimal extent of ester production];
(b) No protonation of ethanol (mildly acidic; pKa of protonated ethanol = -2 to -3) will occur in the presence of a protonated base (pKa typically 6 to 10).

Moreover, no evidence for the presence of alkyl mesilates in a range of mesilate-salt APIs was detected during an MSc project at the University of Strathclyde in 2002. I was alerted to the latter by an EDQM staff member concerned that the Production Statement was about to be introduced solely on the basis of an unvalidated hypothesis (Annex 2).

In the case of Viracept, ® ethyl methanesulfonate was formed during the tableting production process.

Comment: This is not the case; the contamination occurred in the drug substance. In fact, EMS underwent hydrolytic degradation during tabletting and the EMS concentration in contaminated drug product decreased by around 9%/month when stored at 25°C[1]. EMS was generated as a result of an interaction of residual ethanol (used as cleaning agent) with a massive excess of MSA in a reagent-storage tank. The contaminated MSA was then employed for the autumn campaign of nelfinavir mesilate manufacture. A brief summary of the "Viracept incident" is provided in Annex 3. A more detailed account is provided in

[1] https://pubmed.ncbi.nlm.nih.gov/19857795/

various articles such as Snodin & Teasdale, 2015[2] and Gerber and Toelle, 2009[1]. The Viracept incident was unique and cannot be viewed in any way as a precedent for alkyl-mesilate formation during the routine GMP synthesis of mesilate salts.

A publication from a German OMCL has indicated that genotoxic alkyl sulfonates have been detected in certain finished products, though at low levels, below the TTC (threshold of toxicological concern). These impurities may stem from the use of sub-standard starting materials even when they did not occur during synthesis.

Comment: The OMCL report (Wollein & Schramek, 2012) relates to a screening procedure for the presence of alkyl mesilates in mesilate-salt drug products. A careful evaluation of the article indicates that the positive findings were due to analytical artifacts[3]. This evaluation is shown in Annex 4. Interestingly, EDQM ceased using this publication as evidence of alkyl-mesilate formation once they were made aware of these criticisms.

In 2008, following a GMP failure, ethyl methanesulfonate was found in Viracept® (Nelfinavir) and this triggered regulatory discussions. The EPC was asked to establish a Mesilates Working Party (MSL WP) with specific terms of reference: ¬ the drafting of general methods for the determination of lower alkyl alkanesulfonates in alkanesulfonic acids (particularly methanesulfonic acid, MSA) with priority for alkyl mesilates ¬ the determination of methanesulfonyl chloride in MSA ¬ a general method for the determination of methyl mesilate etc. in API mesilates The objective was to ensure that validated sensitive and specific methods to detect and quantify trace amounts of such substances would be available to all the users of the European Pharmacopoeia.

Comment: The MSL WP was in many regards set up on the false premise that the Viracept incident was representative of the routine GMP synthesis of mesilate salts. In addition, there was an inbuilt incorrect assumption that residues of alkyl-mesilate impurities could be present in mesilate-salt APIs. As far as can be ascertained, no investigations were made to clarify whether the "problem" was real or imaginary prior to the development of analytical methods for alkyl mesilates. On the other hand, development of analytical methods relating to the establishment of MSA purity, is helpful. Access to minutes of MSL WP meetings was denied by EDQM on the basis that these were "working documents" even after the work of the MSL WP was terminated[3].

Guideline on the Limits of Genotoxic Impurities

Comment: At the time of the July 2016 BPC meeting this guideline had been effectively replaced by ICH M7[4] on mutagenic impurities. Consequently, reference in a Production Statement to *genotoxic* alkyl mesilates/sulfonates is inappropriate and potentially misleading.

[2] https://pubs.acs.org/doi/abs/10.1021/op500397h
[3] https://pubs.acs.org/doi/abs/10.1021/acs.oprd.8b00397
[4] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m7r1-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit_en.pdf

MC1 Paper, 2016

Ph Int:
The International Pharmacopoeia include the following production statement in API monographs for mesilate salts but not finished products. There are no besilate or tosilate salt monographs in the Ph Int.

> **Manufacture.** The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

The notion that alkyl mesilate formation is particularly likely to occur if the reaction medium contains lower alcohols clearly relies on the disproved side-reaction hypothesis.

ACTION (a) The Secretariat to inform EAG MC1 of the Commission's discussion and of the need to seek further information to support adding a Production statement to the relevant BP formulation monographs. (b) The Secretariat to add a Production statement to the following monographs in a future publication: Benzatropine Mesilate, Loprazolam Mesilate, Prochlorperazine Mesilate.

Comment: The MC1 paper contains no hard evidence supporting the above action point, only a discussion of precedents. An evaluation of the Production Statement on these three monographs indicates that they can be challenged on multiple aspects, in particular that published mechanistic information shows that it is impossible for any formation of alkyl-mesilate impurities during drug-substance production. Detailed comments on the monographs are contained in a recent FoI request.

Annexes: Various papers on mesilate salts.

Comment: There are critical omissions from the referenced articles, in particular the Teasdale et al mechanistic papers originating from research commissioned at the PQRI[5,6], an Elder et al publication on control strategies based mechanistic principles[7] and the Snodin & Teasdale OPRD review article of 2015[2].

MC1 Meeting on 6th December 2016

No further scientific developments.

BPC Meeting on 8th March 2017

XXX said that this matter had been raised within EFPIA (European Federation of Pharmaceutical Industries and Associations). It had been an issue for over 10 years and companies had managed to find a way to ensure compliance. There were concerns that the

[5] https://pubs.acs.org/doi/abs/10.1021/op800192a
[6] https://www.enovatia.com/wp-content/uploads/2018/03/Sulfonate-ester-kinetic-study.pdf
[7] https://pubs.acs.org/doi/10.1021/op300216x

decisions of EDQM had been made on limited data and that EDQM appeared to be unwilling to share this data.

Comment: In over 20 years of investigating the issue of alkyl-sulfonate impurities, EDQM has never provided any credible evidence supporting their claims. And so, I believe their unwillingness to supply such data is because they have none. The story begins with the notice in 2000 in Pharmeuropa implying an hypothesis that there could be a side-reaction producing alkyl mesilates/sulfonates if mesilate-/sulfonate-salt synthesis is undertaken using a short-chain protic solvent such as ethanol. EDQM failed to modify or abandon this hypothesis in spite of contradictory evidence (e.g. 2002 Ahmad project; Viracept incident; follow-up survey to Viracept incident, data from Certification Procedure) that was ignored and, in some cases, covered up. Following the 2015 CHMP/QWP internal review (see later comments), EDQM changed the Production Statement to eliminate any wording alluding to the side-reaction hypothesis. The current statement merely asserts that alkyl sulfonates are potential impurities in sulfonic-acid salts[8]. Attempts to obtain information from EDQM over several years using FoI requests were unsuccessful as documented in Snodin, 2020[3]. In responses to more recent FoI requests there were hints that the MSL WP might be re-established, which did not happen however. Instead, I received a letter from the Director of EDQM which is shown in Annex 5. The letter contains no evidence supporting EDQM's case, and presents a bureaucratic rather than a scientific defence of the Production Statement. Incidentally, "no complaints" is no substitute for evidence. On at least one occasion my objection to a Pharmeuropa proposal for a sulfonate salt was not forwarded to EDQM by the BP secretariat.

MC1 Paper, 12.2017
There is potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified [through review of the manufacturing process], these impurities must not exceed the threshold of toxicological concern/[specific TTC limit].

Comment: It is disappointing that the secretariat's proposed Production Statement completely ignores the mechanistic and other information in various publications[2,5,5,6] that demonstrate the lack of potential for production of mesilate esters during mesilate-salt synthesis using an alcoholic solvent.

Research at the PQRI employed an MSA/ethanol system (1M MSA dissolved in EtOH) in order to determine the mechanism and kinetics of mesilate ester formation. The hydroxyl group is highly resistant to nucleophilic displacement[9] and requires activation before it can participate in any substitution reactions, for example in the presence of HCl or HBr[10]. A freshly prepared solution of HCl gas in anhydrous ethanol, maintained at low temperature, is

[8] https://www.edqm.eu/sites/default/files/press_release_on_mutagenic_impurities_february_2016.pdf
[9] https://www.masterorganicchemistry.com/2015/03/10/tosylates-and-mesylates/
[10] https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Map%3A_Organic_Chemistry_(Bruice)/10%3A_Reactions_of_Alcohols_Ethers_Epoxides_Amine_and_Sulfur-_Containing_Compounds/10.01%3A_Nucleophilic_Substitution_Reactions_of_Alcohols-_Forming_Alkyl_Halides

reported to contain 50-70 ppm chloroethane. The level of chloroethane increases significantly if the solution is allowed to "age"[2].

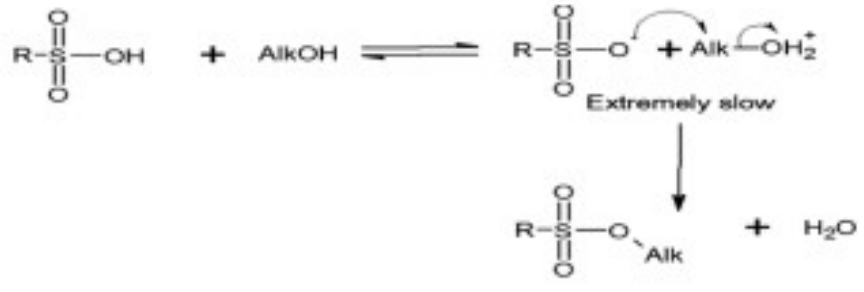
In neutral or mildly acidic conditions there will be absolutely no reaction between chloride ion (which is an extremely strong nucleophile when compared to mesilate anion) and a short-chain alcohol; dissolving sodium chloride in ethanol produces no chloroethane[10]**Error! Bookmark not defined.**. Nucleophilic displacement occurs via an S_N2 mechanism with primary alcohols**Error! Bookmark not defined.**.

Research at the PQRI employed an MSA/ethanol system (1M MSA dissolved in EtOH) in order to determine the mechanism and kinetics of mesilate ester formation. The hydroxyl group is highly resistant to nucleophilic displacement[11] and requires activation before it can participate in any substitution reactions, for example in the presence of HCl or HBr[10]. A freshly prepared solution of HCl gas in anhydrous ethanol, maintained at low temperature, is reported to contain 50-70 ppm chloroethane. The level of chloroethane increases significantly if the solution is allowed to "age"[2]. In neutral or mildly acidic conditions there will be absolutely no reaction between chloride ion (which is an extremely strong nucleophile when compared to mesilate anion) and a short-chain alcohol; dissolving sodium chloride in ethanol produces no chloroethane**Error! Bookmark not defined.**. Nucleophilic displacement occurs via an S_N2 mechanism with primary alcohols**Error! Bookmark not defined.**.

Ester formation occurs in two steps:

- **Step 1** involves protonation of ethanol to form an ethyl oxonium ion; note that this occurs only in strongly acidic conditions (pH 0 or lower)
- **Step 2** is the nucleophilic displacement of H_2O^+ from the ethyl oxonium ion by mesilate anion to form ethyl methanesulfonate (EMS); note that mesilate anion is a very feeble nucleophile (owing to delocalisation of negative charge over three oxygen atoms) so that this part of the reaction is extremely slow. It is also highly temperature-sensitive, the reaction rate increasing four-fold for each 10°C increase in temperature.

