

# Interim Report of the Review of Unlicensed Medicines

## Review of UK regulatory arrangements established under Article 5.1 of European Directive 2001/83/EC

### *Summary*

This interim report outlines progress made on the review of UK regulatory arrangements established under Article 5.1 of Directive 2001/83/EC and seeks feedback on emerging ideas for reform. Art 5.1 contains a derogation allowing Member States, within defined limits, to establish national arrangements for certain products that would otherwise be covered by the requirements of the Directive. Accordingly, UK Regulations exempt from the need for a marketing authorisation a relevant<sup>1</sup> medicinal product which is provided to fulfil a “special need” and in response to a bona fide unsolicited order formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct personal responsibility.

The Review of Unlicensed Medicines was established in 2007 and is overseen by a Steering Group chaired by the MHRA and also comprising the Department of Health, the National Patient Safety Agency, the NHS Purchasing and Supply Agency, and representatives of the three devolved administrations. This interim report is the second consultative document produced by the Review. It follows up the concept paper issued by the MHRA in February 2008 and in doing so reflects the subsequent constructive feedback and dialogue on that first paper.

The objectives of reform are:

#### ***Objectives of reform of UK regulatory arrangements established under Art 5.1 of Directive 2001/83/EC***

- Clinicians should have the ability in appropriate circumstances to exercise their professional judgement to commission the supply of an unlicensed medicine to meet the special needs of an individual patient
- Public health protection should be improved
- There should be clear responsibility and accountability for protecting the safety and rights of patients

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<sup>1</sup> A relevant medicinal product is one that is subject to the provisions of Directive 2001/83 EC as amended.

- Regulatory safeguards should meet the principles of better regulation: proportionality, targeting, consistency, transparency and accountability
- Arrangements should complement and not undermine the wider system for licensing of medicines

To meet these objectives the Review has identified three main themes:

- **The importance of the wider context in which the prescriber takes a decision that an unlicensed medicine is needed to meet the special needs of an individual patient.** The report emphasises that effective use of Art 5.1 arrangements in the interests of patient care depends on a range of parties. The formal requirements of medicines legislation are only one of a number of factors in achieving the desired policy outcome. Full recognition should be given to the positive combined effect that can be achieved through: effective prescribing initiatives, clinician compliance with existing professional guidance, continuing enhancements in the implementation of governance in the health service, sharing of good organisational and professional practice, as well as updated medicines regulatory arrangements. Continuing improvements in the availability of information about the operation of medicines regulation under Art 5.1 can considerably enhance the targeting of wider initiatives relating to safe and effective prescribing undertaken collaboratively by other interested parties. It is also likely that a historic lack of transparency in the arrangements has encouraged fragmentation of demand and made it difficult for companies to identify where there would be sufficient demand to justify application for a licensed product
- **Specific proposed changes to the regulatory requirements for unlicensed medicines supplied under Art 5.1.** These affect principally quality standards, patient information, and pharmacovigilance. The main aim of possible reforms in this area would be to ensure a more systematic approach to public health protection
- **Possible structural reform of the regulatory arrangements by which operators are permitted to manufacture or import unlicensed medicines under Art 5.1.** The aim here is to achieve consistency between regulatory arrangements for UK manufacture and for import; to improve public health protection; and, overall, to follow principles of better regulation. At this stage a preferred option for structural reform is provisionally identified.

The interim report notes that this Review also needs to be considered in the context of other aspects of medicines legislation. For example, changes in regulatory requirements relating to one category of unlicensed medicine can

create incentives for activity to be channelled into other regulatory categories of licensed or unlicensed medicines. These possible knock on effects will be considered further, as more specific proposals are developed.

The Steering Group hopes that, in the light of this interim report, comments and feedback will be submitted by interested parties in particular on:

- How improved medicines regulatory arrangements under Art 5.1, including greater transparency about the operation of the scheme, can facilitate and encourage initiatives by other parties beyond the MHRA to ensure safe and appropriate usage of unlicensed medicines supplied under these arrangements
- Specific proposals for changes to the regulatory requirements
- Outline proposals for reform of structural arrangements under which permission to manufacture/import unlicensed medicines under Art 5.1 is granted. However, there is currently insufficient information about the likely regulatory impact of structural reform, and so feedback is sought. The MHRA intends to undertake a data gathering exercise to help in assessing the feasibility of the proposal.

## ***The Interim Report***

### 1. Introduction

1.1 The purpose of this interim report is:

- To summarise progress made on the Review of Unlicensed Medicines
- To explain the direction of thinking of the Review
- To seek feedback on emerging ideas for reform, including specific information on the impact of an option that is under consideration for a possible structure for reformed regulatory arrangements.

### 2. Background

*Current UK regulatory arrangements under Article 5.1 of Directive 2001/83/EC*

- 2.1 UK Regulations<sup>2</sup> exempt from the need for a marketing authorisation a relevant medicinal product which is provided to fulfil a “special need” and in response to a bona fide unsolicited order formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct personal responsibility.
- 2.2 The requirements for operating under this exemption are summarised in MHRA’s Guidance Note 14: *The supply of unlicensed relevant medicinal products for individual patients*. In brief, where manufacture or assembly of “specials” takes place in the UK the manufacturer or assembler of the product must hold a manufacturer’s “specials” licence granted by MHRA on behalf of the Licensing Authority. There are various other requirements, for example the product must comply with any relevant pharmacopoeial standards; and written records of manufacture/assembly and supply must be kept for at least 5 years.
- 2.3 In the case of importation into the UK, the importer must hold a wholesale dealer’s licence (for import from the EU/EEA area) or a manufacturer’s specials licence (for import from a third country – i.e. from outside the EU/EEA). There is a requirement to notify MHRA 28 days in advance of each importation and the quantity to be imported must not exceed 25 single administrations or 25 courses of treatment where the amount imported is sufficient for a maximum of 3 months’ treatment. The MHRA on behalf of the Licensing Authority is able to object to importation on grounds of non-compliance with the regulations, or safety. Safety concerns include known adverse effects of the product; those arising from product quality such as compliance with Good Manufacturing Practice (GMP) by the manufacturer or other

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<sup>2</sup> The Medicines for Human Use (Marketing Authorisation Etc) Regulations 1994 SI 1994/3144

known quality issues; and efficacy where there are safety implications e.g. an ineffective vaccine may raise serious safety concerns. Again, there are various other requirements, including one for record keeping.

