Medicines & Healthcare products
Regulatory Agency

Licensing procedure for electronic cigarettes and other nicotine-containing products (NCPs) as medicines

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Contents

Introduction

Nicotine-containing products (NCPs) that are presented for cutting down, quitting and reducing the harms of smoking are considered to be medicinal products. The MHRA is responsible for regulating NCPs that are medicinal products, including electronic cigarettes, and continues to encourage and actively support companies to submit medicines authorisation applications for electronic cigarettes and other nicotine containing products.

The European Tobacco Products Directive (TPD) came into force in May 2014 and introduced new rules for nicotine-containing electronic cigarettes and refill containers (Article 20). The UK Tobacco and Related Products Regulations 2016 implemented the TPD in the UK and came into force on 20 May 2016. Article 20 of the TPD specifies a number of regulatory controls for electronic cigarettes which will apply to those electronic cigarette products that do not fall under the definition of a medicinal product. Under Article 20, the European Commission shall, by means of an implementing act, lay down a common format for the required notifications for consumer electronic cigarettes and lay down technical standards for the refill mechanism. Information on the TPD requirements for consumer electronic cigarettes can be found here:
http://ec.europa.eu/health/tobacco/products/index_en.htm
https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products

The following guidance note provides information about the licensing procedure for electronic cigarettes and other NCPs as medicines. Standards dealing with quality and safety aspects for consumer electronic cigarettes and nicotine liquids have been developed by BSi[1] and AFNOR (the French standards association)[2] and European and international standards are in the process of being developed by CEN (European Committee for Standardisation) and ISO (International Organization for Standardization) respectively. For medicinal electronic cigarettes and NCPs, the MHRA would expect the product to meet these standards, where relevant, although additional requirements may be needed to meet safety, quality and efficacy criteria under medicines regulations.

[1]PAS 54115:2015 Vaping products, including electronic cigarettes, e-liquids, e-shisha and directly-related products - Manufacture, importation, testing and labelling – Guide

[2]XP D90-300-1 Mars 2015 Cigarettes électroniques et e-liquides - Partie 1 : exigences et méthodes d'essai relatives aux cigarettes électroniques XP D90-300-2 Mars 2015 Cigarettes électroniques et e-liquides - Partie 2 : exigences et méthodes d'essai relatives aux cigarettes e-liquides

Electronic cigarettes regulated as medicines could be available in strengths and volumes greater than those permitted under the TPD (*i.e.* containing more than 20mg/ml nicotine, more than 2ml for

single use cartridge/disposable products or more than 10ml for refill containers), as well as lower-strength, and lower volume products. This is intended to ensure that products are available that meet appropriate standards of safety, quality and efficacy to help users cut down their smoking and to quit.

The MHRA website contains details and links to all the relevant information that is needed for the licensing procedure and a good starting point can be found in our marketing authorisations, variations and licensing guidance:
https://www.gov.uk/medicines-medical-devices-blood/marketing-authorisations-variations-licensing

Further information can be found in:

- Applying for a licence to market a medicine in the UK:

https://www.gov.uk/apply-for-a-licence-to-market-a-medicine-in-the-uk

- Types of application:

https://www.gov.uk/guidance/apply-for-a-licence-to-market-a-medicine-in-the-uk#types-of-application-legal-basis

- Fees for licence applications:

Note that nicotine is not a new chemical entity so it is expected that application fees would fall within the abridged complex or abridged standard classifications.
https://www.gov.uk/guidance/apply-for-a-licence-to-market-a-medicine-in-the-uk#fees

As an electronic cigarette contains components such as a battery and heating element, legislation relating to medical devices is also relevant. Since, in many cases, the delivery/administration part of the electronic cigarette will be regarded as a medical device, it will need to be CE marked under the medical device regulations.

A good starting point for medical device regulation can be found here:
https://www.gov.uk/medicines-medical-devices-blood/medical-devices-regulation-safety

The relevant Medical Devices Directive is Directive 93/42/EEC:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF

The content and layout of any application need to follow the common EU standards. Further information can be found in:

 EudraLex - Volume 2 - Pharmaceutical Legislation Notice to applicants and regulatory guidelines medicinal products for human use

http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

 Scientific guidelines
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cb

More detailed information on the expected content of an application is provided below but should you have preliminary queries about the licensing of electronic cigarettes as medicinal products please contact: Dr Efua Anno, Manager PLAT 3 efua.anno@mhra.gsi.gov.uk or Mrs Elizabeth Baker, Group Manager elizabeth.baker@mhra.gsi.gov.uk

Frequently asked questions

What is involved in the marketing authorisation application – what do I need to submit?