The mechanism is shown below:

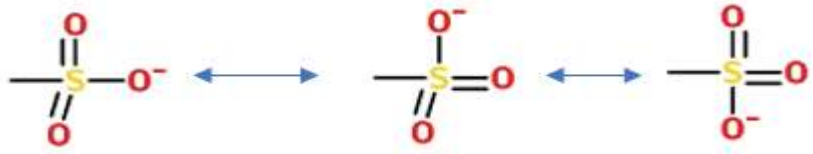


Alk = methyl, ethyl, or *iso*propyl

R = methyl, phenyl or *p*-tolyl

[11] https://www.masterorganicchemistry.com/2015/03/10/tosylates-and-mesylates/

Delocalisation of negative charge for mesilate anion:



Information on the significant reduction in EMS production is shown in Annex 6 indicating an 80% decrease (around 16-fold) at 50°C compared to 70°C. Even more remarkable is the effect of added water. In ethanol containing 5% water, EMS formation is reduced by around 90% (compared to the extent of formation in anhydrous ethanol) (Annex 6). This is considered to be due to the preferential protonation of water rather than ethanol.

During the GMP synthesis of a mesilate salt an equimolar amount of MSA would be added (gradually with stirring, temperature control and possibly pH monitoring) to the base form of the drug substance. Protonation reactions are diffusion-controlled and essentially instantaneous.

Thus, only the basic portion of the drug substance will be protonated. When this has been achieved all added MSA will be neutralised and to there will be no acid remaining to protonate the ethanol solvent.

However, even if a slight excess of MSA is added, this will be insufficient to produce any EMS. Teasdale et al reported that addition of a 2% excess of MSA to the non-nucleophilic base 2,6-lutidine dissolved in anhydrous ethanol maintained at 70 °C for 12 hours produced no detectable EMS (<0.5 ppm)[2]. This finding confirms that strongly acidic conditions and elevated temperatures are required in order to produce even small amounts of alkyl mesilates.

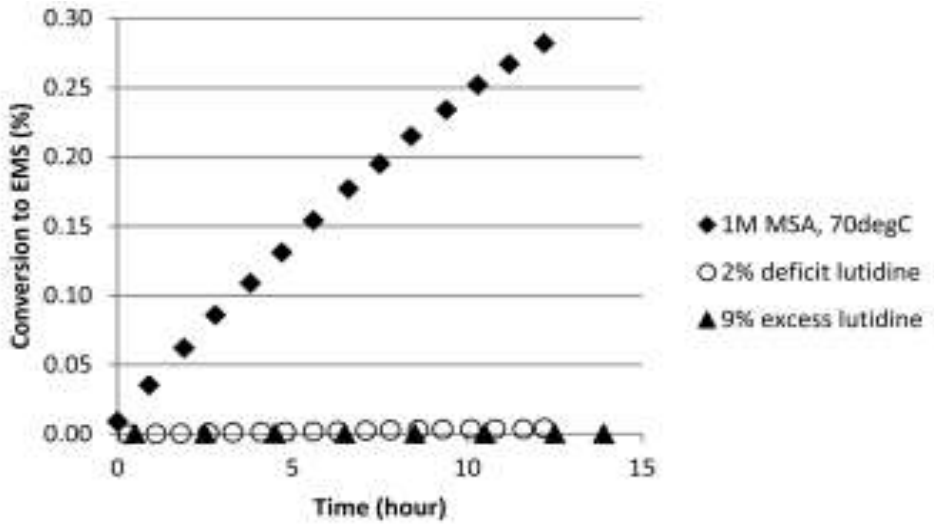
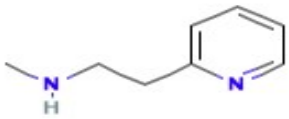


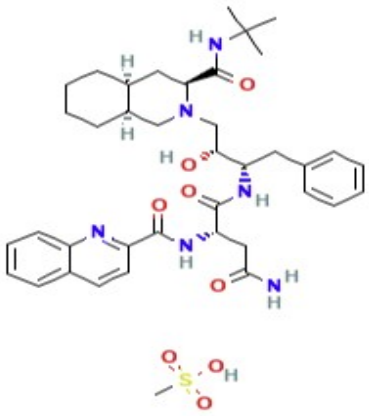
Figure 5. Effect of base (2,6-lutidine) on the extent of EMS formation at 70 °C.

This mechanistic information indicates that in cases where all nitrogen atoms in the base form of the drug substance are protonated (such as in betahistine mesilate) there will be no excess acidity generated and thus no opportunity for EMS formation. In other words, in a GMP

synthesis in which the appropriate molar equivalent amount of MSA is added to the base form of the drug substance, all MSA will be neutralised and so Step 1 of the alkyl sulfonate synthesis will not be achieved, never mind Step 2.]



In cases where the base form of the mesilate-salt drug substance contains unprotonated nitrogen atoms (for example as in saquinavir mesilate, it will be *impossible* to produce acidic conditions).



The issue of limits for alkyl mesilate impurities has no relevance given that such impurities will not be formed during GMP synthesis of mesilate-salt APIs. Nevertheless, it should be noted that the TTC limit is inappropriate because:

- There are published compound-specific limits for all three alkyl mesilates[3];
- Drugs used only for short-term treatment qualify for limits based on the LTL (less than lifetime) concept, one example being loprazolam mesilate.

MC1 Minutes 12.2017

No new information.

COM18(6) 03.2018

No new issues. See previous comments on proposed Production Statement.

BPC Minutes. 03.05.2018

No new developments.

Additional Information

EMA/CMDh Follow-up Survey on Licensed Sulfonic-Acid-Salt Products

In January 2008 EMA launched a survey of approved products containing sulfonic-acid-salt APIs[12]. Questions for MAHs (Market Authorisation Holders) regarding alkyl-sulfonate impurities focused on a variety of speculative hypotheses including side-reactions, reagent-impurities, salt-alcohol interactions and retention of alkyl sulfonates in recycled solvents. No report on the results of the survey has been issued by EMA or any other national agency. However, in 2017 EMA confirmed in response to an FOI request (ASK-16726) that no companies reported toxicologically significant levels of alkyl-sulfonate impurities in the 2008 survey**Error! Bookmark not defined.**.

Internal EMA Review

A letter from the EPC (European Pharmacopoeia Commission) secretariat (signed by Dr. Susanne Keitel, Director of EDQM, and Mrs. Cathie Vielle, secretary to EPC) was sent to Dr. J.-L. Robert (Chair of both QWP and the EPC) on 27.07.15 as follows:

A new article by Snodin et al. indicates that the current paradigm of genotoxicity on alkyl sulfonate (sic) and current regulatory positions may no longer be justified. In order to have a better understanding of the overall impact on the Ph.Eur but also on the assessment of marketing authorisation applications and applications for a certificate of suitability, the European Pharmacopoeia Secretariat seeks the opinion of the Joint CHMP/CVMP Quality Working Party (QWP) on this matter and more precisely on the question whether the current approach needs to be changed.

Various FoI requests produced a few heavily redacted documents, none of which contained any evidence supporting the conclusion from Dr J-L Robert that “the presence and formation of these alkyl sulfonates cannot be totally excluded”. [There appeared to be an obvious conflict of interest on behalf of Dr Robert since he chaired both the EPC and QWP. However, this was rejected by EMA since the only recognised conflicts of interest concern contacts with the pharmaceutical industry.]

The article referenced above (Snodin et al) is actually Snodin & Teasdale, 2015[2] in which evidence is presented to show that the earlier side-reaction hypothesis is not viable

[12] Microsoft Word - TEMPLATE LETTER FOR ALL MARKETING AUTHORIZATION HOLDERS FO… (europa.eu)

mechanistically. And so, it seems no coincidence that in early 2016 EDQM modified the Production Statement for sulfonic-acid salts to eliminate any reference to this hypothesis (see below). Instead, the updated Production Statement simple asserts that alkyl sulfonates are potential impurities – formed by an unspecified mechanism.

"It is considered that [XXX esters] are genotoxic and are potential impurities in [name of the API]. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method [2.5.XX] is available to assist manufacturers."

Article in Chemistry World

An article was published in Chemistry World in July 2020 with the title: Where's the Evidence?: Policies based on false hypotheses can persist in spite of overwhelming contradictory data[13]. Chemistry World took great care to liaise with EDQM on the content of the article. EDQM raised several comments on the draft version but confirmed that the published version (Annex 7) contained accurate statements.

Versions of the Production Statement

As previously mentioned, the initial Ph.Eur Production Statement was set out in Pharmeuropa in January 2004 and an amended version was introduced in 2016. Two versions of the Production Statement are currently employed in the British Pharmacopoeia (BP). These four variants of the Production Statement are set out in Table 1, with comments.

Table 1: Comments on Four Variants of the Production Statement Employed by Ph.Eur and BP

Pharmacopoeia	Text of Production Statement	Comments
Ph.Eur	The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.	Used from 2004-2016. Features the side-reaction hypothesis. Abandoned following the internal CHMP/QWP review.
Ph.Eur	It is considered that [XXX esters] are genotoxic and are potential impurities in [name of the API]. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method [2.5.XX] is available to assist manufacturers.	Announced in a press release in press release in February 2016. The "mystery mechanism" leading to potential sulfonate-ester impurities is not identified.
BP	Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.	Applies to: benzatropine, loprazolam and prochlorperazine mesilates. Features the side-reaction hypothesis. The TTC limit is not universally applicable, for example when therapy is short-term.
BP	It is considered that alkylsulfonate esters are genotoxic and are potential impurities in XXXXX	Applies to: betahistine, codergocrine, dihydrocristine,

[13] https://www.chemistryworld.com/opinion/questioning-european-policy-on-alkyl-mesylate-impurities/4012169.article

	mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods 2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid, 2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances and 2.5.39. Methanesulfonyl chloride in methanesulfonic acid are available to assist manufacturers.	saquinavir and ziprasidone mesilates. Essentially the same as the current Ph.Eur production statement. No information on how potential impurities might be formed.

Evidence (particularly that relating to mechanisms) supporting any variant of the Production Statement could not be found in any of the eight BPC/EAG papers supplied under FoI; all available relevant reports indicate that no alkyl-mesilate impurities are formed during the GMP synthesis of mesilate-salt drug substances. In addition, use of *genotoxic* rather than mutagenic is inappropriate and potentially misleading.

Questions for BPC and EAGs (MC1, MC2, MC3)

(a) Is the mechanistic and kinetic information presented in various publications (for reviews see Snodin & Teasdale, 2015[2] and Snodin, 2020[3]) accepted by BPC and the relevant EAGs? This is considered a reasonable question because BPC has endorsed the production statement on potential alkyl-mesilate impurities in spite of the extensive contradictory evidence. [Potential mechanisms other than the side-reaction hypothesis are discussed and negated in Snodin, 2020[3].]

(b) If the mechanistic information is accepted, it is the case that:
no highly acidic conditions achieved during synthesis = no alkyl mesilates formed.
[Step 1 of the alkyl-mesilate formation mechanism not completed.] Do the BPC and EAGs agree?

(c) In addition, how is it possible at neutral pH (following neutralisation of added MSA via salt formation) for the non-nucleophilic mesilate anion[14] to displace the hydroxyl group from ethanol (or other similar short-chain alcohol), when the strongly nucleophilic chloride ion fails to generate any chloroethane under similar conditions?

(d) If there is no agreement to questions (a), (b) and (c), what explanations (mechanistic or otherwise) can be provided to justify the notion that alkyl mesilates can be considered as potential impurities formed during GMP synthesis of mesilate-salt drug substances?

(e) It would be extremely helpful if BPC were able to obtain information from MHRA on responses to the 2008 survey, and to obtain unredacted minutes from EMA regarding the 2015 internal review. Is this possible?