- 2.4 A “specials” manufacturer, importer or wholesaler may advertise the fact that he can provide this service; however, he cannot advertise a specific product.
- 2.5 A special need for an unlicensed medicine may arise in a range of circumstances. For example:
- There is no equivalent licensed medicine available in the UK to meet the special need of the patient
  - A licensed medicine is available but not in a suitable formulation / presentation (eg in oral liquid form in paediatrics) for the patient in question
  - The equivalent licensed medicine is likely to be unavailable for a significant period (eg because the manufacturer is experiencing difficulties)
  - For commercial reasons either the licence for a product has been relinquished or is maintained but without the product being marketed.

#### *Reasons for a Review*

- 2.6 The main reasons for launching the Review were as follows:
- There is **inconsistency** between the regulatory mechanisms that apply where the unlicensed medicine supplied under Art 5.1 arrangements is domestically manufactured and where it is imported. The main areas of discrepancy are:
    - **Safety:** the MHRA can object on grounds of safety where it is proposed to import a product; however, the MHRA has no immediate powers to prevent the domestic manufacture of an identical product on safety grounds. The possibility exists of making an Order under section 62 of the Medicines Act 1968 to prohibit or restrict on safety grounds the sale, supply or importation of particular medicinal products or types of medicinal products. However, making ad hoc banning orders is not something which it is desirable or feasible to undertake on a frequent basis
    - **Special needs:** the MHRA can object to the procurement of an unlicensed medicine, on the basis that a suitable licensed product exists. However, while an opportunity to make such an objection is built into current arrangements for notification of imports, in the case of domestic manufacture the MHRA would not easily be in a position to raise an objection unless the matter was brought specifically to the Agency’s attention

- There are weaknesses in the **information** available about the usage of the arrangements, which makes **monitoring** difficult. Information about “specials” manufactured in the UK is sparse. In contrast, more information is available about notifications submitted to MHRA under the import notification scheme. However, this latter information also serves to raise questions as to how well the scheme is meeting its intended purpose. **Annex A** shows the number of import notifications received by MHRA in the period 2000 to 2008, and outlines some factors which may have contributed to volatile patterns
- **Targeting** of regulatory arrangements could be improved. There is a limit on the volume of products per notification under the import notification scheme. However, any purpose this restriction could serve as a way of limiting use of the scheme to genuine cases of special need is largely nullified because the legislation does not restrict multiple notifications.

### 3. The Review

- 3.1 In October 2007 the Minister for Public Health agreed that a Review of Unlicensed Medicines should be carried out, led by the MHRA.
- 3.2 The terms of reference of the Review are:

#### **Terms of Reference**

- ***To review the regulatory arrangements operated in the UK under national legislation flowing from the provisions of Article 5(1) of Directive 2001/83/EC under which:***

***“A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.”***
- ***To make recommendations as to how arrangements in the UK flowing from Article 5(1) can most effectively enable patients’ special needs to be met. This includes supporting the delivery of safe and effective health care whilst neither unjustifiably restricting clinical freedoms nor undermining the wider medicines regulatory system.***

- 3.3 It was agreed that the Review should follow the principles of better regulation and in particular should examine a wide range of options as to the type and extent of regulatory arrangements that may enable the desired policy objectives to be met.

3.4 The scope of the Review was restricted specifically to UK arrangements under Art 5.1 of Directive 2001/83/EC – a major topic in its own right. This meant that the following were among issues outside the remit of the review:

- Off label (also known as “off licence”) prescribing of medicines with a marketing authorisation valid in UK
- Investigational medicinal products used in clinical trials
- Medicines exempt from licensing requirements under provisions of the Medicines Act 1968, for example, the section 10 exemption for preparation in a pharmacy, by or under the supervision of a pharmacist, in accordance with a prescription
- The combination (mixing) of medicines in palliative care as detailed in MHRA consultation MLX 356 (which closed 27 February 2009).

We recognise that some of these activities/products raise issues of equal concern and several are being pursued in other fora.

3.5 The Review also is not itself pursuing other action to increase the availability of regulated medicines on the UK market. However, the MHRA will be reviewing the scope for provisions to enhance the availability of medicines for children under a separate initiative.

3.6 The Review was overseen by a Steering Group comprising representatives of:

- The Medicines and Healthcare products Regulatory Agency
- The Department of Health
- The National Patient Safety Agency
- The NHS Purchasing and Supply Agency
- The Scottish Government
- The Welsh Assembly Government
- The Northern Ireland Assembly

MHRA provided chair and secretariat for the Review Steering Group.

3.7 On 28 February 2008 the MHRA issued a consultative concept paper on the Review (attached at **Annex B**) and invited written comments by 30 June 2008. 53 written responses were received. The MHRA also held consultative meetings with interested parties and undertook a number of site visits.

#### 4. Towards reform

##### *Feedback received in the early part of the Review*

4.1 The Steering Group was encouraged by the extent of constructive engagement in the Review by interested parties. The results of this

early work have been used to inform the Review and shape its direction of progress. The comments and discussions thus far have indicated that there is a considerable degree of common ground among a range of interested parties.

4.2 The following propositions were among those attracting considerable support:

- There is a clear need for reform of UK Art 5.1 arrangements
- There is strong case for much greater alignment of regulatory arrangements between those applying to domestic manufacture and to imports
- The existing import notification scheme does not fully meet principles of better regulation
- Regulatory requirements could be better targeted to improve public health protection
- There is scope in some areas to improve understanding of the clinician's responsibilities when using Art 5.1 arrangements
- Improved and more transparent regulatory arrangements including better information on products available could facilitate rational prescribing, and in turn, continuing enhancement in the effective implementation of clinical governance could lead to usage of Art 5.1 arrangements becoming increasingly better aligned with the intended purpose of the scheme.

