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Review of the Production statement in monographs on mesylate salts in the Ph. Eur.: why do we need GMP and a Production statement?

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1. INTRODUCTION

For at least the last decade, there has been an intense regulatory focus on the control of alkyl sulfonates in drug substances presented as sulfonic acid salts. For example, concerns on residues of alkyl mesylates in mesylate salt drug substances were articulated in 2000, resulting in the need for a "Production Statement" to be provided in relation to any mesylate salt drug substance for which a European Pharmacopoeia (Ph. Eur.) monograph is available [1].

The requirement for strict limits on alkyl mesylates, which are alkylating agents that test positive in a number of in vitro genotoxicity assays [2], is based on the hypothesis that these esters can be – readily – formed by the reaction between methanesulfonic acid (MsOH) and a short-chain alcohol (SCA; defined as methanol, ethanol or 2-propanol for the purposes of this article) if a mesylate salt is prepared by addition of an equimolar amount of MsOH to an organic base drug substance dissolved in an SCA. No evidence appears to have been provided by regulatory bodies to show that mesylate ester formation actually occurs during mesylate salt synthesis. However, in an incident occurring in 2007 [3], significant levels (≥ 0.1 %) of ethyl mesylate (ethyl methanesulfonate, EMS) were found in nelfinavir mesilate (Viracept), and it seemed initially that regulatory risk perceptions on alkyl mesylates had been vindicated. However, following a comprehensive evaluation by the CHMP [4] it became clear that the EMS originated from contaminated MsOH. The contamination came about as a result of a massive GMP failure involving the presence of ethanol in a tank used for long-term storage of

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MsOH [3]. In addition, the CHMP report speculates that impurities in the MsOH, such as methyl methanesulfonate (MMS) and methanesulfonyl chloride (MsCl), may have been responsible for the presence of low levels (ppm) of EMS in nelfinavir mesilate prior to the major contamination incident. Adherence to the principles of GMP in the synthesis of pharmacopoeial APIs, as recommended in the recent draft update of the monograph on Substances for Pharmaceutical Use [5], particularly in relation to reagent purity, should be sufficient to eliminate any risk of minor contamination of mesylate salts.

The European Pharmacopoeia Commission (EPC) has recently proposed an amendment to the current production statement on mesylate salts [6], as follows:

> "It is considered that alkylsulfonate esters are genotoxic and are potential impurities in <name of active substance>. The manufacturer must ensure that the manufacturing process conforms to current requirements for risk management, including quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers."

This article presents a short review of the relevant chemical and toxicological evidence relating to alkyl mesylates in mesylate salts and makes a critical evaluation of the proposed revision of the production statement by the EPC.

2. CHEMICAL EVIDENCE ON THE RISK OF ALKYL MESYLATE FORMATION

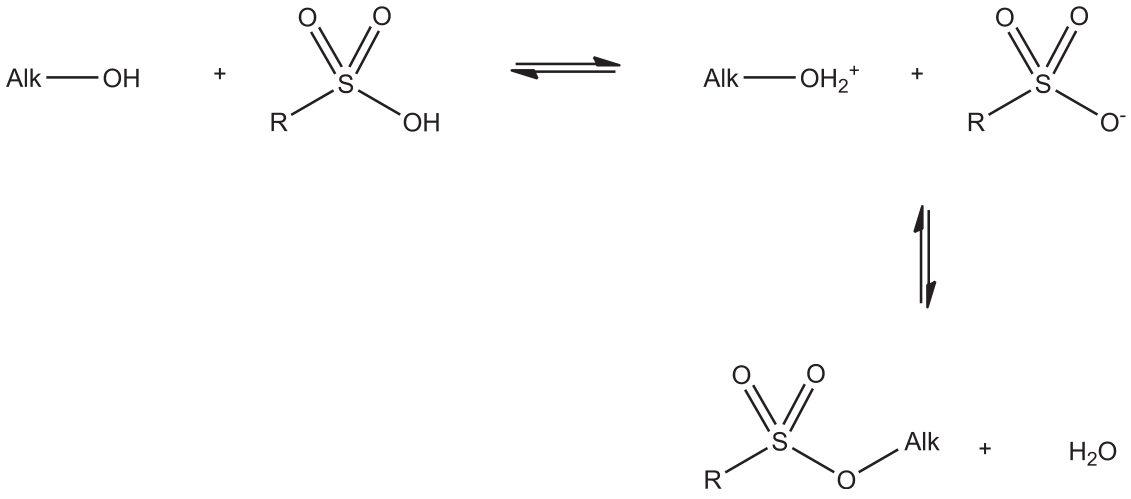
The synthesis of mesylate salts, described in a previous publication [1], normally involves the gradual addition of MsOH to a well-stirred and cooled alcoholic solution of an equimolar amount of organic base. The resulting precipitate of mesylate salt is isolated by filtration and washed with SCA solvent(s) and possibly diethyl ether in addition. The salt may then be recrystallised from (aqueous) ethanol.

