MARKETING AUTHORISATION **RESPONSIBILITIES**

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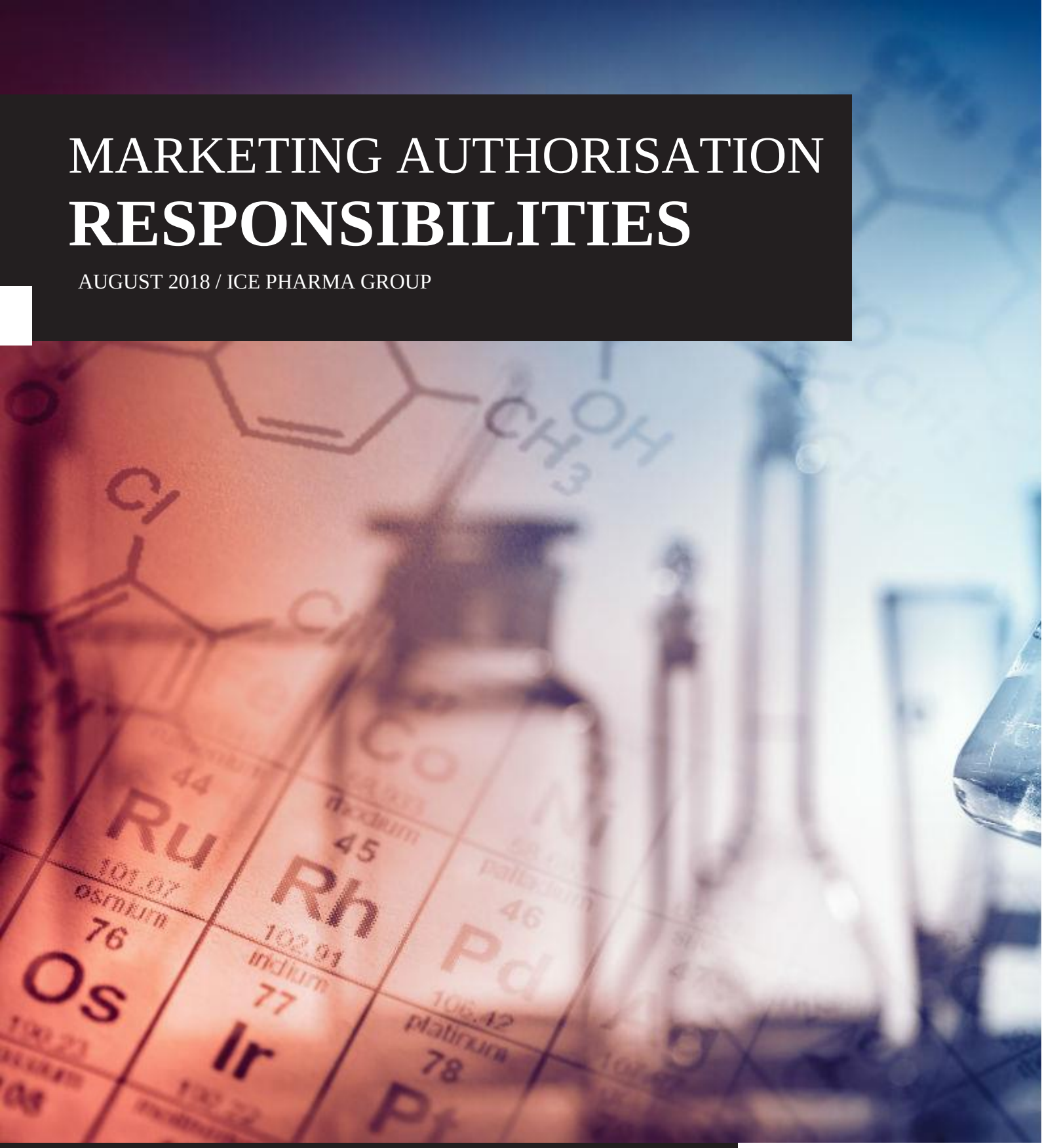