4.3 A number of commentators pointed out that changes in Art 5.1 arrangements could have knock on effects for other areas of regulation. In particular some argued that the scope of the Review should be extended to cover the section 10 "pharmacist's exemption". It was noted that changes to the regulatory requirements under the Art 5.1 arrangements could give rise to an incentive for activity to migrate to the section 10 exemption. Furthermore, it was noted that operators were not always clear on the distinction between the two exemptions.

4.4 As indicated in the concept paper, we have been clear from the outset that there is a possibility that changes in Art 5.1 arrangements could affect behaviour and serve as an incentive for activity to transfer to, or from, other exemptions. We intend as the emerging findings of the present Review of Unlicensed Medicines are further developed to make an assessment of any specific areas of work needed to ensure policy is consistent across relevant exemptions. Potentially significant reforms of the kind discussed in this report need to be undertaken with care. We would therefore also invite commentators on this interim report to highlight any other areas where the possible reforms discussed could have adverse knock on effects, for example in the form of unintended behavioural consequences affecting clinical practice.

4.5 It is also important to bear in mind that work is in progress to consolidate and review the Medicines Act and secondary legislation.

The project consists of two strands running, where possible, in parallel. Strand 1 will focus on the consolidation of existing national legislation; Strand 2 will focus on the potential simplification of legislation. There will be some overlap but the consolidation stage will not introduce any significant new amendments. The project will cover all national legislation governing medicines for human use, including homoeopathic and herbal medicines. European Community medicines legislation will be included within the scope of the project; however, MHRA will not be able to make any substantive changes to provisions implementing Community law other than where the latter contains national discretions. Therefore, in terms of possible reforms and simplification, the focus will be on national legislation.

- 4.6 The MHRA has recently published an informal consultation to seek views from a range of stakeholders about what improvements, clarifications or simplifications would be beneficial and what our priorities might be. Responses to that consultation will also help us to put emerging findings of the Review of Unlicensed Medicines into the context of further potential reviews of legislation (i.e. under Strand 2) so that future discussions can be consistent and properly targeted. There will of course be additional opportunities for interested parties to contribute as the MHRA will be undertaking a number of formal consultations as the project progresses.

#### *Effective use of Art 5.1 arrangements*

- 4.7 Before looking at the specifics of possible reforms it may be helpful to consider the wider context in which individual prescribing decisions are made. This affects the way Art 5.1 arrangements are used in practice.
- 4.8 We have received feedback, in particular from pharmacists, that in some therapeutic areas clinicians, in aggregate, may be using Art 5.1 arrangements to commission an unnecessary variety of a limited number of products. One well publicised example is the use of a large number of different preparations of captopril oral liquid for paediatric patients referred to and discharged by a group of cardiac centres. This view is also supported by data from the import notification scheme. An example would be where 2 and 3 mg tablets are licensed in the UK, but an importer notified for import of 2.5 mg tablets. Also, in the UK, Concerta XL methylphenidate 18 mg modified release tablets are available as a licensed product, but some physicians prescribe Ritalin SR20 20 mg modified release tablets which are then notified for import. In some cases, minor variants on a product may have a clinical justification, but in others they may owe more to custom and practice. This situation will tend to have the undesirable effects of:
- Increasing the possibilities for medication errors
  - Increasing the potential for variability in clinical effect and for adverse reactions

- Making quality control more difficult due to the small scale of production
  - Making it difficult for companies to identify whether there is sufficient demand to apply for a marketing authorisation, and hence hindering the effective operation of the market in licensed medicines
  - Pushing up the price of some medicines.
- 4.9 We have been told that rationalisation of demand may well be possible in some therapeutic areas without any substantive diminution in prescribers' ability to meet the clinical needs of patients. While it is not the role of medicines' regulation to achieve such rationalisation, effective and transparent regulation can help to facilitate the process.
- 4.10 Where there may be sufficient demand for a licensed product it is clearly in patient interests that this route should be pursued. Licensed medicines meet assured standards of safety, quality and efficacy, while the standards required for unlicensed medicines will inevitably be more limited in a number of areas. To take quality as an example, currently regulatory arrangements aim to ensure that "specials" meet standards of good manufacturing practice (GMP), and this is an important safeguard. However, it does not equate to an assessment of the whole pharmaceutical development of a licensed product, including key attributes such as the design of the product and the extent to which the drug is released into the body by the dosage form (bioavailability).
- 4.11 We believe that in addressing the task of ensuring that an Art 5.1 scheme meets its intended purpose, the role of clinical governance and other professional guidance is no less important than the kind of structural reforms to Art 5.1 arrangements discussed at section 5 of this report.
- 4.12 An example of good practice is the recent guidance by The British Association of Dermatologists: "*Preferred Unlicensed Dermatological Preparations (Specials) 2008*". The guidance is designed to rationalise use of "specials". The list of preferred preparations is intended to be updated as circumstances change and there is a process for assessing whether items should be added to the list. There may be scope for other professional groupings to adopt equivalent guidance. The MHRA would wish to work with such initiatives.
- 4.13 The pharmacy White Paper, "Pharmacy in England: Building on Strengths, Delivering the Future", also identifies the need to rationalise the range of "specials" used by NHS hospitals. The Department of Health has commissioned the National Advisory Board for NHS Hospitals Medicines Manufacturing and Preparative Services to take action on this matter. This will also help build capacity to underpin the delivery of NPSA recommendations on safe medication practices.
- 4.14 A related issue is that of risk assessment of specific unlicensed medicines. The prescriber has the responsibility to balance safety and

efficacy issues in assessing whether to prescribe an unlicensed medicine to meet the special needs of his/her patient. However, such decisions are not generally made in isolation and prescribing clinicians will often have help, for example through formularies, guidance and advice of other healthcare professionals, eg pharmacists, in a multidisciplinary setting. From feedback received we believe there may be some duplicative risk assessment in the NHS concerning use of particular unlicensed medicines. There may be scope for collaboration between different health service and professional groupings.

4.15 It is necessary to distinguish the risk assessment made by the clinician from that which is currently undertaken by the MHRA in relation to import notifications. Where prospective imports are notified to the MHRA under the current regulations, the MHRA performs an assessment of each notification. In addition to ensuring that the notification complies with the regulations, including the existence of a special need for the unlicensed product for the treatment of individual patients that cannot be met with available licensed products, a risk assessment against known safety issues is performed. This risk assessment is a negative assessment and will only consider known safety aspects of the drug, including the safety implications of known quality issues or, only where relevant to safety, efficacy. Objections will only be raised to importation where there are known prohibitive safety concerns. This is not a positive assessment of a dossier of data such as applied to a Marketing Authorisation applications, but only considers issues already in the public domain or otherwise already known to the MHRA.