It is possible to evaluate the critical elements of the mesylate salt synthesis, particularly in terms of mechanism and kinetics, from two aspects: the potential reaction of MsOH with an SCA in a binary system and the protonation of an organic base in alcoholic solution by MsOH.

2.1. Binary system of MsOH and SCA

The mechanistic scheme for this reaction is shown in Figure 1.

Figure 1 – *Mechanism of formation of alkyl mesylates from MsOH and a short-chain aliphatic alcohol*



Alk = methyl, ethyl, or isopropyl
R = methyl

Mesylate ester formation has been shown to occur in a 2-stage equilibrium reaction:

1. protonation of the alcohol to form an oxonium ion;
2. nucleophilic displacement of the hydroxonium moiety by a mesylate anion then produces an alkyl mesylate.

A significant concentration of protonated alcohol is needed for the reaction to proceed by the established pathway. Alcohols are weakly acidic and so are not readily protonated. For anhydrous simple aliphatic alcohols, based on ^{13}C-NMR shift data for the carbon atom alpha to the hydroxyl group in the presence of different strengths of sulfuric acid, it has been shown that the threshold level for alcohol protonation is approximately 10 % *m/V* sulfuric acid [7]. Moreover, the mesylate anion is a poor nucleophile owing to the delocalisation of the negative charge over three oxygen atoms, and water formed during the reaction, unless removed, has the potential to hydrolyse any ester to its constituent acid and alcohol [1]. Experimental studies sponsored by the US Product Quality Research Institute (PQRI) have confirmed the various elements of the mechanism of formation of alkyl sulfonates described above [8]. For example, there was no incorporation of ^{18}O into MMS formed in a system containing MsOH and $CH_3{}^{18}OH$, indicating that methyl methanesulfonate formation proceeds by initial protonation of methanol and nucleophilic displacement of the hydroxonium moiety. A subsequent PQRI publication [9] provides detailed kinetic information on the alkyl mesylate formation reaction. This publication also confirmed that a high level of acidity is needed to achieve a critical extent of alcohol protonation sufficient to produce – slow – ester formation.

In terms of the reaction of MsOH (1.04 M = 100 mg/mL) with dry ethanol, the rate constant for EMS formation was determined to be 7.90×10^{-8} s^{-1} at 70 °C [9]. Using the convention that a 10 °C increase in temperature increases the reaction rate 2-fold, the rate constant for EMS formation is predicted to be 2.5×10^{-9} s^{-1} at 20 °C. Thus, during 30 minutes at 20 °C at a concentration of approximately 1 M, the predicted conversion of MsOH to EMS is approximately 0.0005 % *in a binary system with no organic base present*. If this amount of EMS (5 ppm) were present in solution, the concentration in a mesylate salt following filtration and solvent-washing would be much lower.

2.2. Protonation of organic base in SCA solution

Proton transfer from an acid to a (nitrogen) base in solution has been shown to be extremely rapid [10], and to require a negligible amount of activation energy provided that the bond formed is stronger than the bond being broken, i.e. the pK_a of the donor acid is lower than the pK_a of the conjugate acid of the acceptor base – which will almost invariably be the case with the protonation of nitrogen bases by MsOH. The reaction of an amine with the hydronium ion in aqueous solution is generally considered to be diffusion-controlled, or nearly so, and has a rate constant of around 10^{10} $M^{-1}s^{-1}$. In the case of a sterically hindered amine, the rate of protonation may be reduced by up to 4 orders of magnitude [11]. Since SCAs are protic polar solvents, there will be a high degree of solvation of any amine solute. MsOH is normally present in solution as an ion-pair and the extent of ion-pair dissociation will depend to a significant extent on the dielectric constant of the solvent. The dielectric constants of the three SCAs are around ¼ to ⅓ of that of water and so ion-pairing should not significantly impact on the rate of base protonation, and will be partly compensated by the slightly lower viscosity of methanol and ethanol (but not 2-propanol). Proton transfer rate constants for aminobenzoic acids have been reported to be similar in a range of protic solvents (including water, methanol and ethanol) with a forward rate constant of around 10^7 s^{-1} [12]. Proton transfers of this type are considered to be "fast" or "superfast" reactions, requiring special measurement techniques (e.g. relaxation methods) to determine rate constants. The Nobel Prize in Chemistry was awarded in 1967 to Eigen, Norrish and Porter for using such techniques to determine the rates of superfast reactions in solution [13].