DJS, Bristol, UK, 31st August 2021

[14] https://socratic.org/questions/are-triflate-tosylate-and-mesylate-nucleophilic

Annex 1A

Pharmeuropa, 12.1, January 2000, 27[15]

ALKYL MESILATE (METHANESULPHONATE) IMPURITIES IN MESILATE SALTS

The need for limits on methyl, ethyl and isopropyl mesilate esters in active substances presented as mesilates has recently been discussed by the European Pharmacopoeia Commission. These esters are highly toxic and assurance is needed that they are not present in unacceptable quantities in medicinal products. However, they are also very reactive and it is therefore possible that in practice the level of contamination is negligible. Readers of Pharmeuropa are asked to inform EDQM of their opinion on the need for a test and limit in the light of their experience with mesilate salts. Information on analytical methods and the level of such impurities found in practice would be extremely valuable. Seven monographs on mesilates are at present included in the European Pharmacopoeia and would be concerned if a test and limit were to be added:

Betahistine mesilate
Bromocriptine mesilate
Deferoxamine mesilate
Dihydroergocristine mesilate
Dihydroergotamine mesilate
Pefloxacin mesilate dihydrate
Phentolamine mesilate

Please send your replies to:
Council of Europe
European Directorate for the Quality of Medicines
B.P. 907
67029 Strasbourg Cedex 1
France
Fax: + 33 (0)3 88 41 27 71.
E-mail: info@pheur.org.

Annex 1B

Pharmeuropa, 16.1, January 2004, 104[16]

DEFINITION

1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-((2*RS*)1,4-benzodioxan-2-ylcarbonyl)piperazine methanesulfonate.

Content: 98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

CHARACTERS

Appearance: white or almost white crystalline powder.

Solubility: slightly soluble in water, soluble in a mixture of tetrahydrofuran and water (35:15 *V/V*), slightly soluble in methanol, practically insoluble in acetone and in isopropyl alcohol.

It shows polymorphism.

mp: about 281 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *doxazosin mesilate CRS*.

If the spectra obtained show differences, mix 1 part of the substance to be examined and 1 part of the reference substance separately with 10 parts of *ethanol R* and heat to boiling. Reflux the suspension for about 3 h. Cool and filter. Record new spectra using the residues.

[15] https://pharmeuropa.edqm.eu/app/Archives/content/Archives-0/Pharmeuropa_12.01E.pdf

[16] https://pharmeuropa.edqm.eu/app/Archives/content/Archives-0/Pharmeuropa_16.01E.pdf

Annex 2

Email (sent 16.07.04) from EDQM Staff member raising the alarm over the hypothesis being used by senior EDQM staff members that alkyl mesilates could be formed as impurities during mesilate-salt synthesis

Dear David

I appreciated receiving so promptly the publications and extracts which you sent concerning alkylating agents. Please find attached two articles which appeared in Pharmeuropa which are related to this issue.

I can also confirm that a number of mesilate salts were examined in our laboratory initially to identify those which contained traces of alcohols using the general method for residual solvents (2.4.24) and then subsequently those with alcoholic residues were examined for the presence of the mesilate esters by a direct injection GC method [1]. Of 11 mesilates tested 8 contained either methanol or ethanol. The following mesilate salts were examined:

Bromocriptine
Dihydroergotamine
Perfloxacin
Betahistidine
Phentolamine
Dihydroergocristine
Codergocrine
Pergolide
Dihydroergotoxine
Dihydralazine

The limits of detection for the methyl and ethyl esters were less than 10 ppm.

Salts shown to contain either methanol (pergolide) or ethanol (dihydralazine, codergocrine and phentolamine) were tested for the presence of the methyl and ethyl esters respectively. No esters were detected in the batches examined.

It seems that there is little evidence for the formation of these esters.

I would be happy to collaborate to prepare an article for submission to an appropriate scientific journal.

With kind regards,

Dr John Miller
Head of Division III (Lab)
EDQM

Tel : + 333 88 41 21 89
Fax: + 333 88 41 27 71

1. S Ahmad, Investigation of mesylate salts for the presence of mesylate esters. MSc thesis 2002, University of Strathclyde, Glasgow, UK

Annex 3

Summary of Key Aspects of Viracept Incident (from upcoming book chapter)

In summer of 2007, several patients had reported a bad odor and adverse reactions such as nausea to 250mg nelfinavir mesylate tablets [105]. As a result, the pharmaceutical producer performed a root-cause analysis to determine what was causing the odor and nausea. It was determined that the source of the odor was the presence of EMS, which was measured up to 2300ppm.

The manufacturing process of nelfinavir mesylate involved careful addition of an equimolar amount of methanesulfonic acid (MSA) to nelfinavir free base suspended in ethanol. Spray drying of the ethanolic solution was then performed to isolate nelfinavir mesylate. The key source of the EMS was as a contaminant in MSA stored in a holding tank. The tank had previously been cleaned with an ethanol-containing product, and EMS was slowly formed over several months by the reaction between MSA and residual ethanol in the tank. The MSA employed was of an ultrapure grade and so, in normal circumstances, it was possible to react nelfinavir base with this MSA and then isolate pure nelfinavir mesylate by spray drying (to avoid solvate formation). (Impurity data on numerous previous batches of nelfinavir mesylate confirmed its high purity.) The use of spray drying for isolation purposes precluded the possibility of impurity purging as would have been the case if a conventional process of filtration/washing of precipitated mesylate salt were employed. As a result, holding tanks were removed and disposable containers of MSA were used instead.

Mesylate is a very popular choice of salt in the pharmaceutical industry due to its chemical properties and experience with the salt. Mesylate exists as a salt in many currently marketed compounds. The formation of alkyl-sulfonate esters in pharmaceutical syntheses has been further explored in detail demonstrating that the high exposure to EMS was unique to the nelfinavir mesylate scenario, which was subsequently corrected. Under normal pharmaceutical processing conditions, ester formation from the alkyl-sulfonic acid is unlikely since it is thermodynamically unfavored. When adding an equimolar of the active ingredient (base) with the sulfonic acid, proton transfer to form an acid salt occurs instantaneously precluding any side reactions leading to ester formation. Even though it has been well documented that potential formation of alkyl-sulfonate esters like EMS is highly unlikely during pharmaceutical syntheses, there is still a perception of a safety concern due to their innate hazards not necessarily the risk from exposure

Annex 4

Critical Evaluation of Wollein & Schramek Publication[3]

Drug Products. The Commission of the European Union (EU) and the Council of Europe decided in 1994 to create a network of official medicines control laboratories (OMCLs) with the aim of collaboration on the quality control of marketed medicinal products for human and veterinary use. In 1995, EDQM took on this responsibility and subsequently set up the OMCL network and laboratories in this network have been employed by EDQM to provide analytical back-up on surveys of impurities in drug products containing sulfonic acid salt APIs.[48]

In 2012, Wollein and Schramek[49] reported on a screening assay using a GC-MS technique for MMS, EMS, and IMS in mesilate salt drug products and methyl and ethyl besilate in products containing benzenesulfonic acid APIs. Test samples were sourced from pharmaceutical wholesalers. Powdered drug products (plus internal standard) were extracted with *n*-hexane for 15 min, and after centrifuging the supernatant was injected directly to the GC-MS system. The limit of quantitation (LoQ) for alkyl sulfonates was set at 0.04 ppm based on the API content of the drug product. Alkyl mesilates were all below the LoQ for bromcriptine mesilate capsules and doxazosin mesilate tablets. Similar negative findings were obtained for three neat APIs: bromocriptine mesilate, doxazosin mesilate, and trimipramine mesilate. [Their results contradict introductory remarks invoking the side-reaction hypothesis as a source of alkyl sulfonates.] The authors reflect on their sample-extraction technique as follows: "The unpolar solvent *n*-hexane provides major advantages in inhibiting API extraction and assures longer stability of the analytes". These comments probably relate to a previous technique using the considerably more polar solvent acetonitrile (Wollein and Schramek, 2011[50]). The latter publication reported on the use of a screening assay for the analysis of MMS, EMS, and IMS in 12 drug products containing mesilate salt APIs. The analytical technique employed acetonitrile extraction of powdered drug product, centrifugation, and direct injection of the supernatant into GC/MS equipment. Data for MMS (in ppm based on weight of mesilate salt drug substance) are shown in Table 3 for 10 drug products. For reasons already discussed any alkyl mesilates detected in a drug product are expected to originate from the drug substance. Data on two additional drug products are not listed; levels of alkyl mesilates in dihydroergotoxin were below the LoD, and values for desferoxamine were difficult to interpret owing to uncertainty over the MDD and pack size of the drug product. Mean values have been calculated when more than one data point is reported for the same drug/strength. By applying the Cimarosti MMS purge factor of 4100 the implied concentration of MMS in MSA has also been determined resulting in a range of 0.06–231% (based on the reasonable assumption that any MMS

Table 3. Published Data on MMS in 10 Drug Products Containing Mesilate Salt APIs[a]

drug (no. of samples)	dose strength (mg)	dose as mesilate salt (mg)	reported MMS content (μg)	MMS in drug substance (ppm)	implied MMS concentration in MSA (%)[c]
Doxazosin (4)	1.0	1.21	0.145	119.8	49.1
Doxazosin (5)	2.0	2.42	0.168	69.4	28.5
Doxazosin (4)	4.0	4.84	0.173	35.7	15.4
Doxazosin (2)	8.0	9.68	0.228	23.6	9.7
Bromocriptine (2)	2.5	2.87	0.122	42.5	17.4
Bromocriptine (2)	5.0	5.74	0.143	24.9	10.2
Bromocriptine (1)	10.0	11.47	0.361	31.5	12.9
Pergolide (1)	0.05	0.065	0.037	569	230.8
Pergolide (1)	0.25	0.33	0.033	100	41.0
Pergolide (1)	1.0	1.3	0.086	66.2	27.1
Dihydroergotamine (1)	1.0	1.16	0.287	247.4	101.4
Dihydroergotamine (1)[b]	1.0	1.16	0.468	403.4	165.4
Rasagiline (1)	1.0	1.56	0.024	15.4	6.3
Reboxetine (1)	1.0	1.29	0.202	39.1	16.0
Eprosartan (2)	600	735.6	0.682	0.93	0.38
Trimipramine	50	66.3	5.208	79.6	32.6
Maprotiline	50	67.3	0.724	10.8	4.4
Saquinavir (2)	500	571.6	0.085	0.15	0.06

[a]Data from Wollein and Schramek, 2011.[50] [b]Third sample below LoD. [c]Multiply previous column by 4100 (purge factor calculated from data in Cimarosti et al., 2010[26]).

present in the drug substance would originate from the MSA reagent).

For EMS and IMS, the majority of values were at or close to the LoD. In general, there was reasonable concordance between drug products showing high values of MMS and those reported to contain EMS or IMS. Using 10 ppm alkyl sulfonate in the drug substance as a level of concern, only five drug products exceeded this value for EMS and only one for IMS. By contrast, MMS was >10 ppm for 29 samples (out of a total of 32 analyzed). For EMS the highest concentration was 242 ppm (in dihydroergotamine) with an implied content of 116% EMS in MSA. For IMS dihydroergotamine again contained the highest concentration of 278 ppm, representing an implied concentration of 114% in MSA.