SUMMARY

An outline of the essential responsibilities of being the owner of a Marketing Authorisation in Europe together with your obligations to ensure that systems are in place not to have the MA withdrawn.

ice pharma group

ICE PHARMA GROUP

ICE Pharma Group (IPG) is a UK based generic pharmaceutical company with its own Marketing Authorisations (MAs) and experienced operational teams who can manage the manufacturing process through to a final product release into the European market. IPG is MHRA approved, holds GMP and GDP certification, and has approvals to import both APIs and Finished Drugs from outside Europe.

We have Manufacturing and Importation Authorisation (MIA) and Wholesale Distribution Authorisation (WDA) for import and sales of products in Europe.

IPG was founded in the UK in 1999 to source API's and intermediates. The company achieved early success in introducing new Indian and Chinese manufacturers to the generics sector. Eventually moving up the value chain, IPG has built extensive experience through a range of projects and has built a network of highly skilled industry experts in manufacturing generic products, owning licenses and providing support services to new MAH's and more. IPG has also helped launch numerous new generics onto the world markets; providing its customers and partners with technical and commercial expertise, critical to successful project implementation.

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1.0. Summary of regulatory obligations of Marketing Authorisation Holders (MAH):

The MAH is obliged to maintain a quality system which is suitable for covering the following activities:

1.1. Maintaining an accurate and current product Registration Dossier:

The MAH is obliged to keep the dossier which makes up the license up to date. Any changes to the product dossier must be approved by submitting license variations to the Health Authorisation (HA) where necessary before being applied in commercial production of the product. Variations include anything that reflects changes to safety, efficacy and/or quality of the product.

Commission regulation EC 1234/2008 should be followed for guidelines with regards to variations. A classification guideline has been issued by the commission which describes different types of changes, documents and associated Regulator fees for variation applications. IPG Regulatory work stream module covers the main variations.

Note that whilst changes are being assessed at the authorities no MRP or duplications can take place and where an MRP or duplicate is taking place no changes will be accepted by the authorities.

Note that it always wise to lay down your product strategies for up to three years so that the regulatory strategies and pathways can be established. All the responsibilities laid out in this fact sheet always have an important influence

1.2 MA renewal:

An MA is granted for a fixed period as specified in the grant letter: normally five years. It is the responsibility of the MAH to apply for renewal of the MA before it is due to expire and to support the renewal with all the required supporting documentation. In exceptional justifiable cases and with prior permission, the submission of the renewal may be delayed. The date of renewal falls due to the then owner of the MA. If a change of ownership has occurred, then the new owner is obliged to renew the license. If no production has taken place, then an extension under the sunset provisions can be applied for.

1.3. MA compliance:

An MA for a medicinal product is granted on the basis that a company can ensure continuous supply of a product of quality strictly in accordance with the dossier and current GMP.