The findings of the *ad-hoc* expert working group on nicotine containing products, of the Commission on Human Medicines (CHM), recommended a proportionate assessment of any future marketing authorisation applications (MAA) regarding electronic cigarettes and other nicotine containing products (NCPs).

The MHRA has therefore advised potential applicants that an abridged application submitted under Article 10 of Directive 2001/83/EC, as amended, would be appropriate. This legal basis allows for submission of a dossier which is abridged in relation to safety and efficacy by way of a comparative pharmacokinetic (PK) study comparing the new product to an appropriate reference medicinal product.

Given the intended route of administration, an inhaled nicotine product such as Nicorette Inhalator has been advised as being a suitable reference product.

Depending on whether Article 10(1) or 10(3) is used (for electronic cigarettes, it is likely that 10(3) would be the appropriate option), it is not always a directive requirement to show bioequivalence with the reference product. However, in order for conclusions regarding the safety and efficacy of a product to be reached, it is necessary to show where the product 'sits' in relation to other NCPs and cigarettes, in terms of its nicotine PK profile. It will not be sufficient to provide PK data alone and it is expected that a submission would be supported by an extensive literature review on the current knowledge of the use of e-cigarettes. Furthermore, a PK study could usefully include a pharmacodynamic (PD) assessment (*e.g.* visual analogue scale (VAS)) of craving for nicotine in order to supplement PK data. The safety of the product can be supported by literature, assuming that the vapour produced by the device does not contain any components that may raise concerns and that the literature data supports the safety of all components of the formulation *via* the inhaled route.

As per the requirements of the revised pharmacovigilance regulations, all MAAs must be supported by a risk management plan. This must detail both identified and potential risks of the product and the measures to be implemented to minimise these risks. Further information can be found on the MHRA website:
https://www.gov.uk/good-pharmacovigilance-practice-gpvp

In assembling the dossier for an application for marketing authorisation, the European guidelines relating to the quality, safety and efficacy of medicinal products need to be taken into account. These can be found on the European Medicines Agency (EMA) website at the following link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&%20murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cb

The dossier will need to follow the format published by the European Commission in EudraLex Volume 2 - Pharmaceutical Legislation Notice to applicants and regulatory guidelines medicinal products for human use (http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm). In particular, Volume 2B – Presentation and content of the dossier (http://ec.europa.eu/health/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf) provides a very useful overview of the data which make up a marketing authorisation and gives specific reference to many of the guidelines which should be referred to when compiling the data to support a marketing authorisation.

Further information on applying for a marketing authorisation can also be found on the MHRA website (https://www.gov.uk/apply-for-a-licence-to-market-a-medicine-in-the-uk). This gives relevant information in such areas as fees, contacts in the MHRA and applying for a marketing authorisation.

More detailed information on the quality, safety and efficacy requirements can be found in other frequently asked questions. If the applicant has precise, scientific issues or questions then the MHRA provides a formal Scientific Advice service, details of which can be found at https://www.gov.uk/medicines-get-scientific-advice-from-mhra.
It may also be appropriate to seek guidance from a regulatory consultant if the applicant does not have sufficient in-house experience.

What do I need for the quality part of the marketing authorisation application?

Unlike the clinical data requirements, which can differ significantly based on the type of product and/or type of application applied for, the quality data (Module 3) requirements are more clearly defined and apply to all MAA.

Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.

The quality data shall include for the active substance(s) and for the finished medicinal product all relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.

This Module (3) shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s), on the excipients incorporated in the formulation of the finished medicinal product and on the container components (*e.g.* cartridges).

All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient detail to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).

Both the active substance and the finished product should be manufactured at sites which operate in compliance with the principles of Good Manufacturing Practice (GMP). For the finished product manufacturer, the site must be inspected by an EU/EEA competent authority and demonstrate it is GMP compliant before a Marketing Authorisation (MA) for the product can be granted. Further information on the additional licences required in support of a MAA is provided in the answer to Question 14.