An additional check can be made by evaluating the relationship between MMS content and tablet strength, which has been performed for doxazosin mesilate tablets (Table 4). Assuming

Table 4. Doxazosin Mesilate: MMS Content vs Tablet Strength Based on Published Data[a]

	tablet strength (mg)			
	1.0	2.0	4.0	8.0
MMS content (μg)	0.143, 0.134, 0.121, 0.180	0.154, 0.138, 0.178, 0.162, 0.210	0.121, 0.140, 0.203, 0.227	0.227, 0.228
mean content (μg)	0.145	0.168	0.173	0.228
ratios for MMS content	1.0	1.2	1.2	1.6

[a]Data from Wollein and Schramek, 2011.[50]

that MMS is present in doxazosin drug substance at a reasonably stable concentration it would be expected that the absolute amount present in drug products would be proportional to tablet strength, which is shown *not* to be the case. If the authors were minded to posit the side-reaction hypothesis to explain the detection of MMS in almost all samples, this could be countered by (a) methanol, being considerably more polar and more expensive than ethanol, is not a particularly suitable solvent for sulfonic acid salt synthesis and (b) no analysis of solvent residues was undertaken in order to validate such an explanation.

Overall, the 2011 data from Wollein and Schramek are considered to have many hallmarks of artifacts given that MMS was claimed to be present at >10 ppm in 29/32 (90.6%) of products evaluated whereas no other researchers have reported finding MMS at >LoD or LoQ for any mesilate salt APIs; the Wollein and Schramek data are truly unique in this respect, and this fact alone should have triggered a follow-up evaluation of provisional data generated using a screening assay. It is inconceivable that MMS concentrations up to 570 ppm (in pergolide API) would be acceptable to manufacturers and/or regulatory agencies; no attempt was made to verify the results by contacting manufacturers or to cross-validate the assay methods using acetonitrile or *n*-hexane as extractants; purge factor considerations indicate that the MSA reagent would have needed to be heavily contaminated with MMS (in some cases to >100%) to have produced such high concentrations in the APIs; the results for doxazosin mesilate (24−120 ppm MMS) are discordant with those determined using *n*-hexane extraction (<0.04 ppm). Use of acetonitrile (discontinued by Wollein and Schramek) has the potential to cause two problems: first, the solvent is sufficiently polar to extract mesilate salt drug substance (as well as some excipients), and second, at the temperatures employed for GC analysis (250−280 °C), decomposition of the mesilate anion and/or acetonitrile is likely to occur. [Dihydroergotamine mesilate decomposes at its melting point of 219 °C,[51] and acetonitrile decomposition is reported to begin at 263 °C.[52]] Acetonitrile pyrolysis products (based on literature reports using temperatures >500 °C) are hydrogen cyanide and methane,[53] indicating that thermal decomposition at temperatures >200 °C can produce methylating species (such as the methyl cation or radical) which could react with mesilate anion to produce MMS. Detection of EMS and IMS might be explained by transesterification of MMS in the GC equipment by residual ethanol and isopropanol, respectively, in the drug products. Following receipt of the evaluation shown in Table 3, Wollein failed to respond to a number of communications inviting him to defend the published results. There is a precedent for artifact formation of alkyl sulfonates during GC analysis. As part of the description of official Ph.Eur method of analysis for alkyl besilates in besilate salts (Pharmeuropa 2014[54]) it is noted that "This method (head-space GC/MS) is not suitable for clopidogrel besilate since it was observed that methylbenzenesulfonate was obtained during the gas chromatography analysis as an artefact originating from degradation." It should be noted that the Ph.Eur method employed a derivatization technique, and so the mechanism of artifact formation is likely be different from that proposed for the Wollein and Schramek findings.

Annex 5

Letter from Dr Suzanne Keitel

European Pharmacopoeia Commission Secretariat

Mr SNODIN David
Parexel International Limited
The Quays 101 105 Oxford Road
GB - UB8 IDL UXBRIDGE
Royaume-Uni

RZ/PH/2019-03319L
AG/bbun

Strasbourg, 11/07/2019.

Reference: HelpDesk questions (Q105237, Q113498 and Q121065) and draft article entitled "Elusive Impurities-Evidence versus Hypothesis. Technical and Regulatory Update on Alkyl Sulfonates in Sulfonic Acid Salts"

Dear Dr Snodin,

It was with great interest that we read your draft article (cited in reference). However, we feel that both your article and the HelpDesk questions received from you (also cited in reference) reproduce certain misunderstandings concerning our texts, their legal status and application. These concerns are dealt with in the General Notices to the European Pharmacopoeia, which is an indispensable *vade mecum* for the correct interpretation and use of our texts.

While it is not within the scope of this letter to provide a detailed response to the issues you raise, we would nonetheless like to draw your attention to some particularly salient points.

The use of the term "monographs" to describe the general chapters for the control of potentially genotoxic alkyl sulfonates in APIs is erroneous and misleading, as it implies that those texts are mandatory, which is not the case.
The non-mandatory status and the applicability of general chapters and of the Production section are explained in the General Notices:

- *"Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements. General chapters become mandatory when referred to in a monograph, unless such reference is made in a way that indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information."*
- *"PRODUCTION: Statements under the heading Production draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute mandatory requirements for manufacturers, unless otherwise stated. They may relate, for example, to source materials; to the manufacturing process itself and its validation and control; to in-process testing; or to testing that is to be carried out by the manufacturer on the final article, either on selected batches or on each batch prior to release. These statements cannot necessarily be verified on a sample of the final article by an independent analyst. The competent authority may establish that the instructions have been followed, for example, by examination of data received from the manufacturer, by inspection of manufacture or by testing appropriate samples. The absence of a Production section does not imply that attention to features such as those referred to above is not required."*

Address: 7 Allée Kastner, CS 30026, F – 67081 Strasbourg (France)
Tél : +33 (0) 3 88 41 30 30 - Fax: + 33 (0) 3 88 41 27 71 – e-mail: Please use the HELPDESK at the following Internet address: http://www.edqm.eu

The Production section of the monographs on APIs potentially concerned has been drafted in such a way that the non-binding nature of the referenced chapters is unambiguous:

*"PRODUCTION: It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in **API**. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods (...) are available to assist manufacturers."*

If we are not mistaken, this clarification has already been provided to you in the past (see also the press-release entitled "*Potential presence of mutagenic alkyl sulfonates in active substances*", published on 25 February 2016, available here).

We would also like to point out that no comments (either on the 5 draft chapters [Pharmeuropa 21.3, 22.2, 22.3, 25.1 & 26.2] or on the review of the Production statement in monographs for mesilate salts [Pharmeuropa 23.4] and the introduction to the Production statement in the monographs for besilate and tosilate salts [Pharmeuropa 26.3]) were received during the Pharmeuropa public enquiry phase and, to date, the EDQM has not received any complaints directly from manufacturers on the Ph. Eur. control strategy for potentially genotoxic alkyl sulfonates in APIs.

This control strategy was re-evaluated by the Ph. Eur. Commission some years ago, at which time the opinion of the EMA Joint CHMP/CVMP Quality Working Party was sought. The response received prompted the Commission to confirm its approach in March 2016.

Since no new relevant and appropriate data have emerged, the Ph. Eur. Commission once again rejected the request to revise its control strategy in June 2019 and continues to uphold its original approach.

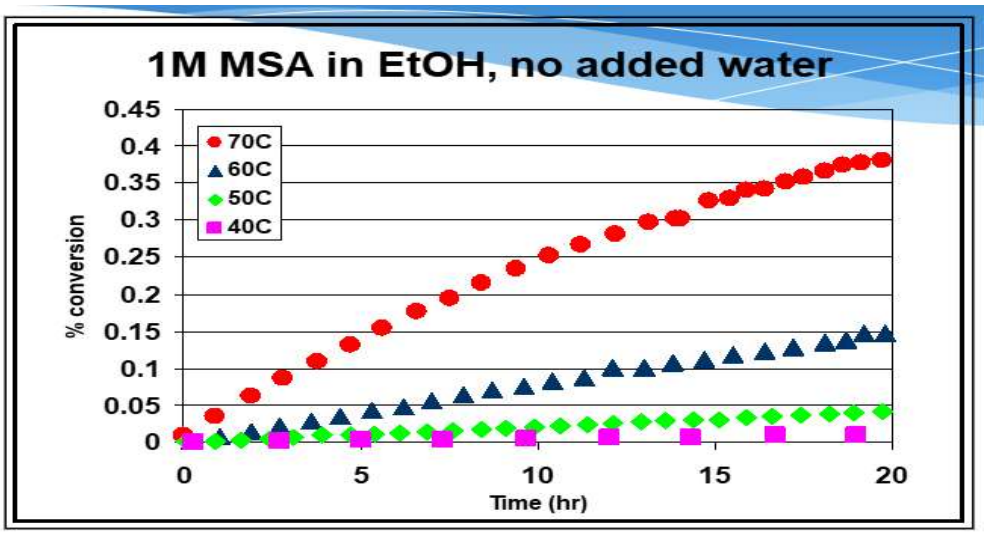
We hope that this provides you with a satisfactory response to the queries you raise, both in your HelpDesk questions and your forthcoming article.

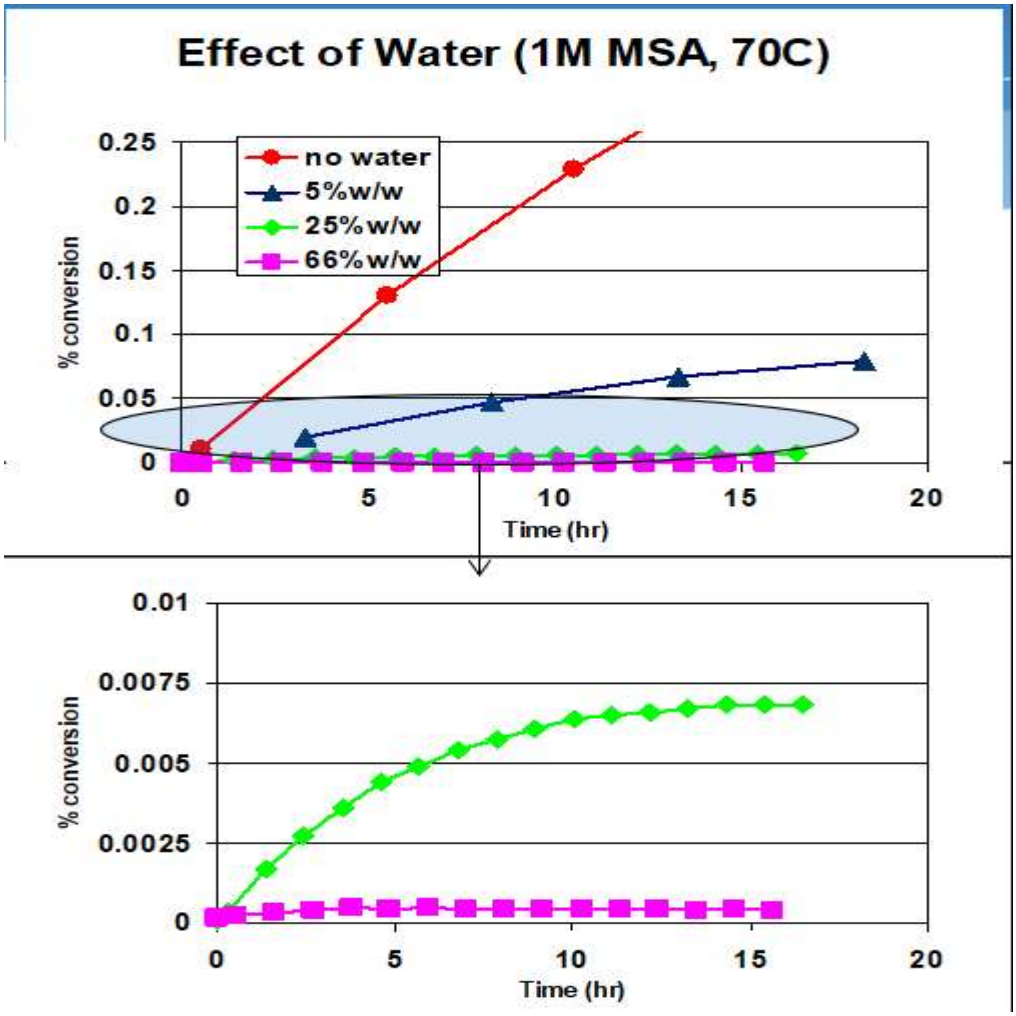
Best regards,

Dr. Susanne Keitel
Director

Annex 6

EMS Formation: Effect of Temperature and Water (data from Teasdale et al, 2010[6])





Annex 7

July 2020 Article in Chemistry World

Policies based on false hypotheses can persist in spite of overwhelming contradictory data

Creating policies on scientific and medical issues is not an easy task. Often, decisions must be made when scientific knowledge is uncertain, and so a policy may be based on false hypotheses. Ideally, any dubious hypothesis is disproved by emerging evidence, but situations can occur where institutional inertia and dogma allow the policy to remain in place. An example of this can be seen in the suggestion that sulfonic acid salt drugs may be unsafe.