Experimental confirmation of the above mechanistic information is available in the case of MsOH protonation of 2,6-lutidine, in that in the presence of an equimolar concentration of this base in ethanol maintained at 70 °C for 14 hours, no EMS was formed [8].

Overall, an ultra-worst-case value for the MsOH protonation rate constant for an amine in an SCA solution is considered to be around 10 000 times slower than the diffusion-controlled rate, around 10^6 s^{-1}. Although it is not possible to accurately predict the rate constant for organic base protonation in these circumstances, it is certain that it would be an exceedingly fast reaction.

The European Pharmacopoeia currently lists 11 drug substances that are presented as mesylate salts: betahistine mesilate, bromocriptine mesilate, codergocrine mesilate, deferoxamine mesilate, dihydroergocristine mesilate, dihydroergotamine mesilate, doxazosin mesilate, pefloxacin mesilate dihydrate, pergolide mesilate, phentolamine mesilate, and saquinavir mesilate. The salts are formed from typical weak bases, most commonly secondary amines with pK_a values in the range 6.9-11.8 (based on information from product monographs and drug databases). The facility of salt formation in aqueous solution is determined by the following equation [14]:

$$pK_s = pK_a + pK_b - pK_w$$

relating to the reaction:

$$B + HA \rightleftharpoons BH^+ + A^-$$

where B is the base, HA is the acid (e.g. MsOH), BH^+ is the protonated base and A^- the counterion (e.g. mesylate).The salt formation constant (K_s = equilibrium constant, K_{eq}) for the reaction shown above is:

$$K_s = K_{eq} = [BH^+][A^-] / [B][HA].$$

SCAs such as methanol and ethanol are described as "neutral" amphiprotic solvents with acid-base properties similar to those of water [15]. Consequently, acid-base equilibria in such solvents are considered likely to be closely similar to those in water.

For a base having a pK_a of around 7, its pK_b will also be 7. The pK_a of MsOH is approximately – 2 [16]. Hence, the pK_s for the reaction of MsOH with such a base would be: (– 2) + 7 – 14 = – 9, equivalent to an equilibrium constant of 10^9. A reaction characterised by an equilibrium constant of this magnitude would clearly go to completion, and the mesylate salt will be formed without difficulty, thus providing complementary evidence to that presented above on the rate of base protonation.

Hajkarimian *et al.* [17] have reported an alternative mechanism for alkyl sulfonate formation for a particular base containing a labile ethoxy side-chain. Ethyl besilate formation was shown to be unaffected by the presence or absence of ethanol, and caused by a reaction between excess benzenesulfonic acid and the ethoxy side chain of the base form of the drug substance. Such side-chain reactions can be prevented by employing no more than a stoichiometric amount of sulfonic acid in the salt-forming reaction. Moreover, based on the mechanism described above involving extremely rapid base protonation, no improvement in the yield of mesylate salt can be expected by using a molar excess of MsOH.

2.3. Conclusions on chemical evidence

The information presented above indicates that there will be at least a 10^{12}-10^{15}-fold difference between the rate constants for organic base protonation and alkyl mesylate generation. Base protonation will effectively be instantaneous in a well-stirred system using a non-viscous solvent such as an SCA. This fast reaction will immediately remove all added MsOH from the system in the form of (precipitated) mesylate salt. Consequently, even an extremely slow rate

of conversion of MsOH to alkyl mesylates (in the range of the estimate shown above) can be discounted. Anecdotal evidence indicates that alkyl mesylate residues are consistently absent in mesylate salts manufactured under GMP conditions.

