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To: interested organizations

9 January 2001

Dear Sir or Madam

CONSULTATION LETTER MLX 270:

Proposal to confirm permanent prohibition in unlicensed medicines of *Aristolochia* species and herbal ingredients which may be confused with *Aristolochia* species

Enclosed with this letter is the consultation document MLX 270. This relates to proposals to make an Order: *The Medicines (Aristolochia and Mu Tong etc.) (Prohibition) Order 2001*. The new Order would confirm the permanent prohibition in unlicensed medicines for human use of *Aristolochia* species and herbal ingredients which may be confused with *Aristolochia* species.

You are invited to make representations about the proposals and a form is attached for your reply. Comments should be addressed to Miss Joy Gay in Room 16/133 at the above address to arrive by 16 March 2001.

Any representations made will be considered carefully by the Medicines Commission, an advisory body established by the Medicines Act 1968 to advise Ministers on issues relating to the Act, before Ministers are asked to take a decision. If you also wish to be heard by the Medicines Commission about the proposals, as allowed by section 62(5) of the 1968 Act, please indicate this in your reply.

To help informed debate on the issues raised by this consultation exercise, and within the terms of the Code of Practice on Access to Government Information ("Open Government"), the Agency intends to make copies of replies received publicly available. Copies will be available shortly after the public consultation has ended.

The Agency's Information Centre at Market Towers will supply copies upon request. Copies may be further reproduced. An administrative charge, to cover the costs of photocopying and postage may be applied. Alternatively, personal callers can inspect the replies at the Information Centre by prior appointment. To make an appointment telephone 0207 273 0351.

We will assume that your reply can be made publicly available in this way unless you indicate that you wish all or part of it to be treated as confidential and excluded from this arrangement. Under the Code of Practice on Access to Government Information,

the Agency will not release confidential replies or replies containing personal confidential information.

Yours faithfully

Richard Woodfield
Group Manager Herbal Policy

CONSULTATION DOCUMENT MLX 270

Proposal to confirm permanent prohibition in unlicensed medicines of *Aristolochia* species and herbal ingredients which may be confused with *Aristolochia* species

INTRODUCTION

1. Progressive regulatory action has already been taken to protect the public from the risk posed by unlicensed medicines containing the toxic herbal ingredient *Aristolochia*. This consultation is about proposals which would ensure the continuation on a permanent basis of the provisions of a current temporary Order which is due to expire on 30 June 2001.

BACKGROUND

2. *Aristolochia* species have long been a component of some traditional Chinese medicines (TCMs). Following the identification in 1999 of cases of renal failure in the UK attributable to the presence of *Aristolochia* in unlicensed medicines, the following progressive regulatory action has been taken:

- in July 1999 an emergency three month prohibition was made on the sale, supply and importation of unlicensed medicines containing *Aristolochia* species (*The Medicines (Aristolochia) (Emergency Prohibition) Order 1999 (Statutory Instrument 1999 No 2109)*)
- in October 1999, following consultation, the provisions were extended on a temporary basis until 30 June 2001 (*The Medicines (Aristolochia) (Temporary Prohibition) Order 1999 (Statutory Instrument 1999 No 2889)*)
- in June 2000, following consultation, the prohibition was widened to cover additionally a number of toxic herbal ingredients which may be confused with *Aristolochia* (*The Medicines (Aristolochia and Mu Tong etc.) (Temporary Prohibition) Order 2000 (Statutory Instrument 2000 No 1368)*). This Order, which replaced SI 1999/2889, is due to expire on 30 June 2001.

3. The Committee on Safety of Medicines (CSM) established a working party in early 2000 to advise on whether further action is required to make effective the prohibition of *Aristolochia* species and under what conditions any prohibitions of herbal ingredients that were believed to be harmless but easily confused with *Aristolochia* species might be lifted or modified without unacceptable risk to public health. The CSM is expected to advise Ministers on the outcome of this work fairly shortly.

THE NEW PROPOSALS

4. This consultation concerns a proposal to make permanent the existing provisions of *The Medicines (Aristolochia and Mu Tong etc.) (Temporary Prohibition) Order 2000 (Statutory Instrument 2000 No 1368)*. This would be achieved by making a new Order: *The Medicines (Aristolochia and Mu Tong etc.) (Prohibition) Order 2001*. A draft is enclosed at Annex 1. The new Order would come into force on 1 July 2001. The reasons for this proposed action are:

- to meet the timetable which will ensure that there is no gap in the protection of the public from the risks posed by *Aristolochia* when the current Order expires at the end of June 2001
- to put this protection onto a permanent basis, so as to avoid the likely need for a series of further successive temporary Orders.