Over half of the top prescription drugs are presented as salts in order to optimise their pharmaceutical properties. Sulfonic acid salts such as mesylate (methanesulfonate) often provide the best technical solution, although hypothetical safety concerns were raised nearly 20 years ago.

In late 2000, the European Department for the Quality of Medicines (EDQM), secretariat to the European Pharmacopoeia, suggested that an ester-forming side-reaction could occur during the synthesis of a mesylate salt by addition of methanesulfonic acid to a pharmaceutical base dissolved in an alcoholic solvent such as ethanol. Thus, a toxic alkyl mesylate (ethyl methanesulfonate; EMS) might be present as an impurity in the mesylate-salt drug substance.

In 2004, the European Pharmacopoeia (EP), introduced a new requirement for any EP-compliant mesylate salt drug substance: the potential for alkyl mesylate formation should be determined, and is ‘particularly likely to occur if the reaction medium contains lower alcohol’. Although supportive evidence was not provided, at the time no objections were raised by industry scientists given the perceived expertise of the EP. Introduction of the policy would have been considerably more problematic if EDQM had released analytical data, obtained as part of a 2002 MSc project, demonstrating the absence of alkyl mesylates in a range of mesylate salt drug substances. Nevertheless, the concept was rapidly taken up by other regulatory bodies including the European Medicines Agency (EMA).

The EP’s policy appeared to be justified three years later, when patients using certain batches of Viracept (a protease inhibitor whose active ingredient is nelfinavir mesylate) complained of a strange taste attributed to the presence of around 0.1% EMS. However, the contamination was caused by a gross failure of good manufacturing practice (GMP): methanesulfonic acid reagent was stored in a tank containing residues of ethanol, leading to production of EMS. In addition, the isolation procedure for the drug substance involved spray drying, which prevented the possibility of impurity purging.

Despite the exceptional circumstances behind the Viracept incident, in early 2008 the EMA launched a survey of all sulfonic acid salt drug substances approved in EU countries along with a range of assumptions that alkyl sulfonate impurities would be found. A report on the outcome of this survey has never been published, but several years later a Freedom of Information request revealed that such impurities were consistently absent. Thus, it is inappropriate and misleading to read across from the unique event of Viracept contamination to the routine GMP synthesis of sulfonic acid salts.

Many process chemists and others in the pharmaceutical industry were concerned that policy (later extended to tosylate (toluenesulfonate) and besylate (benzenesulfonate) salts) was being driven solely by speculation, and so a consortium was formed to investigate the mechanisms and kinetics of

sulfonate ester formation. These studies, undertaken at the independent Product Quality Research Institute (PQRI), quickly established that ester formation is extremely slow, even under forcing conditions, and no ester is detected when an equimolar amount of base is present.

In response to the consortium's findings and several critical publications, the EDQM requested an assessment by an EMA expert group. This review was chaired by a European scientist who was also chair of the European Pharmacopoeia Commission (the decision-making body of the EP) which, on several occasions, has voted unanimously in favour of retaining controls on alkyl sulfonates. The review's conclusion that 'the presence and formation of these alkyl sulfonates cannot be totally excluded' is in stark contrast to the outcome of the PQRI investigations.

Today, manufacturers are required to either analyse drug substances for levels of alkyl sulfonates or to argue on the basis of scientific evidence that they will not be formed. But there is a catch with the latter approach in that both EDQM and EMA have not responded to requests to clarify the parameters supporting such an evidence-based explanation, thus maintaining false perceptions that these impurities might be present. Overall, regulatory policy has perpetuated unjustified concerns about the safety of sulfonic acid salts, possibly leading some drug developers to use suboptimal counterions.

While this is a problem in itself, the history of sulfonic acid salt policy illustrates a wider issue: that it can be incredibly difficult to change direction once a policy has been accepted as the status quo. In an ideal world, chemists should be able to bring pressure to bear on policymakers to 'follow the evidence'. However, this will not occur until there are significant changes in administrative procedures that increase the openness and transparency of the policy development process. Such changes are unlikely to occur quickly (if at all) in this particular case. In the meantime, individual chemists must continue to alert the broader professional community to policies that are not supported by evidence.

Annex 7

Young, Stephen

From: snodind@xiphora.com
Sent: 02 September 2021 11:11
To: Young, Stephen
Cc: Whaley, Michael
Subject: RE: Production Statement on Alkyl Mesilates in Mesilate-Salt Drug Substances

Dear Stephen and Michael

Further to my previous email, I found something that neatly sums up my basic arguments on the impossibility of forming alkyl mesilates during the GMP synthesis of a mesilate salt.

After adding a molar equivalent of MSA to the base form of the API dissolved in ethanol, the pH of the mixture (precipitated salt in ethanol) will be neutral. Thus to produce any alkyl mesilate it's necessary to argue that the non-nucleophilic mesilate anion will displace the hydroxyl group from ethanol. Even the highly nucleophilic bromide ion fails to displace the hydroxyl moiety from a short-chain alcohol.

Kind regards

David

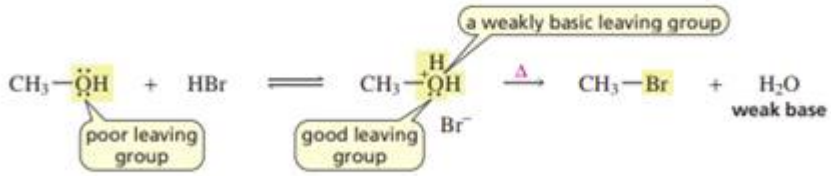
10.1 NUCLEOPHILIC SUBSTITUTION REACTIONS OF ALCOHOLS: FORMING ALKYL HALIDES

An **alcohol** has a strongly basic leaving group (HO^-) that cannot be displaced by a nucleophile. Therefore, an alcohol cannot undergo a nucleophilic substitution reaction.

However, if the alcohol's OH group is converted into a group that is a weaker base (and, therefore, a better leaving group), a nucleophilic substitution reaction can occur.

Converting an OH Group into a Better Leaving Group

One way to convert an OH group into a weaker base is to protonate it by adding acid to the reaction mixture. Protonation changes the leaving group from HO^- to H_2O, which is a weak enough base to be displaced by a nucleophile. The substitution reaction is slow and requires heat (except in the case of tertiary alcohols) if it is to take place at a reasonable rate.



Because the OH group of the alcohol must be protonated before it can be displaced by a nucleophile, only weakly basic nucleophiles (I^-, Br^-, Cl^-) can be used in the substitution reaction. Moderately and strongly basic nucleophiles (NH_3, RNH_2, and CH_3O^-) cannot be used because they too would be protonated in the acidic solution and, once protonated, would no longer be nucleophiles ($^+NH_4$, $R\overset{+}{N}H_3$) or would be poor nucleophiles (CH_3OH).

https://www.pearsonhighered.com/content/dam/region-na/us/higher-ed/en/products-services/course-products/bruice-chemistry-8e-info/pdf/bruice-chap10.pdf

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 31 August 2021 21:32
To: 'Young, Stephen' <Stephen.Young@mhra.gov.uk>
Cc: 'Whaley, Michael' <Michael.Whaley@mhra.gov.uk>
Subject: RE: Production Statement on Alkyl Mesilates in Mesilate-Salt Drug Substances

Dear Stephen

Please find my comments on the 8 documents provided under FoI relating to BPC and EAG minutes from 2016-2018.

Hopefully, the comments are self-explanatory if you have the various documents to hand. I felt it would overload the Word document if I were to embed 8 PDFs. However, I can send these PDFs in a separate email if necessary.

In addition, I can provide full-text copies of the cited articles.

Finally, I'm also attaching a copy of a presentation made a few years ago in Berlin which shows, *inter alia*, information on the consequences of using technical-grade MSA (containing 500 ppm MMS) to synthesise a mesilate salt – basically, none. This is because the purge factors are so enormous when standard isolation procedures are used (such as solvent-washing of precipitated mesilate salt). And recrystallisation is also a highly efficient technique for removing any MMS. [I'm not advocating the use of low-purity MSA or the need for recrystallisation; the salt-forming reaction is very straightforward and robust.]

Please get back to me if you have any queries. By the way, I should be most happy to attend a face-to-face or remote Q&A session with you and/or BPC/EAG members.

Kind regards

David

From: Young, Stephen <Stephen.Young@mhra.gov.uk>
Sent: 31 August 2021 15:15
To: snodind@xiphora.com
Cc: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Subject: RE: Production Statement on Alkyl Mesilates in Mesilate-Salt Drug Substances

Dear Dr Snodin,

Thank you for your email.

We are currently dealing with your two subsequent FoI requests as below

- Benzatropine Mesilate, Loprazolam Mesilate and Prochlorperazine Mesilate
- Betahistine Mesilate, Dihydroergocristine Mesilate, Saquinavir Mesilate and Ziprasidone Mesilate

Please send your thoughts on the minutes so myself and Michael and we will discuss with the relevant Chairs.

With kid regards

Stephen

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 24 August 2021 16:32
To: Young, Stephen <Stephen.Young@mhra.gov.uk>
Cc: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Subject: Production Statement on Alkyl Mesilates in Mesilate-Salt Drug Substances

Dear Stephen and Michael

I've recently acquired via FoI copies minutes from meetings of the BPC and relevant EAGs relating to discussions on introducing a Production Statement on potential alkyl-mesilate impurities into BP monographs for mesilate-salt drug substances.

I believe there are significant errors and omissions in the way that this issue has been approached by the BP, and so I have created a detailed commentary on various statements recorded in the minutes of meetings that took place between 2016 and 2018.

Can you advise me on whether it would be appropriate for me to send my document to you and/or to you and the chairs of the relevant EAGs?

Kind regards

David Snodin

Annex 8

Young, Stephen

From: IE&SFOI
Sent: 16 September 2021 11:17
To: snodind@xiphora.com
Cc: FOI_Policy
Subject: FOI 21/967
Attachments: FOI21-967_reply.zip

16th September 2021

Dear Dr Snodin,

REF: FOI 21/967

1. Introduction

I am writing to you in response to your freedom of information requests received on 20th August 2021. We have treated these two requests together for the purposes of the FOI Act [our **ref: 21/967**]

2. Your request

Your original FOI requests were received on 20th August 2021. Under the FOI Act, the Agency has 20 working days to provide a response, which is 20th September 2021 (please note that this date range includes the public holiday on 30th August).

In your first request you asked:

I wish to make a FoI Request on three BP Monographs: Benzatropine Mesilate, Loprazolam Mesilate and Prochlorperazine Mesilate.