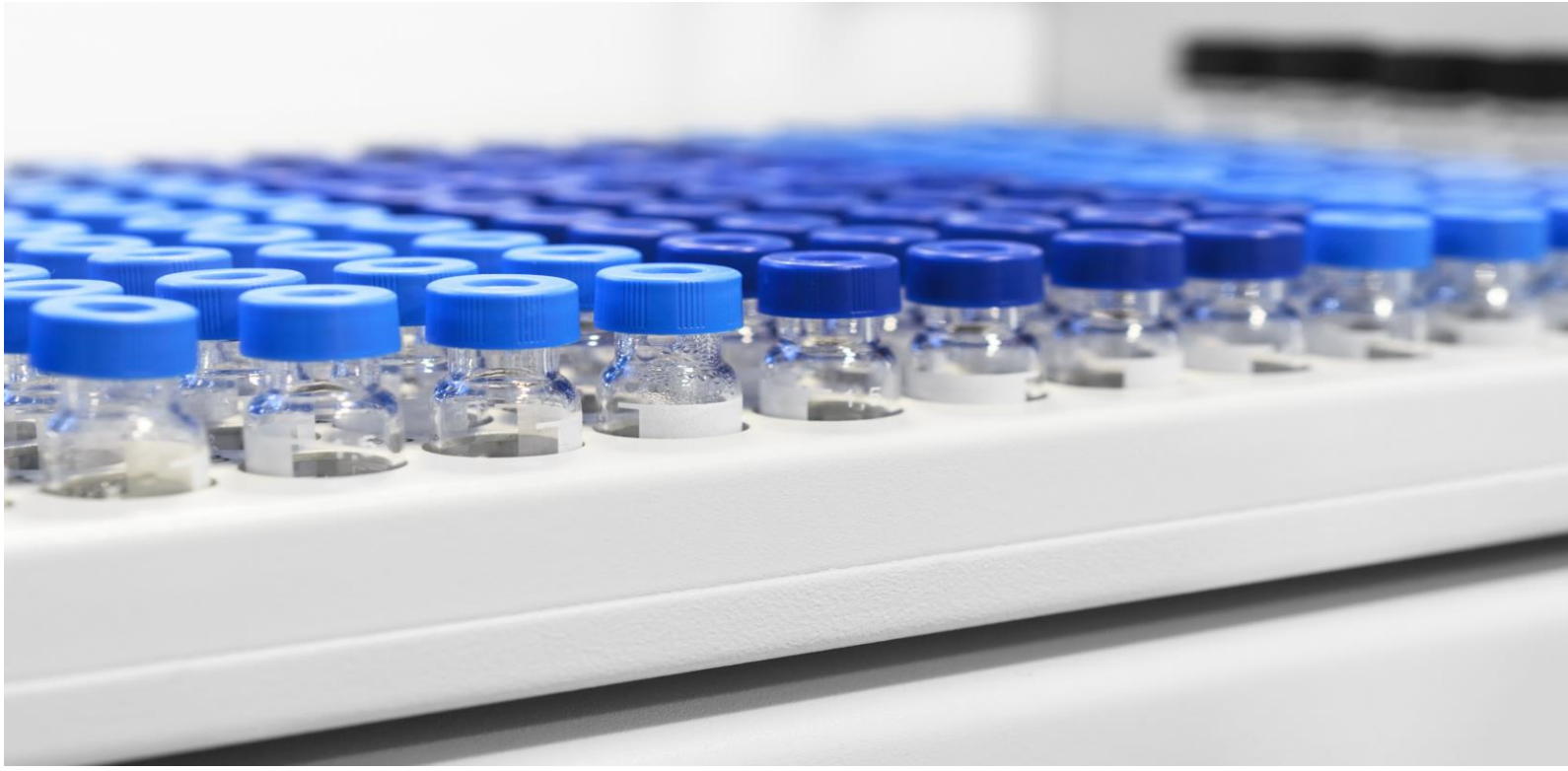
The MAH is expected to follow the rules of GMP, GDP and GCP. Some of the obligations include but are not limited to: (Directive 2001/83/EC refers) and deviations result in loss of all MA's.

- Maintenance of manufacturing site in terms of facilities, resources, equipment.
- Training of personnel involved in all stages of manufacture and release
- Implementation of a proper document approval and change control system.
- Build and implement a quality system to ensure batch to batch uniformity and minimize deviations and out of specification results. An essential component is the annual product quality review of each product.
- Regular audit of suppliers, manufacturing site, warehouses, retention site and contract laboratories to assure conformance to GMP. Particular attention should be paid to GMP status of API suppliers. By regular is meant no less than every three years [with managed corrective action plans] – we recommend tighter time control as the objective of risk assessment falls to the MAH and Regulator audits of the MAH will focus on risk assessment.
- Internal audit by third party expert, normally the external QP, to review compliance and manage corrective actions and improvements.
- Technical Contracts must be in place with all third-party suppliers approved by the QP. It is recommended that commercial counterpart contract is also in place – these should also clearly state the management of quality issues and the methods to handle these commercially.
- The MAH must have a quality system with clear procedures documents and SOP's and ensure that the quality system is reviewed at regular intervals.