4.16 For example, until June 2008, no licensed thalidomide product was available in the UK and unlicensed product had to be manufactured or imported. In June 2008, a licensed product became available in the UK (Thalidomide Pharmion 50mg capsules). In view of the well known serious safety concerns with thalidomide, the MHRA objects to notifications for importation of unlicensed thalidomide products unless there are strong clinical reasons for the use of an unlicensed product. UK manufacturers of unlicensed thalidomide products are expected by the MHRA to adopt a similar position.

## 5. Reform of UK Art 5.1 arrangements

### *Objectives of possible reform*

5.1 The Review is seeking to meet the following objectives:

#### **Objectives of reform**

- Prescribers should have the ability in appropriate circumstances to exercise their professional judgement to commission the supply of an unlicensed medicine to meet the special needs of an individual patient

- Public health protection should be improved
- There should be clear responsibility and accountability for protecting the safety and rights of patients
- Regulatory safeguards should meet the principles of better regulation: proportionality, targeting, consistency, transparency and accountability
- Arrangements should complement and not undermine the wider system for licensing of medicines

### *The role of the prescribing clinician*

5.2 The prescribing clinician's role and responsibility is at the heart of Art 5.1, as it made clear in the legislation itself. GMC guidance (2008): *Good Practice in Prescribing Medicines* sets out points of particular relevance where doctors prescribe unlicensed medicines. The guidance states that the doctor must:

- *Be satisfied that an alternative licensed medicine would not meet the patient's needs*
- *Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy*
- *Take responsibility for prescribing the unlicensed medicine and for overseeing the patient's care, including monitoring and any follow up treatment*
- *Record the medicine prescribed and, where the doctor is not following common practice, the reasons for choosing this medicine in the patient's notes.*

5.3 The position of the patient requires careful consideration in a situation where an unlicensed medicine is prescribed. The 2008 GMC guidance: *Consent: patients and doctors making decisions together* does not seek to give detailed guidance covering the multiplicity of different scenarios that may be encountered where informed consent may be a particular issue, but rather sets out broader principles on which good clinical decisions should be based. There is a particular focus on decision making in the context of investigations and treatments. Among the many relevant points in this guidance are:

- *The doctor must ....give the patient the information they want or need about each option.....the potential benefits, risks and burdens, and the likelihood of success of each option .....whether a proposed investigation or treatment .....is an innovative investigation or treatment designed specifically for their benefit*
- *The doctor uses specialist knowledge and experience and clinical judgment, and the patient's views and understanding of their*

*condition, to identify which investigations or treatments are likely to result in overall benefit for the patient*

- *Clear information about the risks ....presented in a way patients can understand can help them make informed decisions. The amount of information about risks that you should share with patients will depend on the individual patient and what they want or need to know. Your discussion with patients should focus on their individual situation and the risk to them*
- *A doctor undertaking investigations or treatment is responsible for discussing this with the patients. In circumstances where delegation takes place the doctor ....remains responsible for making sure that the patient has been given enough time and information to make an informed decision, and has given their consent, ...before the investigation or treatment begins.*

- 5.4 We have received feedback from various quarters that in some instances, doctors (especially in some hospital settings) may not always be aware that they are prescribing an unlicensed medicine. This situation may be occurring where it is the pharmacist who raises the issue of a need for an unlicensed product in the light of the non availability of a licensed product that may have been envisaged by the prescriber. If some prescribers are on occasions unaware that an unlicensed medicine is to be supplied this indicates weaknesses in compliance both with the GMC 2008 guidelines and with the terms of Art 5.1 itself.
- 5.5 The Royal Pharmaceutical Society of Great Britain fact sheet on the use of unlicensed medicines in pharmacy advises that..*a pharmacist should bring to the attention of the patient that the product does not have a marketing authorisation...As far as possible this should be done without undermining the patient's confidence in either the prescriber or the prescribed medicine.* This is an important safeguard for patients – but we believe it is not intended to detract from the key role of the prescriber.
- 5.6 In order to avoid the unacceptable situation that a prescriber is unaware of having prescribed an unlicensed medicine, the NPSA highlights the key importance of effective, early communication – multidisciplinary where appropriate – concerning the possible supply of an unlicensed medicine. Effective use of Drugs and Therapeutics Committees and other multidisciplinary committee to improve communication and involvement of clinicians is recommended. An approach based on good communications should not detract from the prescribing clinician's responsibility but, rather, help to ensure that s (he) is acting with suitable professional input from colleagues.
- 5.7 Overall, we believe the way ahead in achieving effective patient awareness and involvement in decision making over the possible prescribing of an unlicensed medicine lies primarily in the effective

implementation of good practice and professional guidance rather than through changes in medicines regulation.

- 5.8 Nonetheless, one other option could be considered to underpin communications between healthcare professionals in the event that approaches via guidance and spread of good practice did not deliver the intended outcome. This would be the introduction of a specific legislative requirement for a prescriber to state that they are prescribing an unlicensed product. However, we believe that it would be premature to pursue this option unless and until it was clear that the issue could not be resolved in other ways.

*Framework for deciding which product should be supplied under Art 5.1*

- 5.9 Art 5.1 represents a derogation from the normal requirement set out in European Directive 2001/83/EC that industrially produced medicines placed on the market should have a marketing authorisation based on meeting defined regulatory standards for safety, quality and efficacy. In order to ensure that the UK operation of the derogation is defensible, and in order to protect patients, it is important that users of UK Art 5.1 arrangements take a systematic approach when considering the possibility of supplying a product under these arrangements.
- 5.10 In this context, the key questions to be asked are:

**Key questions**

- Is there a suitable and available product licensed for use in the UK which would meet the patient's needs? If not:
- Is there a suitable and available product unlicensed in UK, but licensed elsewhere in the EU? If not:
- Is there a suitable and available unlicensed product made to EU or equivalent GMP standards?