5. There are likely to be future requirements to extend or modify the prohibitions. This may arise in the first instance from recommendations which may be made by the CSM. More generally, new information about *Aristolochia* may well continue to emerge as international scientific and regulatory interest in, and understanding of, the issue develops. The possibility of systematic improvements in quality assurance procedures in the TCM sector could also have a bearing.

6. The timing of such possible future developments cannot be predicted and they may not readily fit in with the timetable for renewal of temporary Orders. Also any further information is relatively unlikely to affect the public health case for a permanent prohibition on *Aristolochia* in unlicensed medicines. **On that basis the MCA proposes that more reliable public health protection will be afforded by putting in place as soon as possible a permanent Order which can be modified as and when justified by significant new information.** The Agency also believes that this approach is also a more effective use of the legislative process.

7. The proposals are to replicate on a permanent basis the existing provisions in the current Order as follows:

The prohibition on the sale, supply or importation of unlicensed medicines for human use:

- consisting of or containing any species of the genus *Aristolochia*;
- consisting of or containing any of these species:

Akebia quinata
Akebia trifoliata
Clematis armandii
Clematis montana
Cocculus laurifolius
Cocculus orbiculatus
Cocculus trilobus
Stephania tetrandra

The prohibition on the sale, supply or importation of unlicensed medicines for human use:

- presented as consisting of or containing *Mu Tong* or *Fangji*;
- presented as consisting of or containing any of these species:

Akebia quinata
Akebia trifoliata
Clematis armandii
Clematis montana
Cocculus laurifolius
Cocculus orbiculatus
Cocculus trilobus
Stephania tetrandra

All the prohibitions are to be subject to the exceptions set out in article 4 of the draft Order.

FUTURE ACTION

8. As indicated above, we envisage the possibility of a need to modify the prohibitions in the light of further advice from the CSM. Any proposal to extend the prohibitions will be the subject of a further public consultation.

REGULATORY IMPACT

9. A draft regulatory impact assessment is at Annex 2. As the proposed Order replicates existing provisions we do not envisage that it will lead to businesses incurring additional costs. However, if the existing Order were allowed to expire without replacement, public health protection would be weakened. This would be likely to have an adverse impact on public confidence in the safety of traditional Chinese medicines, which in turn could lead to a reduction in trade.

CONCLUSION

10. Comments are invited on the regulatory impact of these proposals.

11. Subject to the outcome of consultation, the further advice of CSM and the Medicines Commission, and the agreement of Ministers we propose to lay a Statutory Instrument in Parliament in time for the new provision to come into force on 1 July 2001.

12. Comments should be submitted in writing to Miss Joy Gay, in Room 16/133 Market Towers, 1 Nine Elms Lane, London SW8 5NQ, to reach her by 16 March.

MCA
January 2001

To:

Miss Joy Gay
Medicines Control Agency
Room 16/133 Market Towers
1 Nine Elms Lane
LONDON SW8 5 NQ

From:

CONSULTATION LETTER MLX 270

Proposal to confirm permanent prohibition in unlicensed medicines of *Aristolochia* species and herbal ingredients which may be confused with *Aristolochia* species

- * We have no representations to make about the proposals in MLX 270
- * Our representations about the proposals in MLX 270 are below/attached
 - * *My reply may be made freely available*
 - * *My reply is confidential*
 - * *My reply is partially confidential (indicate clearly in the text any confidential elements)*

Comments:

Signed: _____

- * *Please delete as appropriate*

STATUTORY INSTRUMENTS

2001 No.

MEDICINES

The Medicines (Aristolochia and Mu Tong etc.) (Prohibition) Order 2001

<i>Made</i>	<i>2001</i>
<i>Laid before Parliament</i>	<i>2001</i>
<i>Coming into force</i>	<i>1st July 2001</i>

As respects England, Scotland and Wales, the Secretary of State concerned with health in England, and, as respects Northern Ireland, the Minister of Health, Social Services and Public Safety, acting jointly, in exercise of the powers conferred upon them by sections 62(1)(a) and (2) and 129(4) of the Medicines Act 1968 ⁽¹⁾ and now vested in them ⁽²⁾ and of all other powers enabling them in that behalf, it appearing to them to be necessary in the interests of safety to make the following Order, after consulting such organisations as appear to them to be representative of interests likely to be substantially affected by the Order pursuant to section 129(6) of that Act, after consulting and taking into account the advice of the Committee on Safety of Medicines pursuant to sections 62(3) and 129(7) of that Act ⁽³⁾, and after taking into account the report of the Medicines Commission made under section 62(5) of that Act, hereby make the following Order:-

Citation, commencement, expiry and interpretation

1. - (1) This Order may be cited as the Medicines (Aristolochia and Mu Tong etc.) (Prohibition) Order 2001, and shall come into force on 1st July 2001.