Note that it always wise to lay down your product strategies for up to three years so that the regulatory strategies and pathways can be established. All the responsibilities laid out in this fact sheet always have an important influence

1.4 Batch release:

- MAH's are responsible for monitoring batch release activities of their product in collaboration with an EU Qualified Person QP (fact sheet 2). Every MAH must appoint a Quality QP for each individual license and no batch of medicinal product can be released into market without the QP's certification/approval. The QP must continually be at the MAH's disposal. The QP must operate independently, be under contract with the MAH, their qualifications be appropriate and registered with the EU regulatory authorities.
- The MAH is responsible for ensuring that each batch of product is shipped with temperature logging equipment. The temperature data must be available for the QP to inspect before he is able to release the product to the market. The MAH must manage and control the supply chain to ensure that the product does not deviate from the stable temperature ranges stated for the product in the dossier.
- Certificate of release by the QP can be given only after the product is QC tested by an approved and contracted EU QC laboratory in the MA. Appropriate prior product test method transfer/validation having taken place to ensure that the dossier methods at the manufacturing site and the QC laboratory are the same using the same equipment.
- As per guidelines set out in the "Rules



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and Guidance for Pharmaceutical Manufacturers and Distributors" (2007 Edition). The control of the flow and traceability of the product throughout the supply chain must be maintained at all times.

- Any company or individual wishing to sell, supply medicinal products or procuring to anyone other than the end-user within the EU must hold a wholesale dealer's license (WL). The MAH must also ensure that their customers, other than registered pharmacies must also possess a WL and that this is regularly checked with receipt of copy certificates. If the product is manufactured outside of the EU, a 'Manufacturers and Importers Authorisation' must also be held. IPG hold such licenses.
- Samples from each commercial batch must be retained both at the site of manufacturer and an independent location chosen and audited by the MAH.

1.5 Specific obligations with respect to license terms and dossier:

1.5.1 Follow the same process of manufacture and method of analysis as per license.

- The validated technology as described in the product dossier must be followed. If this is not possible, an assessment must be made, change control form completed with clear reasons for change, validation must take place along with preparation of stability data and approval by the QP. The Regulator recognizes that changes are often required for commercial reasons like API supplier, batch size and change of site and these need to follow the same change control and approval process.
- Any changes will incur time and cost due to the need for revalidation and submission of appropriate data to the Regulator for approval.
- Manufacturing methods and methods of analysis must also be followed as described in the product dossier. As above, any necessary changes must be evaluated against time and cost and can only be agreed upon written approval from the PL holder.
- It is essential that NO changes are implemented without receiving approval from the regulatory authorities.

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- Any deviations during manufacture must be reported to the MAH by the manufacturer along an analysis of the reasons. Corrective actions much be entered in to. Sometimes a batch to batch variation can be submitted to the regulator along with clear evidence that the deviation does not pose a risk to health and that the QP is supportive.
- A quality complaint process is required, and corrective actions managed.

1.5.2 Raw materials

1.5.2.1 GMP

- Approved Active Substance suppliers are stated in the dossier and must only be used. They must be audited. If the contract manufacturer as part of their internal supplier approval program has not approved these suppliers, they must be audited for compliance against EU cGMP. Technical Agreements must also be in place.
- The API must be analysed in full for compliance prior to its use in the product, and retained samples kept for one year past product batch expiry date.
- The Qualified Person responsible for release of finished product in the EU must also be satisfied that all active substance suppliers conform to EU cGMP. Audits are required. Audits of Active Substance Manufacturers should be performed every 2/3 years.
- Addition of an alternative source of API supplier must be approved by the regulator and supported by QP statement of approval and change contract SOP and vendor approval SOP.
- If excipient suppliers are stated in the product dossier, these must be used and meet the stated pharmacopeia. Otherwise, alternative excipient sources may be used providing they manufacture to EU cGMP and can meet specifications as detailed in the dossier and stability testing is performed to prove a match in the product. It is advisable, but not an obligation, to audit every 3 years. These materials must be analysed for compliance prior to its use in the product, and retained samples kept for one year past product batch expiry date.