- 5.11 We believe that it would be a helpful outcome for the Review if this position is clearly stated and publicised. However, first it is necessary to address a complexity arising from a weakness in the present regulatory arrangements. Where products are imported under Art 5.1 there is currently no regulatory requirement for patient information to be translated into English.
- 5.12 This can, currently, pose a difficult dilemma, for example, as to whether patient safety is better served by (a) supply of a medicine that is not manufactured under EU standards of GMP but is accompanied by patient information in English or (b) supply of a medicine that may fully meet regulated standards elsewhere in the EU but has patient information only in another language. The issue of patient information is addressed at paras 5.17 – 5.21.

### *Quality standards*

- 5.13 During the early stages of the Review the point was made by interested parties that the need for products supplied under Art 5.1 can vary considerable in kind, from the occasional and sporadic – involving very low volume – to large volume, sometimes with regular and predictable batch production.
- 5.14 A wider range of the quality controls normally associated with licensed products, notably stability testing, retention samples and sterility testing, become more realistic where there is batch production of products on a significant scale. Rationalisation of commissioning of unnecessary variants of the same product under Art 5.1 could enable a higher proportion of products to be subject to a more comprehensive range of quality standards.
- 5.15 Monographs of the British Pharmacopoeia (BP) define quality standards for medicines and medicinal substances in terms of analytical methods and assessment. BP monographs are legally enforced in the UK through the Medicines Act 1968. Where a BP monograph for a medicinal product exists, products sold or supplied in the UK must comply with that monograph. The BP has initiated a programme of elaboration of monographs for unlicensed medicines. When published these are mandatory quality standards for unlicensed medicines.
- 5.16 The MHRA's GMP Inspectorate is currently developing guidelines covering expectations for this category of products.

### *Patient Information*

- 5.17 Patient information requirements should be clarified and strengthened. We propose that all unlicensed medicines must be supplied with a Patient Information Leaflet (PIL) written in English and, as a minimum, containing the following information: what the product is; what it is used for ("Action and Use"); circumstances when the product should not be taken; how to take the product; side-effects. It is recognised that in *exceptional* circumstances, where there is an urgent clinical need, it might be permissible for initial supply of an unlicensed medicine to occur without any patient information in the first instance. However, the appropriate information should be made available as soon as possible after the supply of the product.
- 5.18 Monographs in the BP define either or both of the *action* - the physiological effect the medicines has in the body and the *use* - the treatment or condition for which the product is administered. However, these will normally be based on the licensed indication of the medicine. For unlicensed medicines, care is needed when describing the action

and use since the indication for which the product is used may not be known or may differ from the licensed indication.

- 5.19 In addition to providing a PIL, licensed products may also include an information sheet for healthcare professionals. This is often termed a technical information leaflet (TIL), and is generally in the form of an abbreviated Summary of Product Characteristics (SPC). Although a TIL is not mandatory for licensed products, we propose that such information represents best practice that might, in appropriate cases, be provided with unlicensed products.
- 5.20 Product labelling requirements should be specified. The BP general monograph on unlicensed medicines defines mandatory requirements for the labelling of unlicensed medicines. We propose that there should be a specific requirement for product labelling in English. Labelling requirements should follow those set out in the British Pharmacopoeia Volume IV Supplementary Chapter V on unlicensed medicines, to follow MHRA Guidance Note No 25, Best Practice Guidance on Labelling and Packing of Medicines. The items on the label deemed critical for the safe use of a medicine are: name of the medicine; expression of strength (where relevant); route of administration; warnings. In respect of warnings, it is not intended that all warnings should be included but, where possible, *critical* warnings that apply immediately prior to administration should form part of the label. Examples include:

<i>Fatal if given by other routes</i>	Vinca alkaloids
<i>Dilute before use</i>	Concentrated potassium chloride
<i>Contains paracetamol</i>	Paracetamol-containing products

- 5.21 One important question for consideration is whether there should be a requirement to label products supplied under Art 5.1 to state that the medicine is unlicensed in the UK. There could be a case for such a requirement on grounds of transparency. However, such a statement potentially could erroneously convey the impression that the product met no regulatory standards. It could also worry patients unnecessarily, not least if a medicine had for example been fully licensed to European standards in another EU Member State. It would probably not be easy to capture these kinds of complexities in a mandatory written statement. We would welcome views on this issue.

### *Pharmacovigilance*

- 5.22 We found clear support for clarifying and strengthening pharmacovigilance requirements on the basis that unlicensed medicines may be associated with an increased risk of adverse drug reactions. We therefore propose that UK manufacturers and importers of unlicensed medicines are under a positive duty to communicate to the MHRA *all* suspected adverse drug reactions (ADRs) reports received, rather than just those deemed to be serious. This would be

in line with the reporting of suspected adverse drug reactions with “black triangle” products, where all suspected adverse reactions are requested to be reported regardless of the degree of seriousness. There should be a specified time limit for making such reports.

- 5.23 We would also welcome discussion on ways of encouraging adverse reaction reporting by healthcare professionals and patients via the Yellow Card system. This might include reiterating to healthcare professionals that Yellow Card reports on unlicensed medicines are just as important as those for licensed products, and including details of the Yellow Card scheme on the patient information leaflet.

## 6. Structural reform of regulatory arrangements for Art 5.1

- 6.1 As previously indicated, consultation has shown wide agreement that the current structure of UK arrangements does not adequately meet the objectives of the scheme. Accordingly, we have looked carefully at a wide range of alternatives for reform. The assessment of options is explained more fully in the initial impact assessment.

- 6.2 We are proposing that, for reasons explained in the initial impact assessment, the following options do not merit further consideration on the basis that they fall well short of meeting stated objectives:

- No change (*option 1*)
- Apply current import notification arrangements to domestic manufacture as well as imports (*option 2*)
- Apply current arrangements for UK domestic manufacture to imports as well as domestic manufacture (*option 3*)

- 6.3 We also identified two further options, based around developments in clinical governance, that we consider should not be pursued further. These were:

- Limit MHRA role largely to checking that manufacture of Art 5.1 products meet GMP standards; rely wholly on clinical governance and other professional guidance to ensure arrangements are only used for special needs (*option 4*)
- As above, but give MHRA a selective role in vetting special needs, depending on the progress of clinical governance in specific areas (*option 5*).