(2) In this Order –

¹ 1968 c. 67; the expression “the appropriate Ministers”, and the expression “the Health Ministers” which is relevant to the powers being exercised in the making of this Order, are defined in section 1 of that Act as amended by article 2(2) of, and Schedule 1 to, S. I. 1969/388, and by article 5 of, and paragraph 1(1) of the Schedule to, S.I. 1999/3142.

² In the case of the Secretary of State concerned with health in England, by virtue of article 2(2) of, and Schedule 1 to, S.I. 1969/388, and articles 2(1) and 5 of, and paragraph 1(1) of the Schedule to, S.I. 1999/3142 ; and in the case of the Minister of Health, Social Services and Public Safety, by virtue of section 95(5) of, and paragraph 10 of Schedule 12 to, the Northern Ireland Act 1998 (c.47).

³ Section 62(3) refers to “the appropriate committee”, which is defined in section 4(6) of the Act. The Committee on Safety of Medicines was established under section 4 of the Act, by S. I. 1970/1257, for the purposes set out in that instrument.

“the Act” means the Medicines Act 1968;

“EEA Agreement” means the Agreement on the European Economic Area signed at Oporto on 2nd May 1992 (⁴) as adjusted by the Protocol signed at Brussels on 17th March 1993 (⁵);

“EEA State” means a State which is a Contracting Party to the EEA Agreement;

“medicinal product” does not include a medicinal product which is a veterinary drug.

Prohibition of sale, supply and importation of any medicinal product consisting of or containing certain plants

2. Subject to article 4 below, the sale, supply and importation of any medicinal product consisting of or containing a plant (⁶) -

(a) belonging to a species of the genus *Aristolochia*; or

(b) belonging to any of the species -

Akebia quinata,
Akebia trifoliata,
Clematis armandii,
Clematis montana,
Cocculus laurifolius,
Cocculus orbiculatus,
Cocculus trilobus,
Stephania tetrandra,

or consisting of or containing an extract from such a plant, is prohibited.

Prohibition of sale, supply and importation of medicinal products presented as consisting of or containing Mu Tong etc.

3. Subject to article 4 below, the sale, supply and importation of any medicinal product is prohibited where, at the time of the sale, supply or importation -

(a) the label on the product’s container or package; or

(b) any document accompanying the product,

indicates in any language -

⁴ OJ No. L1, 3.1.94, p.3.

⁵ OJ No. L1, 3.1.94, p.572.

⁶ “Plant” includes part of a plant; see section 132(1) of the Act.

(i) that the product consists of or contains *Mu Tong* or *Fangji*,
or any term derived from either of those terms;
or

(ii) that the product consists of or contains a plant specified in article 2(b) above
or an extract from such a plant.

Exceptions to the prohibitions imposed by articles 2 and 3 above

4. – (1) The prohibitions imposed by articles 2 and 3 above are subject to the exceptions specified in the following paragraphs of this article.

(2) The prohibitions imposed by articles 2 and 3 above shall not apply where a medicinal product as referred to in those articles is sold or supplied to, or, in the case of importation, is imported by or on behalf of, any of the following persons-

(a) a food analyst or food examiner within the meaning of section 30 of the Food Safety Act 1990 (⁷);

(b) a food analyst or food examiner within the meaning of Article 30 or 31 of the Food Safety (Northern Ireland) Order 1991 (⁸);

(c) an authorised officer within the meaning of section 5(6) of the Food Safety Act 1990, or Article 2(2) of the Food Safety (Northern Ireland) Order 1991 (⁹);

(d) a person duly authorised by an enforcement authority under sections 111 and 112 of the Act;

(e) a sampling officer within the meaning of Schedule 3 to the Act.

(3) The prohibitions on importation imposed by articles 2 and 3 above shall not apply where a medicinal product as referred to in those articles is imported-

(a) from a member State of the European Community; or

(b) where the product originates (¹⁰) in the European Economic Area, from an EEA State which is not also a member State of the European Community.