Active substance (drug substance)

Nicotine is the subject of a monograph of the European Pharmacopoeia. The application for a MA should therefore ensure that the quality of the active substance is controlled, by a drug substance specification, in line with the European monograph for nicotine and the general monograph on substances for pharmaceutical use.

There are a number of ways in which the applicant can submit the information on the drug substance and a specific guideline has been developed which covers this in detail: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002813.pdf.

Other ingredients (excipients)

Other ingredients should meet European Pharmacopoeia monograph requirements where they exist; if flavouring components do not have such monographs, then they should meet EU food safety legislation requirements. Excipients should be approved for inhalation use or have appropriate toxicological data to support such use.

For glycerol and propylene glycol, potential contamination with diethylene glycol is an issue. Note the European Medicines Agency (EMA) Good Manufacturing Practice (GMP) Q+A (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section6), which although it refers to glycerol should also be taken into account for propylene glycol.

Container closure components (primary packaging)

Container closure components which come into contact with the finished product should meet European Pharmacopoeia monographs where they exist. If the materials are not covered by such monographs, then they should comply with the applicable EU food safety legislation requirements.

The container should comply with child resistance standards (BS EN ISO 8317 for reclosable containers and BS EN 14375 for non-reclosable containers) and be tamper evident.

Further guidance on plastic components can be found in the CPMP Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03). For metal components, there is no particular guidance. The specification should state the grade of stainless steel.

Finished product (drug product)

A description of the product, together with details of the composition of the formulation should be provided in the dossier. As indicated above, details of the development and manufacture of the product are required. Where applicable, evidence of CE marking which is required by Community legislation on medical devices shall be provided. For example, this would be required for electronic cigarettes where the ‘cigarette’ device either contains cartridges of nicotine which can be replaced (*i.e.* the cigarette is for repeat use with multiple cartridges) or can be refilled with nicotine solution. Regardless of this, the device must be demonstrated to be able to consistently deliver the correct dose of nicotine during use and over the shelf life of the product. This should be borne in mind when selecting the battery for a battery-operated device. For more information on CE marking and medical device aspects of electronic cigarettes, refer to other Frequently Asked Questions.

Similarly to the active substance, the finished product should be controlled by appropriate

specifications. Controls would include ensuring the levels of nicotine meet recognised pharmaceutical standards (for example, 95.0 to 105.0 % of the declared content) and its impurities are controlled at safe levels throughout the product shelf-life.

The finished product should also comply with the requirements of the European Pharmacopoeia monograph for Preparations for Inhalation and the British Pharmacopoeia monograph for Nicotine Inhalation Cartridges. Relaxation of any test limits would require robust justification and such requests would be assessed on a case-by-case basis during the marketing authorisation application procedure. As mentioned above, the finished product must be able to consistently deliver the correct dose during use and throughout the shelf-life of the product. This may be demonstrated using the test equipment and conditions described in WHO TobLabNet Official Method SOP 1: '*Standard operating procedure for intense smoking of cigarettes*' and adapting the test equipment and conditions to suit the design of the e-cigarette. If changes are made, these should be fully explained and justified. The regime example given in BSi PAS 54115:2015[1], namely a 55 ml puff of a 3 s duration with 30 s between start of puffs, would be considered acceptable. When using such test equipment and conditions, a dose should be defined as 10 'puffs'. Alternatively, the applicant may decide to use test methodology described in a compendial text or develop their own in-house methodology.

General guidance on pharmaceutical development studies is given in the following two guidelines (available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000362.jsp& mid=WC0b01ac0580028eb2):

- ICH guideline Q8 (R2) on pharmaceutical development (EMA/CHMP/167068/2004);
- CHMP note for guidance on development pharmaceutics (CPMP/QWP/155/96).

The CHMP guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) should also be consulted, if applicable.

The CHMP guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr; available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pdf) discusses the pharmaceutical development studies which are required for inhalation products, which would include electronic cigarettes. Further information on the requirements of the finished product ('specification') is also included in the guideline.

