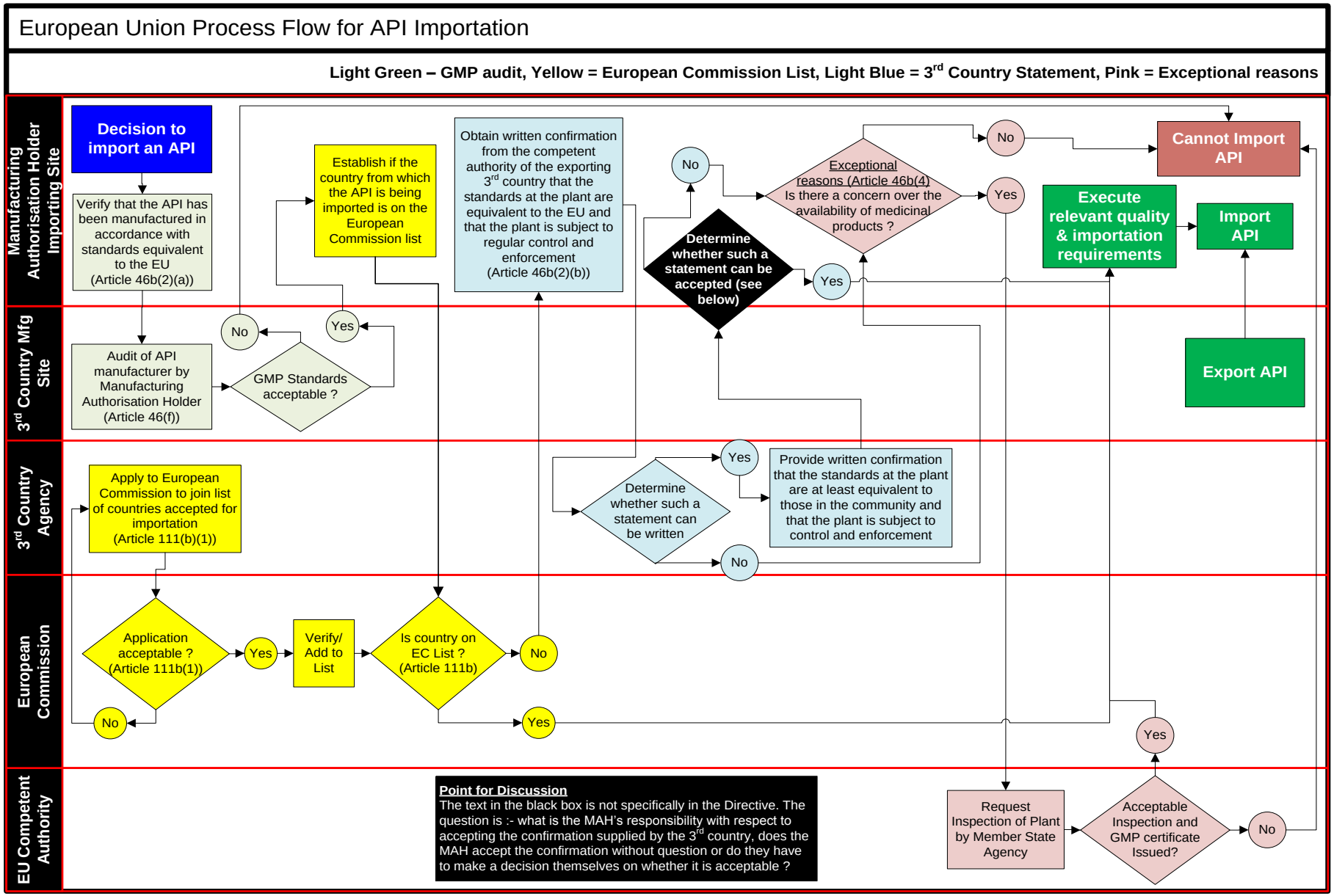
Subject	Falsified Medicines Directive (FMD) Provisions Relating to Importation of APIs from Third Countries (Article 1(4))
Problem Statement	Article 1 of the Falsified Medicines Directive (FMD) requires all manufacturing authorisation holders to ensure that APIs meet the requirements of GMP. Member states likewise have a duty to ensure that all APIs manufactured on their territory meet GMP requirements. Under Article 1(4) of the FMD a new Article 46b is inserted into Directive 2003/81. It is our understanding that the effect of this new Article is such that APIs may only be imported from a third country if one of the following conditions is met: 1. - The active substances have been manufactured in accordance with standards of good manufacturing practice at least equivalent to those laid down by the Union, and - the active substances are accompanied by a written confirmation from the competent authority of the exporting third country that the standards of good manufacturing practice applicable to the plant manufacturing the exported active substance are at least equivalent to those laid down by the Union pursuant to Article 47 of Directive 2001/83, and - that the plant is subject to regular, strict and transparent control and efficient enforcement of good manufacturing practice including repeated and unannounced inspections, ensuring a protection of public health at least equivalent to that in the Union, and that in the event of findings relating to non-compliance, that information shall be supplied by the exporting third country to the Union without any delay. * *Throughout this document we refer to this process of third countries declaring equivalence with EU GMP standards for APIs as 'self-certification'. We recognise that this is not a term used in the legislation but we feel that for the purposes of this document it describes adequately what we understand the nature of the process to be. or 2. The third country appears on a list of countries whose GMP requirements and enforcement procedures for APIs have been judged by the Commission by means of inspection of the regulatory system (possibly with on –site observation of an API inspection) under article 111 b) of the Directive to be equivalent to EU GMP standards for APIs., or 3. The site from which the API has been imported has been inspected by an EU Competent Authority and deemed to meet the EU requirements for GMP for APIs. This procedure is supposedly only for exceptional cases where product supply is threatened and for a limited (but, we understand,