⁷ 1990 c.16; section 30 was amended by section 40 of, and paragraph 8 of Schedule 5 to, the Food Standards Act 1999 (c.28).

⁸ S.I. 1991/762 (N.I. 7); as amended by S.I. 1996/1633 (N.I. 12).

⁹ Section 5(6) was amended by section 40 of, and paragraph 8 of Schedule 5 to, the Food Standards Act 1999 (c.28), and article 2(2) was amended by paragraph 29 of Schedule 5 to, and Schedule 6 to, that Act.

¹⁰ See Protocol 4 (on rules of origin) annexed to the EEA Agreement, as amended by the Decision of the EEA Joint Committee No. 6/94 amending Protocol 4 to the EEA Agreement (OJ No. L95, 14.4.94, p.22).

(4) The prohibitions imposed by articles 2 and 3 above shall not apply where a medicinal product as referred to in those articles is the subject of a product licence⁽¹¹⁾, a marketing authorization within the meaning of regulation 1(4)(a) of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994⁽¹²⁾ or a certificate of registration within the meaning of regulation 1(2) of the Medicines (Homoeopathic Products for Human Use) Regulations 1994⁽¹³⁾.

Revocation

5. The Medicines (Aristolochia and Mu Tong etc.) (Temporary Prohibition) Order 2000⁽¹⁴⁾ is revoked.

Signed by authority of the Secretary of State for Health

2001

Parliamentary Under Secretary of State
Department of Health

Signed by the Minister of Health, Social Services and Public Safety
on 2001

EXPLANATORY NOTE

(This note is not part of the Order)

This Order prohibits the sale, supply, and importation, of any medicinal product for human use which-

- (a) consists of or contains a plant belonging to a species of the genus *Aristolochia* or belonging to any of the species - *Akebia quinata*, *Akebia trifoliata*, *Clematis armandii*, *Clematis montana*, *Cocculus laurifolius*, *Cocculus orbiculatus*, *Cocculus trilobus*, *Stephania tetrandra*, or an extract from such a plant; or
- (b) is presented as consisting of or containing *Mu Tong* or *Fangji*, a plant belonging to any of the species *Akebia quinata*, *Akebia trifoliata*, *Clematis armandii*, *Clematis montana*, *Cocculus laurifolius*, *Cocculus orbiculatus*, *Cocculus trilobus*, *Stephania tetrandra*, or an extract from such a plant.

¹¹ "Product licence" has the meaning assigned to it by section 7 of the Act.

¹² S.I. 1994/3144; as amended by S.I. 1998/3105 and 2000/292.

¹³ S.I. 1994/105; as amended by S.I. 1994/899, 1995/541, 1996/482, 1998/3105, 1999/566 and 2000/592.

¹⁴ S.I. 2000/1368.

These prohibitions are subject to the following exceptions-

- (i) where the sale or supply is to, or the importation is made by or on behalf of, a person exercising functions in relation to the enforcement of food or medicines legislation;
- (ii) in the case of the prohibitions on importation, where the product is imported from a member State of the European Community, or, where the product originates in the European Economic Area, from a State Party to the European Economic Area Agreement which is not also a member State;
- (iii) where the product is the subject of a product licence, marketing authorization or homoeopathic certificate of registration.

This Order was notified to the European Commission in accordance with European Parliament and Council Directive 98/34/EC, Article 8 (OJ No. L204, 21.7.1998, p.37) as amended by European Parliament and Council Directive 98/48/EC, Article 1(4) (OJ No. L217, 5.8.1998, p.18), and in accordance with Council Directive 75/319/EEC, Article 33 (OJ. No. L147, 9.6.1975, p.13).

This Order revokes the Medicines (Aristolochia and Mu Tong etc.) (Temporary Prohibition) Order 2000 (S.I. 2000/1368) which expires on 30th June 2001. The provisions of that Order are re-enacted in this Order.

DRAFT REGULATORY IMPACT ASSESSMENT

1. PURPOSE AND INTENDED EFFECT OF THE PROPOSAL

The issue

Aristolochia is a toxic herbal ingredient used in some traditional Chinese medicines. A number of medicinal plants, which in themselves are considered harmless when correctly administered, are prone to being substituted by, or confused with, *Aristolochia*. Following cases of serious illness attributable to *Aristolochia* in unlicensed medicines the Medicines Control Agency (MCA) carried out a sampling and analysis exercise. This showed that a significant proportion of herbal remedies believed to be at risk of containing aristolochic acids did in fact do so. Progressive regulatory action was taken on the advice of the Committee on Safety of Medicines (CSM) and the Medicines Commission.