The development studies listed in Table 4.2.1 for pressurised metered dose inhalers would normally be expected for this type of product, except for item (f) 'fine particle mass with spacer use', which would not be required. Studies into extractables and leachables should consider the metal contaminants from the manufacturing process or use of the product (*e.g.* heating element), as well as those from the plastic and rubber components. Robustness studies should also investigate resistance to biting/chewing and fire resistance.

The vaporisation products of the electronic cigarette should be studied. The potential transformation of the formulation on thermal decomposition, and the potential for the heating element and associated components (including adhesives and solder) to shed metallic and other particles on heating, warrant investigation.

Foreign particulate matter in the delivered dose should be investigated. Characterisation of individual inhalations (puffs) is expected, although it is appreciated that individual inhalations may vary depending on the individual user.

The length of time (continuous, 'normal/average' and occasional use) a charged product can be used for and the length of time to re-charge the device (full and, if applicable, partial charge) should be determined. The interchangeability of a battery operated device with different re-charging equipment should also be considered and potential risks identified and discussed, together with proposing appropriate measures to mitigate these risks.

Device functionality testing should also be performed. For example, testing whether the e-cigarette shuts off when the reservoir is empty (*i.e.* it does not continue to heat), whether any visual indicator on the e-cigarette functions as intended (*e.g.* on, off, reservoir empty) and whether the e-cigarette overheats during use.

As the design and use of the product may vary, it is not possible to itemise all the individual studies required.

What do I need for the non-clinical (safety) part of the marketing authorisation application?

With respect to safety, the toxicological consequences of heating and vaporising the formulation of nicotine and excipients (including flavourings) during the normal use of the product need to be considered. For example, particular concern has been raised in the literature about the presence of acrolein and other carbonyls such as formaldehyde and acetaldehyde that can be produced as a consequence of the thermal decomposition of glycerol and propylene glycol (*e.g.* Uchiyama *et al*

Journal of Chromatography A. 2010; 1217:4383-8). The potential transformation of the formulation on thermal decomposition, and the potential for the heating element and associated components (including adhesives and solder) to shed metallic and other particles on heating, would warrant further investigation by the applicant to assess the inhalation safety risks and to limit exposure where necessary.

The applicant should also provide a detailed safety review of all the components (*e.g.* flavourings and excipients) in the formulation from the available literature. In particular a review of the safety following inhalation exposure (including long-term exposure), maximum daily dose and target population would be relevant. If no or limited, non-clinical or clinical data exist in the public domain, the applicant should consider conducting appropriate studies in line with the ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995) and the CHMP guideline on non-clinical local tolerance testing of medicinal products (EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1*).

A toxicological evaluation of any potential extractables and leachables originating from all components of the electronic cigarette should also be provided (CHMP guideline on plastic immediate packaging materials CPMP/QWP/4359/03 and EMEA/CVMP/205/04).

What do I need for the clinical (efficacy and safety) part of the marketing authorisation application?

Ultimately the clinical data required for regulatory purposes will vary according to the dosage form. To what extent a nicotine containing product (NCP) will have an effect in a smoker depends on the concentration of nicotine in the individual’s blood (plasma) which that product will produce when inhaled.

Therefore, as a general principle, an applicant will be required to demonstrate that the plasma nicotine concentration which their product will achieve when used correctly is both efficacious and safe. This can be achieved by comparing the plasma nicotine concentration achieved in a group of volunteers with the test product to that achieved with a currently authorised form of Nicotine Replacement Therapy (NRT). This is known as a comparative bioavailability study. The comparator product should be chosen on a like-for-like basis, *e.g.* an inhaled product should ideally be compared to another inhaled product.

Studies of this nature usually take the form of a randomised crossover design. Further details of the design of suitable comparative studies can be found in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, available at

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf).

An appropriate number of healthy volunteer smokers are randomly assigned to one of two groups: test product or reference product. Each subject will use their allocated product in a standardised manner and their blood will be sampled periodically. There will then be a break period to allow the nicotine in the plasma to be fully cleared from the body before the groups 'cross-over' and the study is repeated. Their blood samples will be analysed for nicotine content and the concentrations measured will be compared to allow the comparative pharmacokinetics (maximum concentration, total exposure) to be determined. If the applicant can show that the two plasma concentrations are similar over a given time period, then one can infer that the two products are likely to be similarly efficacious and safe.

