COMPLIANCE
GOVERNANCE

MARKETING AUTHORISATION HOLDER GUIDE 2021

Prepared by
IPG Pharma Ltd

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Marketing Authorisation in Europe together with your obligations to ensure that systems are in place not to have the MA withdrawn.

Issue: January 2021
Valid to : January, 2022

WHAT IS

INCLUDED WITHIN THIS DOCUMENT

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PROFILE

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The Pillars of Compliance

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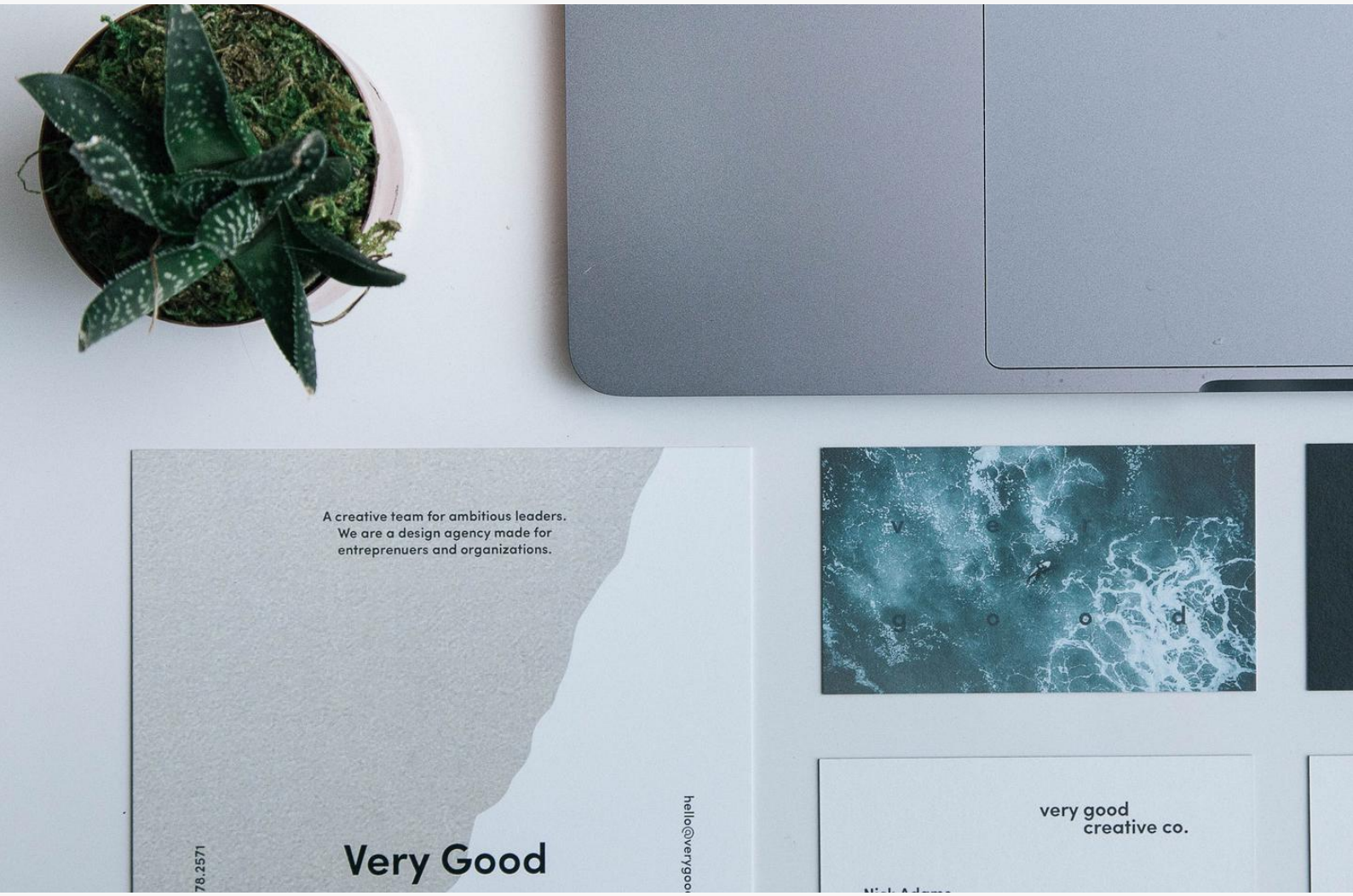
We bring together our experience and knowledge to build project strategies that span multiple functions across the pharmaceutical journey to bring a product to market



COVER LETTER

Greetings!

We have condensed the Marketing Authorisation Holder's Responsibilities into a simple, easy to read document with additional fact sheets to help you to understand the scope of work needed to be a MAH.

ICE Pharma Group (IPG) was founded in 1999 as pharmaceutical services operation specialising in global business development and licensing, regulatory and quality management, sourcing and procurement.

We have a 20-year history in industry meaning that we have built strong relationships on a global scale and a deep network of connections. More recently gaining MHRA/FDA approvals for new facilities in China for injection anti-infectives and oncology drugs. IPG has been successfully supplying the UK NHS and other EU countries with hospital products since 2012.

With our vast expertise we hope to assist you in growing your business and finding pharmaceutical solutions for your success.

David Bilton
Chief Executive Officer

LETTER

WHAT WE DO

IPG Pharma is a generic pharmaceutical company with its own Marketing Authorisations (MAs).

Nothing we therefore do is theory; we have to practice what we preach. Our experienced operational teams manage the supply chain from API through to a final product release into the European market. IPG has held MHRA approvals during the past 13 years for Manufacturing and Importation Authorisation (MIA) and Wholesale Distribution Authorisation (WDA) for import and sales of products in Europe along with GMP and GDP.