Access is requested to any documents relating to the Production Statement for the three drug substances noted above. In particular:

1. *Documents, based on public-domain or other evidence, justifying the notion that alkyl mesilates could be formed as potential impurities during the GMP synthesis of a mesilate-salt drug substance;*
2. *Documents setting out the key elements of an acceptable risk assessment demonstrating that alkyl-mesilate impurities will not be formed and that no confirmatory analysis is required;*
3. *Documents justifying the potentially misleading description "genotoxic" in relation to alkyl mesylates contrary to the more precise term "mutagenic" employed in ICH M7 (R1);*
4. *Documents justifying a limit for any alkyl-mesilate impurity equivalent to the Threshold of Toxicological Concern (TTC) rather than:*
    a. *A published compound-specific limit;*
    b. *A limit based on the Less-than-Lifetime (LTL) concept, as appropriate.*

In your second request you asked:

FoI Request on Four BP Monographs: Betahistine Mesilate, Dihydroergocristine Mesilate, Saquinavir Mesilate and Ziprasidone Mesilate.

Access is requested to any documents relating to the Production Statement for the three drug substances noted above. In particular:

1. *Documents, based on public-domain or other evidence, justifying the notion that alkyl mesilates could be formed as potential impurities during the GMP synthesis of a mesilate-salt drug substance;*
2. *Documents setting out the key elements of an acceptable risk assessment (based on "the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation") demonstrating that alkyl-mesilate impurities will not be formed and that no confirmatory analysis is required;*
3. *Documents justifying the potentially misleading description "genotoxic" in relation to alkyl mesylates contrary to the more precise term "mutagenic" employed in ICH M7 (R1);*
4. *Documents justifying the different wording of the Production Statement in the BP monographs for benzatropine mesilate, loprazolam mesilate and prochlorperazine mesilate.*

3. Our response

Since the BP Commission has considered this matter from a policy perspective rather than on an individual basis, we do not hold substance-specific documents relevant to your requests. For convenience we have separated the various requests and grouped them together to provide as full a response as possible.

Any documents relating to the Production Statement for the drug substances noted above.

We have included relevant documents (emails, meeting papers and minutes) discussing the development of the production statements as annex 1. Please note that all redactions in these documents are personal information which is exempt under section 40(2) of the Act.

Documents, based on public-domain or other evidence, justifying the notion that alkyl mesilates could be formed as potential impurities during the GMP synthesis of a mesilate-salt drug substance

We have included a report of analysis carried out by the MHRA Laboratory as part of a joint survey carried out with other laboratories as annex 2. These data showed that, whilst most samples tested did not contain alkyl sulfonate impurities, several samples did contain these impurities at low levels.

Documents setting out the key elements of an acceptable risk assessment demonstrating that alkyl-mesilate impurities will not be formed and that no confirmatory analysis is required;

I can confirm we do not hold the information that you requested. The EMA set out guidance on this point in their letter to manufacturers in January 2008 (EMA document ref: EMEA/44714/2008). The BP Commission has not set out any different expectations for risk assessments.

Documents justifying the potentially misleading description "genotoxic" in relation to alkyl mesylates contrary to the more precise term "mutagenic" employed in ICH M7 (R1);

I can confirm we do not hold the information that you requested. We note your comments regarding these two terms and will review the terminology we use to ensure that it is correct.

Documents justifying a limit for any alkyl-mesilate impurity equivalent to the Threshold of Toxicological Concern (TTC) rather than:

a. A published compound-specific limit;

b. A limit based on the Less-than-Lifetime (LTL) concept, as appropriate.

I can confirm we do not hold the information that you requested.

Documents justifying the different wording of the Production Statement in the BP monographs for benzatropine mesilate, loprazolam mesilate and prochlorperazine mesilate.

I can confirm we do not hold the information that you requested. The reason for this difference is that the Betahistine Mesilate, Dihydroergocristine Mesilate, Saquinavir Mesilate and Ziprasidone Mesilate monographs are reproduced from the European Pharmacopoeia and so these use the EDQM wording. On the other hand, the Benzatropine Mesilate, Loprazolam Mesilate and Prochlorperazine Mesilate monographs are National monographs, so use wording as agreed by the British Pharmacopoeia Commission. The relevant minutes and emails you have been provided with include background on how these statements were arrived at.

If you are unhappy with our decision, you may ask for it to be reviewed. That review will be undertaken by a senior member of the Agency who has not previously been involved in your request. If you wish to pursue that option please email: info@mhra.gov.uk

Due to the ongoing Covid-19 situation, we are not able to accept delivery of any documents or correspondence by post or courier to any of our offices.

After that, if you remain dissatisfied, you may write to the Information Commissioner at;
The Information Commissioner's Office
Wycliffe House
Water Lane
Wilmslow
Cheshire
SK9 5AF
They will make a decision on whether or not we have interpreted the FOIA correctly in handling your request.

Yours sincerely

IE&S FOI Team
MHRA
Inspection, Enforcement and Standards
cc FOI_Policy

Annex 9

Young, Stephen

From: Whaley, Michael
Sent: 20 September 2021 13:28
To: snodind@xiphora.com
Cc: Young, Stephen
Subject: RE: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Dear David,

Many thanks for the additional comments relating to Dabigatran Etexilate Mesilate.

I'll pass these on to my colleagues who are compiling the response to the Pharmeuropa documents.

Michael

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 20 September 2021 12:43
To: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Cc: Young, Stephen <Stephen.Young@mhra.gov.uk>
Subject: RE: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Dear Michael and Stephen

Having done more research on DEM, I would like to add two more points to my previous comments:

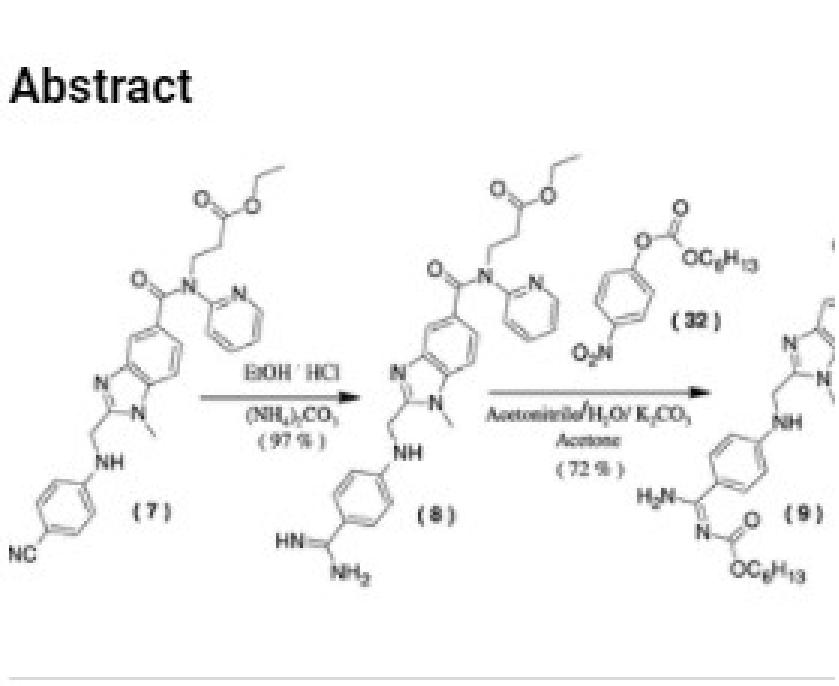
- All references to the synthesis of DEM refer to the use of acetone as solvent in the mesilate-salt-formation step, thus casting doubt on the (incorrect) concept of a side-reaction with an alcoholic solvent;
- DEM is obtained in almost quantitative yield with absolutely no evidence for hydrolysis of the carboxylic-acid ester or carbamate moieties (which is obviously predictable when one considers the pKa of the most basic nitrogen atom combined with the fact that all added methanesulfonic acid will be neutralised).

Kind regards

David Snodin

Synthesis of Dabigatran Etexilate Mesylate (1)

Acetone (7.0 L) and dabigatran etexilate (**9**, 1.0 kg, 1.59 mol) were charged to the reactor, and the suspension was heated to 40–45 °C until dissolution; the clear solution was filtered over a celite bed and the bed was washed with acetone (1.0 L). The combined filtrate was cooled to 25–30 °C; to the resulting suspension, a solution of methane sulfonic acid (prepared by using methane sulfonic acid 0.15 kg, 1.56 mol diluted with 4.5 L acetone) was added. The precipitated salt was stirred at 25–30 °C for 1.0 h and then cooled to 17–23 °C and stirred for 1.0 h. The precipitated salt was filtered and washed with acetone (1.0 L). The resulting wet material was dried for 5 h at 40–45 °C to furnish 1.090 kg (95% yield) of **1**. HPLC purity: 99.92%; content of **8**: not detected; content of **28**: not detected; content of **29**: not detected; content of **32**: not detected; content of **33**: 0.02%; content of **34**: 0.01%; content of **35**: not detected; content of **36**: 0.01; content of **37**: not detected; content of **38**: not detected; content of single largest unknown impurity: 0.01%; total impurity:



https://pubs.acs.org/doi/10.1021/acsomega.8b00846

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 03 August 2021 21:34
To: 'Whaley, Michael' <Michael.Whaley@mhra.gov.uk>
Cc: 'Young, Stephen' <Stephen.Young@mhra.gov.uk>
Subject: RE: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Dear Michael

As promised, here is an updated version of my comments on the proposed Ph.Eur Monograph for Dabigatran Etexilate Mesilate.

By all means get back to me if anything is unclear.

Kind regards

David Snodin

From: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Sent: 03 August 2021 14:18
To: snodind@xiphora.com; Young, Stephen <Stephen.Young@mhra.gov.uk>
Subject: RE: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Dear David,

Many thanks for your comments on the Dabigatran Etexilate Mesilate monograph published in Pharmeuropa.

Unfortunately I'm unable to open the word document you attached. I'm not entirely sure why. Would you be able to reattach and send again?

Many thanks,

Michael

From: snodind@xiphora.com <snodind@xiphora.com>
Sent: 30 July 2021 07:19
To: Young, Stephen <Stephen.Young@mhra.gov.uk>
Cc: Whaley, Michael <Michael.Whaley@mhra.gov.uk>
Subject: Updated Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Dear Stephen and Michael

Please use this updated version of my comments on Dabigatran Etexilate Mesilate rather than the one sent yesterday.

Kind regards

David

From: Young, Stephen <Stephen.Young@mhra.gov.uk>
Sent: 29 July 2021 18:10
To: snodind@xiphora.com
Subject: Automatic reply: Comments on Pharmeuropa Proposal for a Ph.Eur Monograph on Dabigatran Etexilate Mesilate

Thank you for your email

I am out of office on leave until Monday 9th August.

Michael Whaley (michael.whaley@mhra.gov.uk) is deputising

Mobile numbers for myself and team are below
Steve – 07584362157
Michael – 07766602258
Graziella – 07471359107

Many thanks
Steve

DHTermsAndConditions

Annex 10

Alkyl Sulfonates in Sulfonic-Acid Salts: Fact or Fiction?

Genotoxic Impurities
Berlin, September 2016

David Snodin
Principal
Xiphora Biopharma Consulting
snodind@xiphora.com

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1

Beginnings (2000)

Pharmeuropa 2000 Enquiry (12.01)

Enquiry

ALKYL MESILATE (METHANESULPHONATE) IMPURITIES IN MESILATE SALTS

The need for limits on methyl, ethyl and isopropyl mesilate esters in active substances presented as mesilates has recently been discussed by the European Pharmacopoeia Commission. These esters are highly toxic and assurance is needed that they are not present in unacceptable quantities in medicinal products. However, they are also very reactive and it is therefore possible that in practice the level of contamination is negligible. Readers of Pharmeuropa are asked to inform EDQM of their opinion on the need for a test and limit in the light of their experience with mesilate salts. Information on analytical methods and the level of such impurities found in practice would be extremely valuable. Seven monographs on mesilates are at present included in the European Pharmacopoeia and would be concerned if a test and limit were to be added:

Betahistine mesilate
Bromocriptine mesilate
Deferoxamine mesilate
Dihydroergocristine mesilate
Dihydroergotamine mesilate
Pefloxacin mesilate dihydrate
Phentolamine mesilate

Please send your replies to:
Council of Europe
European Directorate for the Quality of Medicines
B.P. 907
67029 Strasbourg Cedex 1
France
Fax: + 33 (0)3 88 41 27 71.
E-mail: info@pheur.org.