	renewable) period of time (the length of the validity of the GMP certificate) and will apply where neither 1) nor 2) above apply. Successful implementation of these provisions requires a clear mutual understanding between industry and regulators as to the practical requirements of the provisions and the means to achieve them. Failure to do so may result in unnecessary supply chain issues for API's and consequently medicinal products. A diagram representing EFPIA's understanding of the implications of the FMD provisions for importation is attached in ANNEX 1.* *The diagram represents EFPIA's interpretation of the Directive's provisions and should not be construed as a recommendation
EFPIA Position	EFPIA supports the need for adequate oversight and control of the importation of an API into the European Union. The FMD includes important provisions for establishing some control requirements which will sit alongside the important role that the Manufacturing Authorisation Holder has for ensuring that reliable, safe and GMP compliant API's are used in the manufacture of medicinal products. It is important to ensure that the requirements are clear to all parties and consistently implemented. It is EFPIA's opinion that the following areas need to be addressed at an early stage and agreement reached on their implementation. <u>General Points</u> 1. The Falsified Medicines Directive specifies that the provisions relating to the new Article 46(b) must be implemented by Member States within two years of publication of the Directive. The Directive was published on 31 May 2011 and sot this will require compliance by Summer of 2013. Consequently, it will be necessary to have mechanisms and approvals in place for third countries complying with the requirements of the criteria by that time. Failure to do so may result in disruption of the supply chain for APIs and cause problems of medicinal product supply to the European and global markets. 2. If a third country will neither 'self-certify' nor seek accreditation under the 111b) list what circumstances would be deemed as exceptional such as to allow the third option described in the background section ? 3. What is the situation regarding imported medicinal products containing active pharmaceutical ingredients manufactured

	in third countries? Do the expectations of the FMD apply or is this governed by the QP declaration and audit process ? <u>Approved list of third countries</u> 1. What incentive is there for a third country to seek listing under Article 111b) when effectively it can 'self-certify' under Article 46 ? 2. Will membership of the 'approved list' of third countries be subject to review ? If the answer is yes, how frequently and by what means ? 3. How will the list of approved countries be communicated to industry <u>'Self- Certification' of equivalence to EU GMP by a third country</u> 1. Will there be any scrutiny or evaluation of the statements from 'self-certifying' countries by EU authorities? Against what criteria can these countries 'self-certify'? 2. Can the Qualified Person (QP) accept a 'self-certification' without question, and, providing a satisfactory audit has been carried out, import the API ? <u>API Inspections</u> 1. What circumstances would trigger an EMA inspection of a third country API manufacturer ? 2. Will EDQM inspections continue independently or be part of this program? 3. What latitude is there to accept inspection by a PIC/s member as being equivalent to an EU competent authority or MRA authority inspection? EFPIA seeks early discussion with the Commission and EMA as to the implications of the new provisions and to help ensure that they are implemented in an appropriate manner that mitigates the risk of disruption to medicinal product availability.
Rationale	It is essential that there should be no disruption of the API supply chain as a result of the implementation of the FMD. The process for transition must be transparent and effective and application of the provisions proportionate


European Union Process Flow for API Importation
Light Green – GMP audit, Yellow = European Commission List, Light Blue = 3rd Country Statement, Pink = Exceptional reasons
Manufacturing Authorisation Holder Importing Site
3rd Country Mfg Site
3rd Country Agency
European Commission
EU Competent Authority
Decision to import an API
Verify that the API has been manufactured in accordance with standards equivalent to the EU (Article 46b(2)(a))
Establish if the country from which the API is being imported is on the European Commission list
Obtain written confirmation from the competent authority of the exporting 3rd country that the standards at the plant are equivalent to the EU and that the plant is subject to regular control and enforcement (Article 46b(2)(b))
Exceptional reasons (Article 46b(4)) Is there a concern over the availability of medicinal products ?
No
Yes
Cannot Import API
Execute relevant quality & importation requirements
Import API
Export API
Determine whether such a statement can be accepted (see below)
Audit of API manufacturer by Manufacturing Authorisation Holder (Article 46(f))
GMP Standards acceptable ?
Apply to European Commission to join list of countries accepted for importation (Article 111(b)(1))
Determine whether such a statement can be written
Provide written confirmation that the standards at the plant are at least equivalent to those in the community and that the plant is subject to control and enforcement
Application acceptable ? (Article 111b(1))
Verify/ Add to List
Is country on EC List ? (Article 111b)
Point for Discussion
The text in the black box is not specifically in the Directive. The question is :- what is the MAH's responsibility with respect to accepting the confirmation supplied by the 3rd country, does the MAH accept the confirmation without question or do they have to make a decision themselves on whether it is acceptable ?
Request Inspection of Plant by Member State Agency
Acceptable Inspection and GMP certificate Issued?