Furthermore, the above study could usefully include a pharmacodynamic (PD) assessment (*e.g.* visual analogue scale (VAS) of craving for nicotine) in order to supplement pharmacokinetic data.
In addition to the above, full supportive data from the published literature will be required to demonstrate safe and efficacious levels of nicotine for each claimed indication and to show how the product can be compared to those data.
For the presentation of biopharmaceutical and bioanalytical data, Appendix IV of the guideline on investigation of bioequivalence should be consulted.

The MHRA provides a formal Scientific Advice service, details of which can be found at: https://www.gov.uk/medicines-get-scientific-advice-from-mhra
Applicants are advised to ask the MHRA for specific scientific advice when designing the studies for their data package.

The licensed indications for e-cigarettes should always include the 'quit' indication, *i.e.* 'to aid smokers wishing to quit or reduce prior to quitting'. It is also preferred to include the 'reduce harm' indication, *i.e.* 'to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them'. It is not acceptable to license the product with only the 'reduce harm' indication.

Please explain more about how the medical device regulations affect my marketing authorisation application?

This will depend on the design of the electronic cigarette.

Products that are intended to administer a medicinal product may be regulated as either medical devices or as medicinal products, depending on the nature of the individual product.

Where the device and the medicinal product form a single integrated product designed to be used exclusively in the given combination and which is not refillable the whole product will be regarded as a medicinal product and require a marketing authorisation, although the 'device' elements will need to meet the relevant essential requirements of Annex 1 of the medical device Directive 93/42/EEC.

Where the device and the medicinal product are separate entities and the device may be re-used or re-filled (for example an electronic cigarette that has separate cartridges) then the device will need to be CE marked as a medical device under Directive 93/42/EEC.

Thus in addition to a marketing authorisation, CE marking of the administration part of the electronic cigarette as a medical device may be required.

Two or three piece electronic cigarettes or refillable one piece electronic cigarettes

The MHRA considers the part of the electronic cigarette containing the battery together with any associated charging accessories to be a Class IIa medical device as an active therapeutic medical device.

This means that a separate application needs to be submitted to a duly designated Notified Body in order to get the device elements of the electronic cigarette assessed and then CE marked. Further information about Notified Bodies can be found within the Medical Devices section of the MHRA website at (https://www.gov.uk/government/publications/notified-bodies-for-medical-devices).

Although it often contains the heating element, the cartridge containing the nicotine solution is considered to be part of the medicinal product. Note that the heating element section is required to comply with the relevant essential requirements in Annex 1 of the Medical Devices Directive 93/42/EEC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF) and evidence of this will be required. It is assumed that the safety and performance of the cartridge will also be examined by a Notified Body at the same time as the battery, since the two are intrinsically linked. Thus the company needs to consider the interaction between the 'device' and the heating element within the cartridge.

One piece disposable electronic cigarettes

It is currently possible to submit a marketing authorisation application (MAA) without any submission to a Notified Body, but documentation would need to be supplied demonstrating that the medical device aspects of the product comply with the relevant essential requirements in

Annex 1 of the Medical Devices Directive 93/42/EEC in relation to the safety and performance of the device (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF). However, it should be noted that there is a proposal to amend the medical device legislation such that the device components need to be the subject of a medical device CE mark or have undergone an assessment by a Notified Body as though it was going to be CE marked.

What is the cost of a marketing authorisation application?

As the licensing fees are reviewed annually, see the following link for current pricing: https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees
An electronic cigarette would be expected to be a so-called complex application as it is likely to be submitted under Article 10(3).

Once approved, periodic fees would also be due.

The fees for any medical device requirements are set by the individual Notified Body and would be in addition to any licensing fees.

After submitting my marketing authorisation application, how long does it take to process?

From receipt of a valid UK national marketing authorisation application (MAA), the MHRA aim to assess the application within 100 calendar days. There is usually a list of outstanding points which the applicant then needs to resolve and the timings from thereon will in part be determined on the speed of the applicant's response and the number of issues to be resolved. The MHRA aims to assess the responses, to any outstanding points, within 30 calendar days. The application process would normally take up to 210 days (excluding the time taken to provide further information or data required).

Will separate marketing authorisations be needed for an electronic cigarette and packs of refill cartridges?