- 6.4 In our view, continuing enhancements in the effective operation of clinical governance could play a major role in helping Art 5.1 arrangements to deliver fully their intended purpose. However, we do not think it is realistic to expect clinical governance to bear the full weight of responsibility for ensuring that prescribers only use Art 5.1 in accordance with the terms of the legislative scheme. Neither do we consider it realistic, as a structural part of the scheme, to tailor MHRA input according to the extent and effectiveness of clinical governance

across a multiplicity of situations eg in primary, secondary, tertiary care, NHS and the private sector. The risks of activity straying well outside the terms of the scheme and of undermining the medicines' licensing system and its associated safeguards for patients would be too high.

- 6.5 We have given more extensive consideration to two specific options: a reformed notification system, and a list system. These options are summarised below:

***Features of a possible list system (option 6)***

- The system would apply to both UK manufacture and imports.
- The MHRA would maintain and publish three lists:
  - List (i): products to which there is no objection to import/manufacture by a holder of a licence covering this activity
  - List (ii): products to which there is objection to import/manufacture
  - List (iii): products which are under assessment.
- If a product is not listed the applicant seeking to import or manufacture must notify the MHRA; there would be fast track provisions in case of clinical urgency.
- Items on list (i) could be subject to specific restrictions – eg a requirement to notify MHRA of each supply of the product in cases where there is a need for close monitoring.
- Reasons for inclusion of items in List (ii) would be stated; applicants nonetheless seeing a case to import products on List (ii) would be required to state how the relevant concerns responsible for the List (ii) status had been addressed and would require a letter of non objection from MHRA.
- Inclusion of items on List (i) and (ii) would be subject to a time limit, eg normally 1 year but less in the case of known transient features such as a shortage of a licensed product. Items on Lists could be renewed, withdrawn or amended.
- Items not on List (i) or (ii) would be acknowledged by MHRA and placed on List (iii). The MHRA would have a set time limit (eg 28 days) before deciding whether to place the item on List (i) or (ii). Where the MHRA needed to ask the applicant for further information the clock would stop.

***Features of a possible reformed notification system (option 7)***

- The system would apply to both UK manufacture and imports.
- Notification would be made by a holder of a licence covering permission to manufacture or import Art 5.1 products.
- The notification would state the quantity proposed to be manufactured/imported. There would be no restriction on the quantity of a product able to be notified in a single notification.
- MHRA would as now have a 28 day period, following acknowledgement, in which to object, and the ability to waive the 28 days if appropriate.
- As with current arrangements there would be provisions to fast track applications in cases of clinical urgency.
- A validity period would be introduced for MHRA letters of non objection to import or manufacture. This validity period would normally be 1 year.
- If a licence holder wished during the validity period to manufacture or import more than the originally notified quantity a further notification would be required.

- 6.6 A revised notification system appears to have the potential to meet the objectives of reform. In particular, it could significantly improve consistency, targeting and proportionality of regulatory arrangements. Although this is not inherent in the structure of the arrangements, transparency could also be enhanced through publication of information about the operation of the scheme. One important advantage of transparency concerning the numbers of notifications for different products is that this could help to illuminate to companies where they may be sufficient demand for a licensed product.
- 6.7 As regards accountability of regulatory arrangements under a revised notification system, enhanced availability of information about the operation of the scheme should be helpful in promoting accountability. In addition, it is important that operators within the scheme have opportunity for comeback if they disagree with an MHRA proposed/actual objection to import/manufacture of a particular product under Art 5.1 arrangements. In our view it would be overly cumbersome to introduce a formal appeal mechanism relating to the import or manufacture of each and every one of the many thousands of different products that potentially are likely to come within the scheme. Instead, we consider the main requirement is that those responsible for making notifications should have the opportunity to supply further information, notably for example where the MHRA has said that it is not satisfied on the evidence provided that there is a special need that

would not be met by an available licensed product. The MHRA would, as now, continue to take advice where necessary from the independent expert advisory body, the Commission on Human Medicines. This is likely to be particularly applicable in cases where the MHRA needs advice on the safety of a product an operator has proposed to supply under Art 5.1. Ultimately, where MHRA continued to refuse permission the option of judicial review would be open to a dissatisfied operator.

- 6.8 A list system has potential strengths in the area of consistency, transparency and proportionality. However, as analysis in the initial impact assessment shows, the MHRA foresees significant problems with this option. Quality is specific to the individual product and it is not easy to see how this aspect could readily be captured in a list system without excessive complication, with individual list entries accompanied by extensive and sometimes frequently changing detail about which sources of an imported product were, or were not acceptable. It could be difficult to achieve effective targeting under this option. Potentially weaknesses could also arise from lack of information about how many products are actually supplied under a list system. Our current thinking is that a list system as outlined above may ultimately prove not to be a realistic option.
- 6.9 Our provisional view is that the option of a reformed notification system may represent the best way forward. However, in order to determine its feasibility we consider it necessary to have better information on the likely impact. It is probable that such arrangements would lead to an overall reduction in notifications by importers. However, the scheme would require introduction of a potentially substantial number of notifications by UK manufacturers. Research is necessary to assess the burden on businesses and whether this would be commensurate with the benefits; also to ensure that the likely volume of activity would be manageable by MHRA.
- 6.10 We believe it should be feasible for business, both importers and manufacturers, if given sufficient information about the possible parameters of the scheme, to develop reasonable estimates for what the impact of the scheme would have been if it had been in operation at a recent point in time. It should be possible for operators to estimate approximately how many foreseen notifications and how many, unforeseen (both urgent and non urgent) notifications they would have needed to make in a year. This information would help MHRA to assess the likely feasibility and impact of such arrangements and the implications for fees.

### *Fees*

- 6.11 As a trading fund MHRA must recover its costs. In principle it appears that a reformed notification scheme would enable MHRA to target its input, and hence its resources, where this will be most effective. In the

event that the further feedback we are seeking demonstrates that this is a realistic option a possible fee structure would be included in a further consultation.