Regulatory concerns have been expressed regarding the risk of the potential for alkyl mesylate formation during alcoholic granulation of a mesylate salt drug substance [18]. What is the mechanism for such a reaction and what are the kinetics? No information has been provided by regulators to support this proposition. Alkyl mesylate formation would be impossible unless highly acidic conditions prevailed. Moreover, if no alkyl mesylate is formed during synthesis throughout which the SCA solvent is in intimate contact with precipitated mesylate salt, it seems inherently unlikely that EMS might be formed by ethanol granulation of a mesylate salt drug substance. Associated concerns regarding the potential for EMS formation in vivo following administration of an alkyl mesylate salt with concurrent consumption of an alcoholic drink can be discounted for a number of reasons. Firstly, gastric acidity (pH ≥ 1) is insufficient to achieve ethanol protonation; even if small amounts of protonated ethanol were formed, reaction with water and/or chloride ion, both being much stronger nucleophiles than the mesylate anion and present in significantly higher concentrations, would effectively preclude EMS formation. The ethanol concentration is unlikely to exceed 30 % (for example through dilution by gastric contents of a spirit containing 40 % ethanol), and Teasdale et al. [9] showed that no EMS is produced from MsOH in a 67 % water/ethanol system maintained at 70 °C for 16 hours.

3. TOXICOLOGICAL ASSESSMENT

In recognition of the foregoing evaluation of the chemical evidence indicating an absence of alkyl mesylate formation under GMP conditions, it is considered unnecessary to make an assessment of the toxicological data in relation to the synthesis of mesylate-salt drug substances. On the other hand, since alkyl mesylates may be present in drug substances or synthetic intermediates in circumstances unrelated to mesylate salt formation, for the sake of completeness some comments are provided below on appropriate limits for MMS, EMS and 2-PrMS (2-propyl methanesulfonate) as potentially genotoxic impurities (PGIs).

Whereas the EU guideline on limits of genotoxic impurities [19] and the Q&A supplement [20] recommend a default limit of 1.5 µg/day for a DNA-reactive (Ames-positive) impurity, there are a considerable number of exceptions listed in the guidance. These include:

- Impurities for which carcinogenicity bioassay data are available; for such compounds the EU guideline indicates explicitly that the TTC (Threshold of Toxicological Concern) limit should not be applied. Although no particular technique for deriving a PDE (Permitted Daily Exposure) from carcinogenicity bioassay data is recommended in the EU guideline, several publications/presentations [21, 22, 23] have independently described the methodology shown below as applied to MMS.
- Impurities for which an in vivo threshold has been demonstrated; this is the case for EMS.

3.1. MMS

The TTC concept is based on linear extrapolation of TD50 values (in mg/kg/day – a measure of carcinogenic potency, representing an increased carcinogenic risk of 1 in 2) for groups of genotoxic and non-genotoxic carcinogens. Consequently, it is considered justifiable to determine PDEs for individual compounds using a similar process. Assuming a patient body weight of 50 kg and a cancer risk at a probability of 10^{-5}:

$$\text{PDE (µg/day)} = (\text{TD50} \times 50) / 50000 = \text{TD50} \times 10^{-3}.$$

In other words, the PDE for a compound for which a TD50 value is available has the same numerical value as the TD50 but in units of µg/day. In view of the overestimation of risk built into the linear extrapolation process, PDEs obtained in this manner should be considered to be highly conservative estimates of safe human doses.

Since the TD50 for MMS is reported to be 31.8 mg/kg/day [24], a PDE of 32 µg/day can be determined using the methodology shown above.

3.2. EMS

Depending on assumptions and methodology, a number of different PDEs can be determined for EMS [25]. EMS is a highly unusual case in terms of impurity qualification since compound-specific data are available on animal/human NOELs (no observable effect levels) and on relative animal/human systemic exposure. Use of such compound-specific pharmacokinetic exposure data has long been considered to provide the most reliable approach for quantitative extrapolation of animal toxicity data to humans [26]. Moreover, calculation of safety factors based on relative animal/human systemic exposure is standard practice in EU non-clinical safety assessments [27], and the use of toxicokinetic data can play a critical role in reducing uncertainty in risk assessment [28].