No, if the refill cartridge pack contains the same cartridge(s) provided with the electronic cigarette, then it would be permissible for the initial pack (electronic cigarette, cartridge, charger) and refill cartridge pack to be two presentations on the same marketing authorisation.

Will separate marketing authorisations be needed for disposable and rechargeable versions of an electronic cigarette?

Yes, separate marketing authorisations will be needed.

If my electronic cigarette contains no nicotine do I need a marketing authorisation?

If the electronic cigarette does not contain nicotine or any other active substance, then it is not considered a medicinal product under the definitions of Directive 2001/83/EC, as amended. Consequently, a marketing authorisation is not required.

If data can be provided to show that the non-nicotine containing product can be used to treat specifically nicotine addiction, then the product can be considered to be a medical device under the Medical Device Regulations. Consequently, it must be registered with a Notified Body and CE marked. The medical claim would be limited to the treatment of nicotine addiction.

If I want to have more than one strength of electronic cigarette, do I need more than one marketing authorisation?

Yes, a separate marketing authorisation is needed for each strength.

If I want to have more than one flavour of electronic cigarette, do I need more than one marketing authorisation?

Yes, a separate marketing authorisation is needed for each flavour.

Do I need a marketing authorisation if my product is an e-liquid or nicotine liquid only?

If a medical claim is made, it would be possible to apply for a MA for the nicotine liquid only. However, it would be necessary to demonstrate that the liquid is safe and effective in specified electronic cigarettes or other vaporising devices. Furthermore, such electronic cigarettes or vaporising devices would need to be registered as medical devices and carry a CE marking. As the respective manufacturer may alter their product over time, there would need to be an agreement with the manufacturer that all relevant changes to their electronic cigarette or vaporising device are notified to the nicotine liquid manufacturer/supplier, as well as the Notified Body. The applicant for a nicotine liquid MA would need to consider the potential for misuse (including overdose) of the liquid.

What requirements are there relating to manufacture, import, export and wholesaling?

The MHRA has a manufacturing and wholesaling section on its website dealing with these activities:
https://www.gov.uk/medicines-medical-devices-blood/manufacturing-wholesaling-importing-exporting-medicines

The requirements will vary depending on where the different functions are performed.

Sites which are involved in the manufacture of the medicinal product will need to be approved by an EU/EEA medicines competent authority. Sites which are involved in the manufacture of the medical device will be approved by an EU/EEA Notified Body. Good liaison between the different parties is essential. Likewise, clarity of the different operations performed by the different sites is required. If the same site is involved in both medicinal product and medical device manufacture, then ensure that the requirements of EU GMP (Good Manufacturing Practice) and the Medical Device directive (Quality System; ISO 13485) are covered. The company should do a gap analysis to consider areas not covered by GMP but that are relevant to the Quality system of the device.

Sites which are only involved in the manufacture of the medical device will need to be inspected by an EU/EEA Notified Body. Further information on Notified Bodies can be found in the Medical Devices section of the MHRA website:
https://www.gov.uk/government/publications/notified-bodies-for-medical-devices

The following information relates to the medicinal product:

The product is manufactured in UK, EU/EEA or third country for sale in UK
If the product is manufactured in the UK, the manufacturer will require a manufacturer's licence that authorises the manufacture/assembly, quality control testing and batch release of this type of product. The manufacturer will require a Production Manager, Quality Control Manager and Qualified Person. The manufacturer will have to comply with GMP.

If the product is manufactured in a third country and imported into the UK for use in the UK, the importer will require a manufacturer's licence that authorises the import of this type of product. The importer will need a Qualified Person (to authorise batch release) and will have to comply with GMP, which will include the quality control testing of the product within the EU/EEA. The

manufacturing site in the third country will also need to be inspected (by the UK inspectorate unless already inspected by an EU/EEA Competent Authority) to ensure compliance with GMP.

If the product is manufactured in the EU/EEA, then the manufacturing site will need to be inspected (by an EU/EEA competent authority) to ensure compliance with GMP. If the site is only used for nicotine containing products, then it may be that the concerned EU/EEA member state does not consider the product to be a medicinal product, in which case the applicant is advised to consult with the MHRA.

If the product is subsequently distributed by way of wholesale dealing in the UK, the distributor will need a wholesale dealer's licence that authorises the wholesale distribution of such a product. The holder of a wholesale dealer's licence requires a Responsible Person and must comply with Good Distribution Practice (GDP).