- 6.12 Looking further ahead, if the health service and professional groups take up opportunities for rationalising what may in some areas be unnecessarily complicated patterns of demand relating to multiple variants of the same product, this in turn is likely to lead to some reduction in, arguably unnecessary, regulatory costs.

## 7. Next Steps

- 7.1 MHRA invites feedback on this report and comments on the recommendations.
- 7.2 MHRA will be seeking feedback, in particular from manufacturers and importers of “specials”, on the impact of the possible regulatory changes, including a revised notification system.

## 8. Summary of recommendations

### *Wider recommendations about the direction of progress in promoting effective use of unlicensed medicines*

- 8.1 MHRA should work with professional and health service bodies concerned with arrangements for the prescribing of unlicensed medicines to meet patients’ special needs so as to ensure that information about the operation of UK Art 5.1 arrangements can support initiatives intended to improve the effectiveness of such prescribing.
- 8.2 MHRA, NPSA and professional bodies should continue to take measures where necessary to encourage adherence to good practice in the prescribing of unlicensed medicines, and to monitor the effectiveness of those measures.
- 8.3 Those in the health service concerned with risk assessment of unlicensed medicines should consider the scope for sharing knowledge and workload.

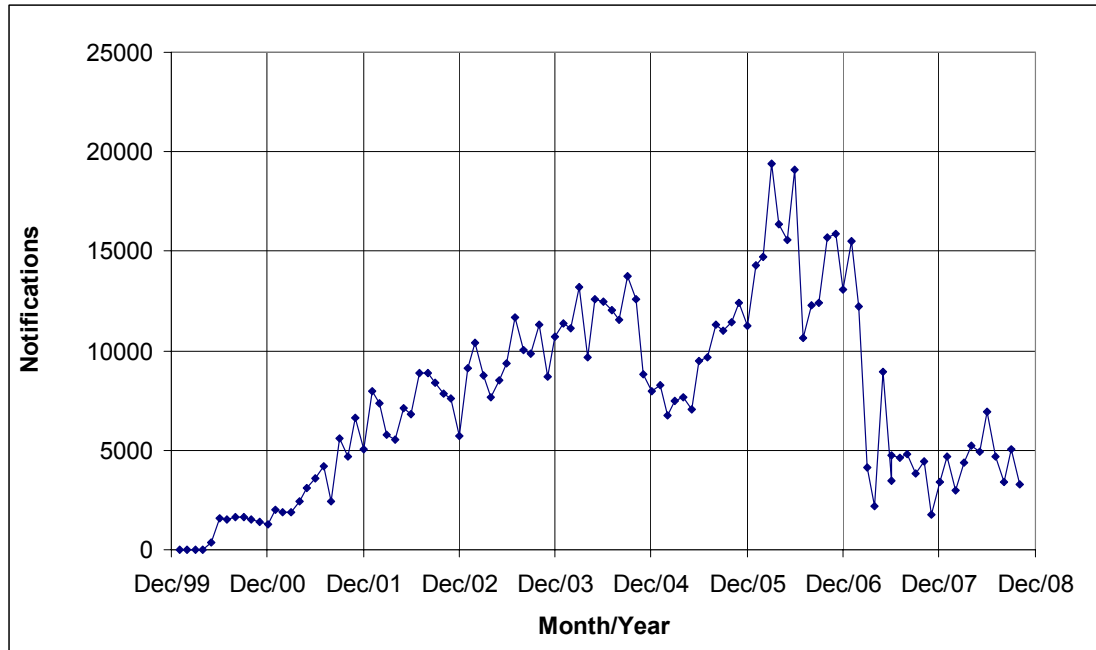
### *Specific recommendations concerning UK Art 5.1 regulatory arrangements*

- 8.4 The possibility of introducing a specific legislative requirement for the prescriber to state that they are prescribing an unlicensed medicine should be kept in mind as a possible future option but should not be pursued at this stage while initiatives to promote good practice are pursued.

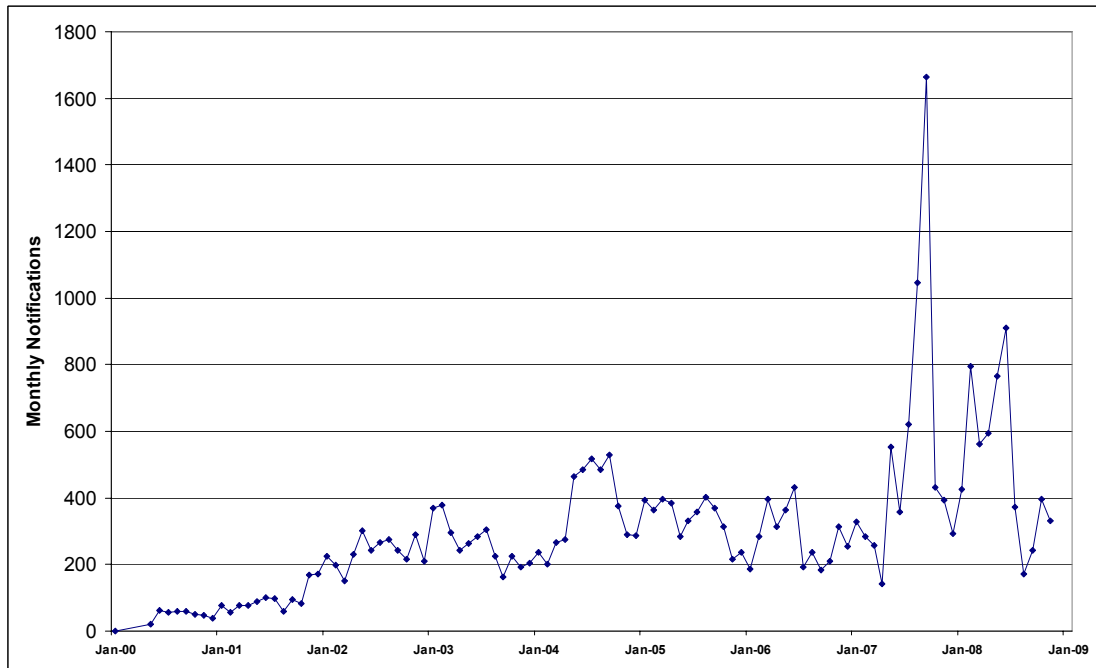
- 8.5 Guidelines, under development by MHRA's GMP Inspectorate, should give pointers as to how the standards expected of manufacturers of Art 5.1 products should reflect the scale and nature of production.
- 8.6 All Art 5.1 products should be supplied with a Patient Information Leaflet (PIL) in English.
- 8.7 Minimum information contained in the PIL should be: what the product is; what it is used for ("action and use"); circumstances when the product should not be taken; how to take the product; side effects.
- 8.8 As a matter of good practice, where appropriate, Art 5.1 products should include an information sheet for healthcare professionals.
- 8.9 Products should be labelled in English. Labelling should follow existing BP and MHRA guidance. Essential items are: name of the medicine; expression of strength (where relevant); route of administration. Critical warnings that apply immediately prior to administration should be included where possible.
- 8.10 Feedback should be sought on the advantages, or otherwise, of requiring products to be labelled that the medicine is unlicensed in the UK.
- 8.11 UK manufacturers and importers should be under a duty to communicate to the MHRA all suspected adverse drug reactions, and not only those deemed to be serious.
- 8.12 Feedback should be sought on ways to encourage suspected adverse reaction reporting with unlicensed products.
- 8.13 Feedback should be sought on options for reforming regulatory structural arrangements under which permission is granted to manufacture or import an unlicensed medicine under Art 5.1. In particular, views are sought on the feasibility of the option of a reformed notification system.