The Medicines (Aristolochia and Mu Tong etc.) (Temporary Prohibition) Order 2000 (Statutory Instrument 2000 No 1368) currently prohibits the sale, supply and importation of unlicensed medicines for human use containing, or presented as containing, a number of herbal ingredients which are either toxic or which may be confused with the toxic ingredient *Aristolochia*.

Objectives

The objective is to protect public health.

Risk assessment

In 1999 44% of the MCA's sample of products believed to be at risk of containing aristolochic acids did so. This result may have occurred through a mixture of deliberate or accidental substitution of ingredients and/or contamination. This situation presented a significant public health risk. Although the traditional Chinese medicine sector is investigating improved quality controls, the risk of *Aristolochia* entering the supply chain remains.

2. OPTIONS

Three main options have been identified:

Option 1: to allow the current Order to **lapse** when it expires at the end of June 2001.

Option 2: to replace the current Order with a further **temporary** prohibition to continue the existing provisions of the Order.

Option 3: to replace the current Order with a further Order continuing the existing provisions on a **permanent** basis

Issues of equity or fairness

In principle it is undesirable to place a prohibition on the use of ingredients which are not believed to be inherently harmful. However, there is clear evidence that in general manufacturing standards in the unlicensed traditional Chinese medicine sector are not currently such as to permit confidence that ingredients at risk of confusion with *Aristolochia* will be rigorously controlled and authenticated by systematic quality assurance procedures operating through the supply chain.

The proposed prohibition is being put in place on the understanding that it may be extended or modified as further evidence becomes available.

3. BENEFITS IDENTIFIED AND QUANTIFIED

The proposed legislation will benefit the public by ensuring the continuation of the current protection against the toxic herbal ingredient, *Aristolochia*. Exposure to this ingredient can lead to nephrotoxicity and carcinoma. Additional costs to the NHS incurred, for example, with dialysis treatment and transplantations and other concomitant expenses could also be avoided.

4. COMPLIANCE ISSUES FOR BUSINESS

Business sector affected

Manufacturers of medicinal products come under business sector 24421 (Manufacture of medicaments) *Business Monitor PA1003 – Size analysis of United Kingdom Business (1996)*.

Actual costs over lifetime of proposal

The proposed Order continues an existing provision and should have no policy or implementation costs over and above any associated with the existing Order.

Guidance

No specific guidance for business about this Order is planned since the provisions simply continue existing law and are self explanatory. However, on a wider level the MCA is preparing guidance for relevant trade and practitioner associations operating in the ethnic medicines sector. This will highlight some of the issues which have arisen where there is misunderstanding of, and/or non compliance, with existing law. Among the subjects covered will be *Aristolochia*.

5. SUMMARY AND RECOMMENDATIONS

Option 1: (to allow the current Order to **lapse** when it expires at the end of June 2001).

This option would reduce public health protection. The further likely outcome would be reduced public confidence in the traditional Chinese medicines sector on the basis of increased risk of *Aristolochia* entering the supply chain.

Option 2: (to replace the current Order with a further **temporary** prohibition to continue the existing provisions of the Order.)

This option would maintain the existing level of public health protection for the duration of such a further temporary Order. However, it is clear that the risk of *Aristolochia* being found in unlicensed medicines is likely to remain an issue for some considerable time to come. This option would be likely to entail repeated use of successive temporary Orders.

Option 3: (to replace the current Order with a further Order continuing the existing provisions on a **permanent** basis.)

This option would maintain the existing level of public health protection. It would recognize the continuing nature of the problems arising from *Aristolochia*. Making a permanent Order does not preclude Ministers' modifying or extending its provisions through a further Order as further evidence emerges.

6. ENFORCEMENT, SANCTIONS, MONITORING AND REVIEW

The ban will be enforced by the MCA's Enforcement Unit as part of its existing compliance and enforcement responsibilities in protecting public health. Offenders will be liable to prosecution and unlicensed medicines will be included in the Agency's regular product monitoring programme. The scope for modifying the prohibition, in particular in relation to ingredients not believed to be inherently harmful, will be reviewed in the light of work being carried out by an expert Working Group of the CSM.