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1.5.2.2 Specifications:

- The specifications of starting materials (excipients and actives) must be followed according to specifications as described in the product dossier.
- QC testing undertaken must be performed in accordance with current EU Good Manufacturing Practice as applies to QC testing laboratories.

1.5.3 Validation batch and batch size

- Current validated pack sizes and batch size/range as per license must be used.
- Tablet sizes and primary packaging in the dossier must be complied with.
- Validation batch sizes must not exceed the registered batch sizes in the dossier or go outside of the range
- Batch sizes can be changed as far as appropriate validation permits and stability data is in support. Increase should not be in more than ten times multiples.
- Validation batches must be representative of the commercial scale which will be routinely used.

At least one batch of the product must be sold in the market per annum in order for the license to remain active or an application for exemption from invalidation must be applied for.

1.5.4 Artwork

- All artworks must have prior approval from the Regulator. Any changes proposed must be evaluated and approved and be passed through the artwork approval system in the Quality systems. Colour

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- coding for strength awareness is now an obligation and must be complied with. Artwork history needs to be maintained.
- Patient Information Leaflets must be user readability tested according to guidelines. The Readability data and expert report must be submitted to the Regulator. Due to timelines this should be done at the earliest possible time but no later than 9 months before the intended first commercialization date following any MA purchase or if fresh application before submission. Leaflets must also be available in alternative 'accessible' formats if requested. PIL readability.
- All EU artworks for self-administered medicine require Braille embossing on the outer packaging. Article 56(a) of Council Directive 2001/83/EC gives more information on the Braille requirement.
- All printed materials must only have one language. Translation will need to be conducted for any non-English speaking markets at a stage appropriate to the regulatory plan.

1.5.5 Safety Updates

- The safety of products is constantly being reviewed by the Regulator. Occasionally changes to the SPC and PIL is required as a result and these changes are issued by the Regulator and must be implemented by a set timeline as dictated by the Regulator. Following the submission of periodic safety update reports resulting from pharmacovigilance an update to the SPC and PIL could also result.

1.6 Technical Agreements Required

Technical agreements need to be in place between the MA holder and:

- Finished Product Manufacturer
- EU distribution provider site
- Batch release site
- Qualified Person
- Qualified Person Pharmacovigilance
- Medical Advisor
- Active Substance Manufacturer(s)
- Third party auditors
- Sample retention site
- Customer product safety co-operation.

Implement, maintain and periodically review to an agreed program as part of the Quality System.

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1.7 Pharmacovigilance

- Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The MA holder must have a system for handling Pharmacovigilance that covers all of their marketed products in the EU. Failure to comply will lead to removal of all licenses.

- Must have a named QP for Pharmacovigilance (QPPV) for all products.
- Must have a medical advisor available to support the QPPV and products
- Training on the handling of any adverse drug events is essential.
- Service Agreement between QPPV and MA holder is required.
- Must maintain procedures which continually monitor the safety of their products

MAH's will be audited by the Regulator for compliance with safety (Pharmacovigilance) and the obligations concerned with GMP (Good Manufacturing Practice) of the product. This is performed under a risk-based system and occurs typically every 2 years.

The obligation for Pharmacovigilance commences from the day that a license is in your company's name.

Important Note

The IPG fact sheets do not substitute or purport to replace the MAH obligations to fully understand the details contained within the European Commission's Regulations and Guidelines concerning the manufacture and control of Medicines.