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Beginnings (2004)

2004 Production Statement

MONOGRAPHS

Alkyl mesilates

An enquiry concerning alkyl mesilate impurities in mesilate salts was made via a note in Pharmeuropa 12.1. In the light of information and comments received, the European Pharmacopoeia Commission has decided that the following approach will be used in the monographs concerned.

The following production section will be included in all monographs on mesilate salts.

The production method must be evaluated to determine the potential for formation of alkyl mesilates, which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.

Tests for alkyl mesilates will not be included in monographs. The methods required to demonstrate

absence of alkyl mesilates at a suitable limit of detection are not suited for routine use and validation of the process is a better approach.

The monographs concerned, published in Supplement 4.7 are:

- Betahistine mesilate
- Bromocriptine mesilate
- Deferoxamine mesilate
- Dihydroergocristine mesilate
- Dihydroergotamine mesilate
- Pergolide mesilate
- Phentolamine mesilate

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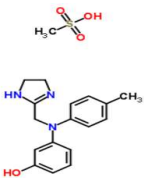
Basic Hypothesis

Example:

Phentolamine mesilate



Normally synthesised from the base form using an alcohol solvent (MeOH, EtOH or iPrOH) + a molar equivalent of methanesulfonic acid (MSA)

Hypothesised that one or more of MMS, EMS or IMS could be formed as by-product.

Concept eventually adopted by regulatory agencies worldwide (but without any supportive evidence)

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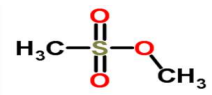
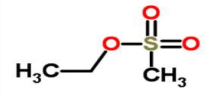
Alkyl Mesilates (= alkyl esters of MSA)

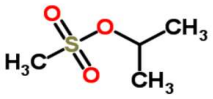
MMS



EMS



IMS



[Similarly for alkyl tosilates and besilates]

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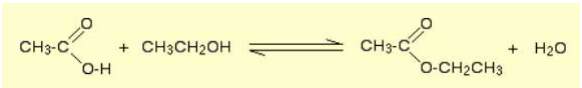
Ester Formation - General

Acid + Alcohol produces Ester + Water

Applies to oxy-acids (carboxylic, sulfonic, phosphoric, ..



To produce ethyl acetate a trace of strong acid is needed as catalyst

Equilibrium (65% conversion) is reached after a week at room temperature or overnight under reflux

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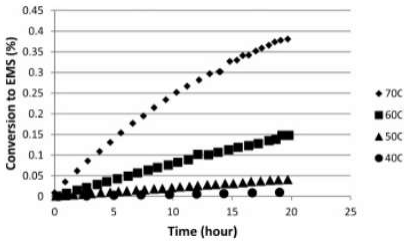
Ester Formation - Sulfonates

EMS formation from 1M MSA + excess anhydrous EtOH at different temperatures



Ester formation rate at 70 °C approximately 10^{-7} sec^{-1} for EMS, MMS and IMS. Pseudo first-order reaction. Temperature coefficient is x4 per 10 °C.

At 30 °C ester formation rate with 1 M MSA estimated as **3 ppm per hour**

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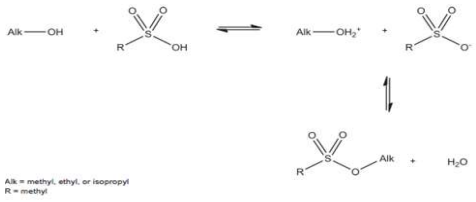
Mechanism of Sulfonate-Ester Formation

- Step 1: alcohol protonation
- Step 2 (rate-determining, slow): nucleophilic displacement of hydroxonium ion



Comment: Sulfonate anion is an extremely feeble nucleophile with negative charge dissociated across 3 oxygen atoms. Competes poorly with water.

By contrast, chloride ion is a much stronger nucleophile (with implications for chloroalkane formation in synthesis of HCl salts)

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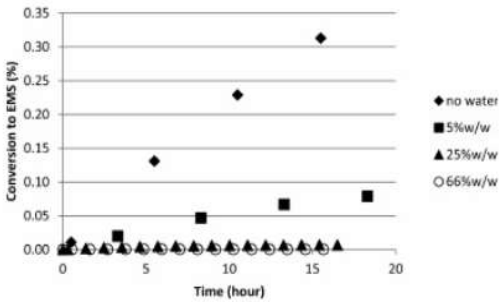
Effect of Water on EMS Formation at 70 °C



- Note: 5% water = 50 g/L = 2.8M, which outcompetes mesilate anion in terms of nucleophilicity.
- EMS formation would be effectively eliminated at 20 or 30 °C

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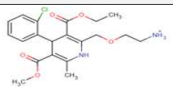
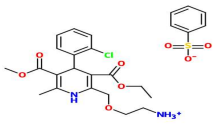
Salt Formation: Addition of Sulfonic Acid to Organic Base in Ethanol Solution

- Example: Amlodipine besilate

pKa Values for Conjugate Acids of Amlodipine and Ethanol

	Protonated Amlodipine	Protonated Ethanol
Structure		
pKa	9	-2



- Protonation of amlodipine will be favoured 10^{11}-fold vs ethanol protonation
- Protonation is essentially instantaneous (diffusion-controlled); no protonation of solvent will occur if equimolar amounts of base and BSA are employed
- "Side-reaction" hypothesis of alkyl sulfonate formation is negated

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Hypothetical/Potential Sources of Alkyl Sulfonate Impurities

Source	Comment
1. Side reaction	Negated by complete and rapid base protonation
2. Reaction between sulfonic-acid salt and solvent	Completely non-viable at neutral pH; even with protonated ethanol reaction with sulfonate anion is extremely slow. [Salts commonly recrystallized from ethanol.]
3. Excess (5%?) of sulfonic acid	Will generate ≈ 0.2 ppm alkyl sulfonate/h at 30 °C
4. Alkyl tosilates/besilates formed by pre-dissolution of TSA/BSA in ethanol	Negligible amounts formed; ≈ 3 ppm/h at 30 °C if 1M solutions used
5. Reagent impurities: TSA/BSA	No alkyl-sulfonate-precursor impurities; commercially produced as hydrates
6. Reagent impurities: MSA	MMS potential impurity (up to 500 ppm) in technical-grade MSA; formed from MSA anhydride if distillation poorly controlled

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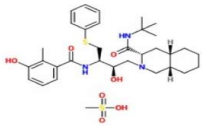
Impurity Sources 1 and 2: Experimental Evidence



- Viracept (nelfinavir mesilate; EMS (≥ 0.1%) contamination incident in 2007
- Salt synthesised by addition of high-purity MSA (< 1 ppm MMS + EMS) to equimolar amount of nelfinavir base dissolved in EtOH
- Mesilate salt isolated by spray drying of reaction mixture (avoiding presence of ethanol solvate)
- Batches manufactured between 2001 and 2007 showed MMS + EMS < 0.5 ppm
- Shows
  - No evidence for side-reaction
  - No EMS produced by interaction of EtOH with nelfinavir mesilate

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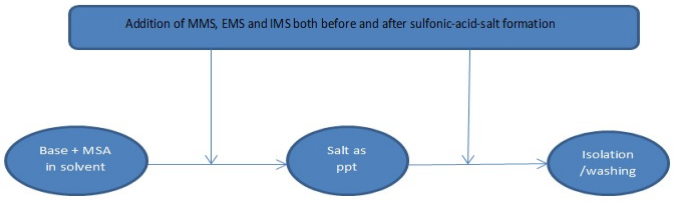
Inherent Purge Factors During Salt-Forming Reaction

- Enormous solubility difference in EtOH between alkyl sulfonates and sulfonic-acid salts
- Cimarosti et al, 2010, OPRD



- PURGE FACTORS are: >4100, >4794, >4100 for MMS, EMS and IMS respectively.

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Summary on Alkyl-Sulfonate Impurities

- Sources 1 & 2 discounted on the basis of mechanistic and experimental evidence
- Sources 3-6 discounted based on enormous inbuilt purge factors
- Real-world example
  - MSA reagent contained 500 ppm MMS
  - But MMS in imatinib mesilate drug substance < LoD (0.02 ppm)
  - MMS stays in solution and is readily removed during deliquoring/precipitate-washing

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Alkyl Sulfonates: Experimental Data (OPRD, 2012)

manufacturing step	class of amine	sulfonic acid[a]	stoichiometry (equiv of acid)	solvent (vol)	temp. (°C)	water added	daily exposure limit (μg)[b]
final	secondary	CSA	0.95	ethyl acetate	45–55	none	<0.1 (AZ)[c]
final	secondary	MSA	0.95	isopropyl alcohol/ethanol	up to 60 cooled to 20	none	<1.5 (AZ)[c]
final	tertiary	MSA	1.1	butanol, MSA added as aq soln (70% w/w)	up to 90	~5% w/w	<1.5 (AZ)[c]
final	primary	MSA	1.05	methanol, butyl acetate	methanol reflux	7.5 mol equiv (to aid crystallization)	0.20 MMS 0. 22 EMS (AZ)
final	primary	BSA	1.0	isopropyl acetate/ipa	40	none	<0.1 (AZ)[c]
penultimate	tertiary	MSA	1.2	isopropyl alcohol (8)	60	none	<0.08 (BMS)[c]
final	tertiary	MSA	0.9–1.2	methanol (10–15), ipa	45–55	none	<0.02 (Lilly)[c]
penultimate	primary	pTSA	1.0	isopropyl alcohol (10)	70	trace from pTSA	<1.5 (GSK)[c]
final	tertiary	MSA	1.0	ethanol (20–30)	up to 82	none	<1.5 (Roche)[c]
final	tertiary	MSA	0.970–0.995	ethanol (~25)	6–35	none	<1.5 (Roche)[c]

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Toxicologically-Based Limits (ICH M7)

- Lifetime and less-than-lifetime (LTL) limits (μg/day) for alkyl mesilates and tosilates (besilates)
  - MMS: Linear extrapolation of TD_{50}
  - EMS & IMS: PDE based on threshold dose for in-vivo mutagenicity
  - Alkyl tosilates/besilates: default ICH M7 generic limits

duration of exposure	up to 1 month	1–12 months	1–10 years	>10 years
MMS	2544	424	212	31.8
EMS	8320	1386	693	104
iPrMs	200	33.3	16.7	2.5
alkyl tosilates	120	20	10	1.5

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Regulatory Aspects

Issue	Comment
1. Strathclyde University MSc thesis (2002)	No alkyl mesilates detected
2. Viracept incident fall-out (2008)	Flawed EMA/CMDh consultation
3. Extension of Production Statement (2008-2015)	Formation of Mesylate WP and establishment of Ph.Eur assay methods
4. SWP/QWP Reviews (2015)	SWP: no alkyl sulfonates formed; QWP: unlikely but cannot be completely excluded

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Regulatory #1: MSc Thesis

Leaked from EDQM in 2004:

Of 11 mesilates tested 8 contained either methanol or ethanol.

The limits of detection for the methyl and ethyl esters were less than 10 ppm.