Referring to the EMS contamination incident mentioned above, the EMS concentration in the drug substance was around 0.1 %, and exposure over 3-6 months in patients using contaminated nelfinavir mesilate has been estimated to be 0.055 mg/kg/day [29], equivalent to 2.75 mg/day in a 50 kg patient. A threshold dose of 25 mg/kg/day EMS in terms of genotoxicity was established in a mouse 28-day toxicity study; this was also determined to be the NOEL based on a variety of considerations such as the presence of clear no effect levels in bone marrow, liver and GI-tract tissue with several dose levels tested below the NOEL. Potential adverse effects of EMS such as cancer, birth abnormalities and heritable effects are considered to be sequelae of its genotoxic activity. Hence, the thresholded dose-response relationships should also apply to these endpoints. The animal/human NOELs are considered applicable to long-term administration of EMS since they are determined on the basis of mechanistic parameters (i.e. DNA repair); every mouse-liver cell can repair 380 000 DNA ethylation adducts caused daily by EMS administered at a dose of 50 mg/kg/day without making errors leading to a measurable increase in mutations or chromosomal aberrations. Moreover, activities of the DNA-repair enzyme, O^6-methylguanine methyltransferase (MGMT) appear to be higher in humans than in rats and mice [31].

Animal (mouse) and human exposure/NOELs for EMS with accompanying pharmacokinetic parameters are shown in Table 1 (taken from Müller & Gocke, 2009 [25], Lavé et al., 2009 [30] and Müller et al., 2009 [31]).

Table 1 – *EMS: Doses/NOELs and PK parameters*

Dose (mg/kg/day)	$AUC_{0-\infty}$ (µM.h)	C_{max} (µM)
Mouse NOEL, 25	350	315
Human exposure, 0.055	13	0.85
Human NOEL, 2.0	350	31

In relation to the estimated maximum patient exposure to EMS of 0.055 mg/kg/day, a safety factor based on relative mouse/human AUC of at least 28 can be calculated. This lower value is due to the conservative prediction of a longer half-life of EMS in man versus mouse, rat and monkey. Based on the estimated human C_{max} the safety factor for affected Viracept patients is calculated to be 370, since C_{max} is mainly dependent on the volume of distribution, which

for EMS differs minimally across species. The AUC-based safety factor is considered by Müller et al. [31] to constitute a minimal value since C_{max} is likely to be a much better metric in relation to DNA alkylation. Eder et al. [32] reported that EMS reacts in biological systems predominantly as an S_N2 alkylating agent and so, since DNA concentrations are expected to be relatively stable over the short half-life of EMS (10-20 minutes in the mouse), it can be inferred that plasma/cellular concentration of EMS will be the principal determinant of the rate of DNA alkylation.

Overall, pharmacokinetic modelling of EMS data indicates a human NOEL of 2 mg/kg/day, equivalent to 100 mg/day in a 50 kg patient supported by a "worst-case" AUC-based safety factor of 1 and by a more realistic C_{max}-based safety factor of 10. Given the confidence that can be attributed to the above calculation of a human NOEL, it is highly debatable whether an additional safety factor is required in order to determine a human PDE [31]. Müller & Gocke [25] argue that, at most, a 10-fold safety could be applied effectively as a temporary precaution until independent confirmation of their findings is achieved.

An alternative, ultra-conservative approach to the estimation of a PDE for EMS is also provided by Müller & Gocke [25] using the procedure described for residual solvents in the ICH Q3C (R5) guideline [33]. The methodology employs various types of generic "assessment factors" and in the case of EMS a worst-case overall assessment factor of 12 000 has been determined which, based on the mouse NOEL of 25 mg/kg/day, produces a PDE of 2.08 µg/kg/day, equivalent to 104 µg/day in a 50 kg patient. A similar calculation using the human NOEL of 2 mg/kg/day with an assessment factor of 1000 produces a similar PDE of 100 µg/day. Performing a risk assessment by applying generic safety factors and discarding compound-specific data would normally be considered less than ideal in the regulatory context. However, the development of consensus methodology is needed before compound-specific data can be used with confidence as an integral part of the risk assessment of PGIs. If a PDE for EMS of 100 µg/day is deemed to be appropriate, it should not be forgotten that patient exposure over 3-6 months to EMS via administration of nelfinavir mesilate contaminated with EMS was around 25 times this amount, and considered by experts appointed by the EMA (European Medicines Agency) to pose no increased risk of carcinogenicity to affected patients [34]:

> "*...animal studies have shown that there is a threshold level below which ethyl mesylate does not have a harmful effect on the DNA (25 mg per kilogram and per day in the mouse). Company experts have used special models that allow results from animal studies to be 'extrapolated' to humans. This has allowed them to calculate the threshold value for patients who have been exposed to ethyl mesylate (2 mg per kilogram and per day). This level has been endorsed by the experts from the CHMP's Safety Working Party. Patients who took Viracept tablets at the highest level of contamination were exposed to levels of ethyl mesylate of about 0.05 mg per kilogram per day. As these levels are below the threshold, the CHMP concluded that patients exposed to contaminated Viracept are not at an increased risk of developing cancer, and that they do not need to be followed up as was previously planned.*"

Overall, an ultraconservative PDE of 100 µg/day, based on the use of generic assessment factors, may be acceptable for the time being until more sophisticated risk-assessment techniques are developed and agreed.

3.3. 2-PrMS

Based on the value of its Swain-Scott *s* constant (0.29 versus 0.83 for MMS) [1], 2-PrMS is expected to be a more potent alkylating agent than MMS, and possibly slightly more potent than EMS. However, in the absence of in vivo genotoxicity/carcinogenicity data, it is considered prudent to apply the TTC limit of 1.5 µg/day.

4. DISCUSSION AND CONCLUSIONS

Although the issue of alkyl mesylate formation seems firmly embedded in the regulatory psyche, the only justification presented for the Production Statement has been the speculative hypothesis originally mentioned in a Pharmeuropa note in 2000 [35]. The critical risk assessment presented here has highlighted that the concerns are based much more on hypothesis and assumption rather than on evidence and good science. It is a major disappointment that the EPC has not taken account of both published and in-house evidence as part of its reassessment of the Production Statement. A recent example of such good practice is provided by the proposed updating of the EMA guidance on biosimilar medicinal products [36] in which the review will be conducted "in light of experience gained and to propose changes where necessary".

In theory, there are 2 scenarios in which alkyl mesylate formation can occur:

- reaction of SCA with MsOH impurities such as MMS or MsCl;
- reaction between MsOH and SCAs during mesylate salt synthesis.

Production of trace amounts of alkyl mesylates by the former reaction seems plausible and the Viracept incident provided some presumptive evidence for its occurrence [4]. As already indicated, the most appropriate means of control of such impurities is by the application of GMP principles [3]. In terms of the second scenario, much mechanistic and experimental evidence clearly shows that alkyl mesylate formation will not occur when equimolar amounts of organic base and MsOH are employed. Consequently, it seems completely unnecessary for the EPC to advocate a continuation the Production Statement requirement for mesylate salts. If the EPC believes that the Production Statement is still required, in addition to the application of GMP, then appropriate evidence (such as a demonstration that alkyl mesylates are produced even under GMP conditions using highly pure MsOH) should be published and made available for peer review.

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Background note and comment on the article by Snodin *et al.* on Ph. Eur. monographs on mesylate salts

J. M. Midgley[2]

This letter is the follow-up to the document: 'Review of the Production statement in monographs on mesylate salts in the Ph. Eur.: why do we need GMP and Production statement?', published above.

In 2000, the EPC's concerns over the (potential) genotoxicity of alkylsulfonate esters led to the insertion of a Production Statement – a mandatory section of the monograph, unless otherwise stated – into the monograph on pefloxacin mesilate, which was under elaboration at the time. Subsequently the monographs for the other 10 mesylate salts were revised by inclusion of the Statement.

The Guideline on the limits of genotoxic impurities [1] came into effect in 2007. Subsequently the EPC published its Policy Statement, Potentially genotoxic impurities (PGIs) and European Pharmacopoeia monographs on substances for human use [2]. The detailed policy is completely consistent with that for impurities in general, which is clearly apparent from general chapter *5.10. Control of impurities in substances for pharmaceutical use* [3] and general monograph *Substances for pharmaceutical use (2034)* [4]. In the current context, the following statements in the Policy Statement are particularly noteworthy.

- (Section 1) Problem Statement: which says, inter alia, "The Production section of monographs may also draw attention to the need for attention to PGIs".
- (Section 2) Action: This includes a statement that "The policy must take due account of the CHMP Guideline..."
- (Section 4) Policy to be applied: both the text and the table in the Appendix.