The import notification scheme – patterns of usage

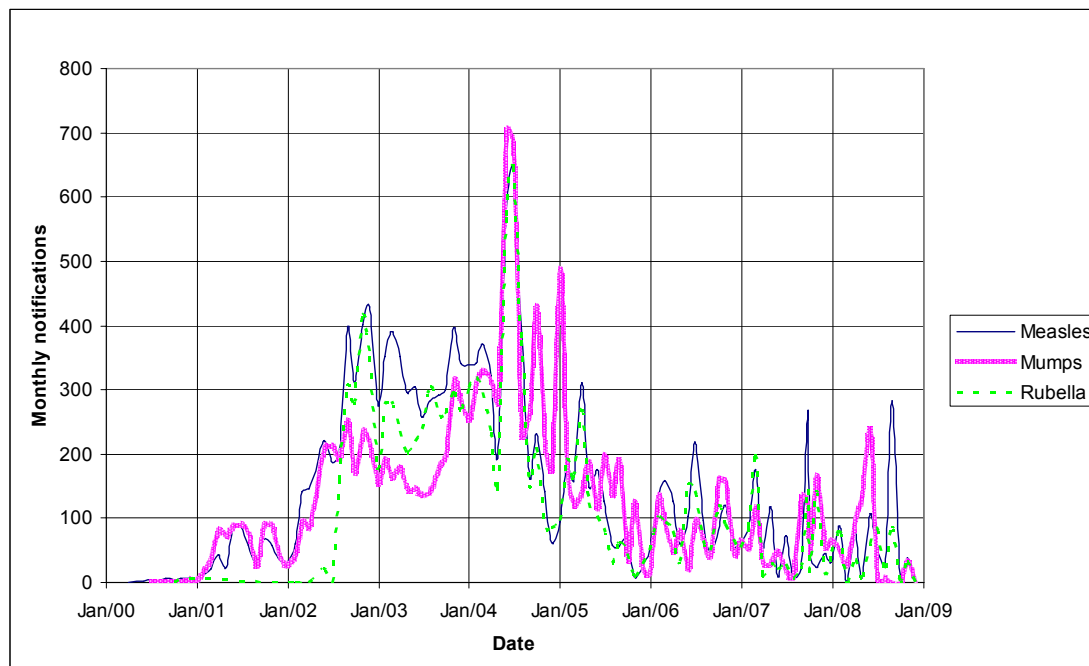
**Graph 1 Monthly import notifications for all unlicensed medicines to 30 Nov 2008**



**Graph 2 Monthly import notifications for Melatonin products to 30 Nov 2008**



**Graph 3 Monthly import notifications for monocomponent measles, mumps and rubella vaccines to 31 Dec 2008**



Variations in the monthly numbers of notifications for importation of unlicensed products received under the import notification scheme may be influenced by several factors. In Graphs 1 to 3, some of these factors are illustrated.

Graph 1 shows the total numbers of notifications over the lifetime of the MHRA imports database to 30 Nov 2008. The decrease in notifications in late 2003 is for unknown reasons, although it may be linked to commercial and organisational factors, such as an impending management buyout of a major importer. In April 2007, fees were introduced for assessment of import notifications. This coincides with another precipitous decrease in total notification numbers. One plausible hypothesis is that the fact that under the present arrangement a permission to import is not time limited, combined with the previous absence of fees, may have led to some stock piling of permissions, which were then run down following the introduction of fees. However, any such linkage is not certain, and a number of importers have said that changes in their notification levels were not due to the introduction of fees.

Graph 2 shows a general increase in the number of notifications for melatonin products, currently the largest category of notifications. Between 2004 and 2007 the numbers are fairly constant, but after this period there is a noticeable increase in numbers of notifications. The reason for this is not known. The large spike in the graph is due to notifications from a single importer on entry into this market. A licensed product came onto the market in mid-2008, and this together with MHRA concerns over the quality of non-pharmaceutical products imported from the USA led the MHRA in some circumstances to query the justification for importation of these unlicensed products. The graph suggests that recently the MHRA actions have had some effect, but the longer term trends are as yet unknown.

Graph 3 shows the effects of the MMR controversy, where use of the combined vaccine was alleged to be associated with the development of autism in inoculated

children. Following extensive media coverage in early 2004 of the lack of evidence for such a link, a decline in notifications for monocomponent vaccines followed. The sharp peak during 2004 is due to changes in notification practices following legal advice that more than one notification for the same product could be made in a single day. Most recently, international availability problems of Merck Mumpsax have forced a decline in notifications for this product. It is effectively the only monocomponent mumps vaccine that can currently be imported into the UK.

These examples illustrate just a few of the factors that affect the numbers of notifications made for import of unlicensed medicines. Most of the factors discussed were not easily predictable.