Salts shown to contain either methanol (pergolide) or ethanol (dihydralazine, codergocrine and phentolamine) were tested for the presence of the methyl and ethyl esters respectively. No esters were detected in the batches examined.

It seems that there is little evidence for the formation of these esters.

S Ahmad, Investigation of mesylate salts for the presence of mesylate esters. MSc thesis 2002, University of Strathclyde, Glasgow, UK

[Unable to obtain copy of thesis from University, project supervisor or EDQM contact (now retired)]

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Regulatory #2: EMA/CMDh Survey

European Medicines Agency
Inspections

London, 24 January 2008
Doc. Ref.: EMEA/44714/2008

THE FOLLOWING LETTER IS INTENDED FOR ALL MARKETING AUTHORIZATION HOLDERS FOR MEDICINAL PRODUCTS CONTAINING ACTIVE SUBSTANCES IN THE FORM OF MESILATES, (DI)ISETIONATES, TOSILATES OR BESILATES.

REQUEST TO ASSESS THE RISK OF OCCURRENCE OF CONTAMINATION WITH MESILATE ESTERS AND RELATED COMPOUNDS IN PHARMACEUTICALS.

- Survey deliberately designed to avoid any collation/evaluation of data to assess a variety of highly speculative statements, eg alcohols for wet granulation, side-reaction hypothesis, ..
- EMA,2016: no evidence that supports any of the statements, But refused to remove document from its website

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Regulatory #3: Mesylate WP; Tosilate and Besilate Esters

- Pharmeuropa 2014

"It is considered that alkyl toluenesulfonate esters are genotoxic and are potential impurities in sultamicillin tosilate dihydrate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method *2.5.40. Methyl, ethyl and isopropyl toluenesulfonate in active substances* is available to assist manufacturers."

"It is considered that alkyl benzenesulfonate esters are genotoxic and are potential impurities in [name of active substance]. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method *2.5.41. Methyl, ethyl and isopropyl benzenesulfonate in active substances* is available to assist manufacturers."

- Press Release 2015

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

25 March 2015, Strasbourg, France
151st SESSION OF THE EUROPEAN PHARMACOPOEIA COMMISSION

- And a chapter on *Methyl, ethyl and isopropyl benzenesulfonate in active substances* (2.5.41). With the adoption of this chapter, the Mesylate working party has successfully completed its work programme as the following general chapters have been finalised: 2.5.37. *Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, 2.5.38. *Methyl, ethyl and isopropyl methanesulfonate in active substances*, 2.5.39. *Methanesulfonyl chloride in methanesulfonic acid*, and 2.5.40. *Methyl, ethyl and isopropyl toluenesulfonate in active substances*.

These texts will enter into force on 1st April 2016 in the 37 European signatory States and will be published in Supplement 8.7.

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Regulatory #3: Comments

- Extension to tosilates and besilates positioned as "potential impurities"
  - No mechanisms proposed
  - No experimental or other supportive evidence
- Mesilate WP
  - Press release of 2015 indication completion of work programme
  - But EDQM refused on 2 occasions to release WP report

Dear Sir,
Please note that the Code of Practice for the work of the European Pharmacopoeia states in chapter 8 'Working documents issued by the Secretariat are for use by the intended recipient and shall not be disclosed to third parties, except as described below.'
As a consequence the EDQM cannot grant you an access to the official documents of the Mesylates working party.

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Regulatory #4: SWP/QWP Reviews

- Review requested by EDQM
- SWP (2015)

SWP 30th June 2015

X.4.	Publication on Alkyl sulfonates in sulfonic-acid salts SWP: [redacted] **Action**: for discussion	Peter explained that the assumption of the presence of genotoxic impurities was erroneous. Will be discussed further in the QWP. M7 quality experts are informed.

SWP 29th September 2015

X.4.	Publication on Alkyl sulfonates in sulfonic-acid salts SWP: [redacted] EMA: tbc **Action**: for update	Very short discussion. Overall SWP is in agreement with the paper. Feed-back from QWP expected (can these impurities be found in MPs?) *Post-meeting note*: QWP has responded to EDQM. Letter available for info in MMD

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Regulatory #4: SWP/QWP Reviews

- QWP Review

Minutes of 76th QWP meeting; 30th September 2015

QWP has received a letter from EDQM in which the group was requested to providean opinion on new information on alkyl sulfonates.

Members had a closer look at the article from Snodin et al. Group acknowledged the scientific rationale in this article and that the formation of alkyl sulfonates is very low and very much depends on the reaction conditions. This makes the presence of these mutagenic impurities at toxicologically significant levels unlikely.

However, as the presence and formation of these alkyl sulfonates cannot be totally excluded, QWP proposes the following approach: MAHs should justify via Risk Assessment that alkyl sulfonates are not expected to be present for their product, which may be sufficient.

Depending on the outcome of this RA supportive analytical data might or might not be required.

With regards to the Ph. Eur texts (and in particular the presence of a Production section in monographs), QWP consider that amendment of the current texts is not necessary.

Outocme of the discussion will be presented to CHMP for adoption and then letter will be sent to EDQM. Message will be passed to industry via published CHMP minutes.

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Regulatory #4: QWP Letter

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 2 October 2015
Doc. Ref: EMA/CHMP/QWP/668388/2015

Dr S. Keitel
EDQM, Council of Europe
7 Allée Kastner
CS 30026
67081 Strasbourg
FRANCE

Subject: QWP response to EDQM request for opinion on new information on alkyl sulfonates

Dear Dr Keitel,

Thank you for your letter dated 27th July 2015 in which you are requesting the Quality Working Party for opinion on new information on alkyl sulfonates.

Quality Working Party had a look at the article from Snodin *et al.* We acknowledge the scientific rationale in this article and that the formation of alkyl sulfonates is very low and very much depends on the reaction conditions. This makes the presence of these mutagenic impurities at toxicologically significant levels unlikely.

However, as the presence and formation of these alkyl sulfonates cannot be totally excluded, QWP proposes the following approach: MAHs should justify via Risk Assessment that alkyl sulfonates are not expected to be present for their product, which may be sufficient.
Depending on the outcome of this RA supportive analytical data might or might not be required.

With regards to the Ph. Eur texts (and in particular the presence of a Production section in monographs), QWP consider that amendment of the current texts is not necessary.

With kind regards,

Dr Jean-Louis Robert
CHMP/CVMP QWP Chair

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Follow-up on Regulatory #4

- FoI requests to EMA/EDQM for evidence supporting "cannot be totally excluded" claim
- EMA

As previously clarified, the EDQM had requested the Quality Working Party's opinion on the matter, providing only the publication from Snodin et al..

It should be noted that the Quality Working Party (QWP) acknowledged the scientific rationale in the article, that the formation of alkyl sulfonates is very low and very much dependant on the reaction conditions. This makes the presence of these mutagenic impurities at toxicologically significant levels unlikely (as stated in your article). However, as the presence and formation of these alkyl sulfonates cannot totally be excluded, the QWP has proposed the following approach: MAHs should justify via a Risk Assessment that alkyl sulfonates are not expected to be present for their product, which may be sufficient. Depending on the outcome of this Risk Assessment, supportive analytical data may or may not be required.

- Please note that the opinion of all the experts who participated in the discussion, was taken into account.
- The QWP has taken a precautionary approach and will at this point maintain this position.

NOTE: Assertion, not evidence; EDQM provided no data, only the Snodin/Teasdale publication

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Follow-up on Regulatory #4

- EDQM

A publication from a German OMCL indicated that genotoxic alkyl sulfonates have been detected in certain finished products, though at low levels below the TTC (threshold of toxicological concern).

These impurities may stem from the use of sub-standard starting materials, even when they did not occur during synthesis. The QWP recommended not to suppress the general chapters and the production statements.

COMMENT: The trade-journal publication is by Wollein & Schramek, 2011, using acetonitrile extraction of mesilate DPs; in a 2012 EJPS publication, hexane is claimed to be the best solvent producing negligible co-extractants.

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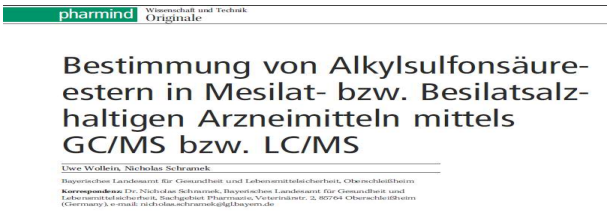
Wollein & Schramek, 2011



pharmind Wissenschaft und Technik Originale

Bestimmung von Alkylsulfonsäure-estern in Mesilat- bzw. Besilatsalz-haltigen Arzneimitteln mittels GC/MS bzw. LC/MS

Uwe Wollein, Nicholas Schramek

Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit, Oberschleißheim

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- MMS claimed to be detected in 33/36 DPs!
- If MMS associated with DS, concentration should be proportional to dose strength – **not so** for doxazosin, bromocriptine and pergolide

Doxazosin

Tablet Strength (mg)	1.0	2.0	4.0	8.0
MMS content (µg)	0.143, 0.134, 0.121, 0.180	0.154, 0.138, 0.178, 0.162, 0.210	0.121, 0.140, 0.203, 0.227	0.227, 0.228
Mean content (µg)	0.145	0.168	0.173	0.228
Ratios for MMS content	1.0	1.2	1.2	1.6

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Wollein & Schramek, 2011(implied MMS concentrations in MSA)

Drug	Dose strength (mg)	Dose as mesilate (mg)	Reported MMS content (µg)	MMS in drug Substance (ppm)	*Implied MMS concentration in MSA (%)
Doxazosin	1.0	1.21	0.145	119.8	49.1
Bromocriptine	2.5	2.87	0.122	42.5	17.4
Pergolide	0.05	0.065	0.037	569.2	233
Dihydroergotamine	1.0	1.16	0.468	403.4	165
Rasagiline	1.0	1.56	0.024	15.4	6.3
Reboxetine	1.0	1.29	0.202	156.6	64.2
Trimipramine	50	66.3	5.208	79.6	32.6
Maprotiline	50	67.3	0.724	10.8	4.4

*Multiply previous column by 4100

- **Comment: The data in the 2011 publication are highly suspect most likely due to analytical artefacts created by co-extractants, MeCN being an unsuitable DP extraction solvent. Hexane/MeCN methods require cross-validation.**

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Alkyl Sulfonates Regulatory: Conclusions

- Concept based on misguided speculation
- No attempt by reg agencies to challenge their hypotheses – contradicts basic principle of the scientific method
- Almost complete disregard for chemical mechanisms
- Clear examples of suppression of negative evidence
- No feedback from FDA, HC or TGA
- EMA/EDQM still trying to salvage some credibility based on assertion and/or dubious data

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Alkyl Sulfonates as a Viable Supertanker?

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Alkyl Sulfonates as an Obsolescent Beached Supertanker?

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Recommendations

- Still more to do to bring regulatory policy in line with scientific data
  - All quiet from FDA, HC and TGA
- Push back on agencies and demand EVIDENCE before responding to any deficiency questions
- COLLABORATE in order to generate database on synthesis conditions and sulfonate-ester levels
- Ideally additional data needed to firmly establish PURGE FACTORS

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Key Publication

Snodin D Teasdale A. Mutagenic Alkyl-Sulfonate Impurities in Sulfonic-Acid Salts: Reviewing the Evidence and Challenging Regulatory Perceptions. *Org Process Res Dev*. 2015, 19 (11), 1465–1485.

Free full-text article available on-line:
http://www.academia.edu/18836249/Mutagenic_Alkyl-Sulfonate_Impurities_in_Sulfonic_Acid_Salts_Reviewing_the_Evidence_and_Challenging_Regulatory_Perceptions.

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