The licences can only be obtained following satisfactory inspection by the UK Inspectorate. They should be consistently reviewed against current GMP/GDP practices and will be re-inspected to ensure ongoing compliance at regular intervals. Further details of inspections and the costs associated can be found at: https://www.gov.uk/medicines-medical-devices-blood/good-practice

The product is manufactured in the EU/EEA or a third country and imported into the UK for export to a third country (It is not for sale in the UK)

A company importing a medicinal product for subsequent export to a third country will require a Wholesale Dealer’s Licence.

It is recommended that if the product is not going to be marketed in the UK then the product should not enter UK territory but should be supplied direct to the intended market.

The product is manufactured in the UK only for export into the EU/EEA or a third country

It is likely that a manufacturer’s licence would be required although given the current legislation and potential review a definitive position at this time cannot be provided. If an importing EU/EEA country considers the product to be a medicinal product, then a manufacturer’s licence would be required. For other countries, the MHRA should be consulted for the latest information should the manufacturer be in this situation.

Are there any labelling and packaging requirements I need to be aware of?

Title V of Council Directive 2001/83/EC (the medicines directive) includes details of the information which must be included on the labelling of the medicine along with the information required in the patient information leaflet which will need to be included in the pack (unless all the necessary information is on the outer pack). Additional guidance is available from the MHRA website: https://www.gov.uk/medicines-packaging-labelling-and-patient-information-leaflets

There is a Best Practice Guideline on the Labelling and Packaging of Medicines which describes in detail how the labelling requirements are applied in practice. https://www.gov.uk/government/publications/best-practice-in-the-labelling-and-packaging-of-medicines

A similar document exists for the preparation of the patient information which accompanies all medicines. Patient information must be subject to user testing with target patient groups to make sure it is clear and easy for people to use. https://www.gov.uk/government/publications/best-practice-guidance-on-patient-information-leaflets

In addition to the statutory information which must appear on the labelling and in the patient information leaflet, additional information can be included provided it is consistent with the marketing authorisation, is considered useful for the patient/consumer and importantly is not promotional.

MHRA offers scientific advice meetings to applicants to discuss with applicants how best to display the information on the pack and in the patient information leaflet so as to ensure regulatory compliance. Detailed information is at https://www.gov.uk/medicines-get-scientific-advice-from-mhra

What are the advertising requirements I need to be aware of?

The promotion of all medicines must comply with Part 14 of the Human Medicines Regulations 2012.

An advertisement for a medicine must:

(1) comply with the particulars listed in the Summary of Product Characteristics (SmPC);

(2) encourage the rational use of the product by presenting it objectively and without exaggerating its qualities; and

(3) not be misleading.

Advertisements directed at the public should be presented in such a way that it is clear that the message or material is an advertisement and that the product being advertised is a medicine. The advert must include the name of the medicine and the common name where the product contains only one active ingredient. They must also include one or more indications for use of the product and an invitation to read the label. There are also a number of specific requirements including prohibitions on advertising to children under 16, supplying free samples and celebrity or healthcare professional endorsement.

Separate requirements apply to advertising to healthcare professionals and other suppliers of medicines.

Medicinal claims may not be made for unlicensed medicines (see “If my electronic cigarette contains no nicotine do I need a marketing authorisation?” for further information). It is also prohibited to promote a medicine undergoing assessment but yet to receive a marketing authorisation.

Further guidance in all these areas can be found in the MHRA Blue Guide, Advertising and Promotion of Medicines in the UK.

The control of medicines advertising in the UK is based on a long-established system of self-regulation. The statutory powers of the MHRA, acting on behalf of Health Ministers, underpin and support this system. For OTC medicines you may also find it helpful to consult the guidance provided by the Proprietary Association of Great Britain (PAGB) and the Advertising Standards Authority (ASA) and their Committees of Advertising Practice.

Does a retailer need to be a pharmacy?

If the licence granted permits the product to be sold and supplied as a General Sales List (GSL) medicine then the retailer does not need to be a pharmacy. People can buy general sale medicine packs from retail outlets such as corner shops and supermarkets, and these are not limited to pharmacies. These medicines are also available for self-selection in pharmacies.