Throughout it is abundantly clear how acceptance criteria are derived and applied in pharmacopoeial monographs (i.e. based on Marketing Authorisation Application (MAA) and evaluation by the Competent Authority).

In 2008 a GMP failure caused the occurrence of ethyl methanesulfonate in Viracept and this triggered a broad regulatory discussion. There was a request to the EPC to establish a MSL WP with specific terms of reference, amongst which was the drafting of general methods for the determination of lower alkyl alkanesulfonates in alkanesulfonic acids (particularly methanesulfonic acid, MSA) with priority for alkyl mesylates; this was later extended to the determination of methanesulfonyl chloride in MSA. The WP was to elaborate a general method for the determination of methyl mesylate, etc., in API mesylates. 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 users of the Pharmacopoeia. Consistent with the policy of the EPC, considerations of safety in general, and the establishment of acceptance criteria in particular, were not included in the remit of the WP and this is clearly stated in the publication of the proposed revised Production Statement in Pharmeuropa [5].

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In 2010, the UK Delegation asked the EPC to request the WP to review the need for, or revision of the wording of, a Production Statement in the monographs for mesylate salts. This was timely in view of the advances that had been made in previous years in understanding the chemistry – largely based on well-known chemical principles – underlying the formation, and to some extent the stability, of alkyl mesylates. This is well described by Snodin et al. in their review article (see above). In its review, the WP recommended that the Production Statement should be retained. In the proposed revised general monograph *Substances for pharmaceutical use* (2034) [6] there is an explicit requirement that the manufacture of active substances must take place under conditions of good manufacturing practice. However, the Pharmacopoeia should make additional provisions to protect patients against the use of potential sub-standard starting materials. In addition, the Production Statement is available to all users of the Pharmacopoeia, including independent analysts, who may not be aware of the possibility that traces of alkyl mesylates may be present in the active substance as a result of the use of impure MSA. It was considered prudent to seek the advice of the CHMP Quality Working Party (QWP) and Safety Working Party (SWP) on the proposed revised Production Statement, together with the concomitant required revision to general monograph 2034. As stated in the publication in Pharmeuropa 23.4 [5], these bodies endorsed both of the proposed revisions and added a statement to the Production section of the general monograph to the effect that the manufacture of active substances must take place under conditions of good manufacturing practice.

When the requirements of the revised Production Statement are taken into account with the increase in understanding of the chemistry involved in the formation of mesylates, there is every reason to believe that manufacturers should be able to preclude, or at least minimise, the formation of alkyl mesylates in the manufacture of mesylate salts of active substances. Moreover, the information should assist manufacturers of mesylate salts in presenting well-reasoned cases in the MAA and benefit assessors in the review process, which would ultimately determine the appropriate means of control for each substance/process.

Confidentiality lies at the core of the regulatory process. Consequently there is an understandable lack of transparency in providing information on whether or not such impurities have been/are produced in the manufacture of mesylate salts formulated into medicinal products that have been the subject of MAAs (or dossiers for substances submitted for Certification of the Pharmacopoeia).

Unfortunately the situation with respect to the risk of these substances to human health is not so well defined and, until it is considered that there are sufficient valid data available to warrant an official review of their safety (for example, along the lines of that referred to in reference 36 of the review article by Snodin et al.), the Production Statement in monographs reflects current regulatory expectations and as such will continue to fulfil its purpose in the protection of public health.

[1] Guideline on the limits of genotoxic impurities. Ref: EMEA/CHMP/QWP/ 251344/2006. EMA; 2006 Jun [available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf, accessed 2012 Mar 29].

[2] Potentially genotoxic impurities and European Pharmacopoeia monographs on substances for human use. *Pharmeuropa* 2008;**20**(3):426-7.

[3] Control of impurities in substances for pharmaceutical use, general chapter 5.10. Ph. Eur. 7th Edition. Strasbourg, France: Council of Europe; 2010(vol 1).

[4] Substances for pharmaceutical use, monograph 2034. Ph. Eur. Suppl. 7.5. Strasbourg, France: Council of Europe; 2010.

[5] Review of the Production Statement in monographs for mesilate salts. *Pharmeuropa* 2011;**23**(4):691.

[6] Substance for pharmaceutical use, monograph 2034. Pharmeuropa 2011;**23**(4):691-3.