We have gained significant expertise.

We specialise in providing pharmaceutical products and creating unique pharmaceutical business solutions to help our customers get the best out of their business.

Generics

IPG has also helped launch numerous new generics onto the world markets.

Providing customers and partners with technical and commercial expertise, critical to successful project implementation. For further details download the slide deck from our website.

MAH RESPONSIBILITIES OUTLINE

ESSENTIAL QUALITY FACTORS

Quality Management

1. Create and maintain a quality system that is adequate for the activities required, this should cover as a minimum, change control, CAPAs, deviations, recalls, customer complaints, supplier approval, self-inspection programme.

Staff Training

2. Internal staff training programme and ongoing review

Product License

3. Maintain an accurate and current product registration dossier associated with their product licence.

Changes

4. Do not allow any changes to the product by the manufacturing site prior to a variation being submitted to the regulatory authority, or the licence will be out of compliance.

a. Variations

Renewal

5. MAH will need to apply for a renewal of their product licence, it usually lasts for 5 years

MAH RESPONSIBILITIES OUTLINE

Pharmaconvigilence

6. Pharmacovigilance (PV) needs to be in place, with a QPPV, Deputy QPPV and Medical advisor.

Reviews

7. Annual Product Quality reviews (APQRs)/ Reports.

Stability

8. Stability requirements.

a. Why needed and for how long?

b. Trend analysis, - links to APQRs.

MAH RESPONSIBILITIES OUTLINE

9. Supplier Audits

These are to ensure each supply partner is working to their area of the regulations/product licence. Ensure a schedule is created and adhered to. These are on a risk basis, but none the less always within 3 years.

a. Active pharmaceutical Ingredients sites
b. Finished product manufacturing sites
c. Contract Quality Control testing laboratories
d. Batch Release site
e. Pharmacovigilance contractors
f. Outsourced Regulatory partners
g. Outsourced MIA partners
h. Outsourced WDA partners
i. Any utilised Third-party auditors
j. Contract Qualified Persons Pharmacovigilance
k. Contract Qualified Person

MAH RESPONSIBILITIES OUTLINE

10. Ensure Quality Technical Agreements are in place and followed by all outsourced partners (as above list)

11. Ensure Quality Technical Agreement in place with any contract Qualified Person (QP)

12. MAH is responsible for the final disposition, along with the batch releasing QP and RP, for any recall and for informing the local authority so that they can agree the recall classification.

13. Approval of the artwork designs and ensuring that no unapproved artwork is used during manufacture, alongside the QP.

If its not documented, it hasn't happened.

IPG Philosophy

MAH RESPONSIBILITIES OUTLINE

ADDITIONAL KNOWLEDGE

A

What is an eCTD dossier?

A CTD dossier (Common Technical Dossier) means the contents is arranged in the same format every time. This makes for ease of use and everyone knows the what any section is meant to contain.

B

What is a Drug Master file (DMF) and CEP

A Drug Master File (DMF) contains all the information about the manufacture and control of an API (Active Pharmaceutical Ingredient) presented in a common format. It comes in two parts. The closed part which contains all the confidential details of how to make the API which only the Regulator sees and the open part (also called the applicants part or technical package) used in support of the dossier.

A CEP (Certificate of Suitability to the monographs of the European Pharmacopeia) issued by the EDQM (European Directorate for the Quality of Medicines and Healthcare) to declare that an API is suitable for use. If there is no European Pharmacopeia (EP) for an API then there can be no CEP. The CEP when granted is for APIs and is based essentially on the EDMF.

C

Technical Transfers

A technology transfer is required when a pharmaceutical company wants to change from an existing manufacturing site to a new manufacturing site or move from one process of manufacture to another, or one manufacturing facility to another.

D

What is a Risk Management Plan (RMP) ?

A Risk Management Plan (RMP) is a document that describes the safety profile and efficacy of a pharmaceutical product and should contain a plan to evaluate risks and cater for remedial actions.

MAH RESPONSIBILITIES

Summary of regulatory obligations for Marketing Authorisation Holders (MAH)

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

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, this is because all audits should be within 3 years. All the responsibilities laid out in this fact sheet always have an important influence.

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.

MAH RESPONSIBILITIES

Summary of regulatory obligations for Marketing Authorisation Holders (MAH)

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.

MAH RESPONSIBILITIES

Summary of regulatory obligations for Marketing Authorisation Holders (MAH)

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 Qualified 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 and Guidance for Pharmaceutical Manufacturers and Distributors" (2017 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 (WDA). The MAH must also ensure that their customers, other than registered pharmacies must also possess a WDA 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.

Samples from each commercial batch must be retained both at the site of manufacturer and an independent location chosen and audited by the MAH.

MAH RESPONSIBILITIES

Specific obligations with respect to license terms and dossier:

5. Obligations:

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 MA holder.

It is essential that NO changes are implemented without receiving approval from the regulatory authorities.

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 specific 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.

MAH RESPONSIBILITIES

Raw materials

6. 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

7. 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.

MAH RESPONSIBILITIES

8. 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.

9. 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 coding for strength awareness is now an obligation and must be complied with. Artwork history needs to be maintained.

Patient Information Leaflets (PIL) 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.

MAH RESPONSIBILITIES

Raw materials

10. Safety Updates

The safety of products is constantly being reviewed by the Regulator. Occasionally changes to the SPC (Summary Product Characteristics) 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.

11. 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

Contract RP (Responsible Person)

Contract RPi (Responsible Person Import

MAH RESPONSIBILITIES

12. 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.

13. Technical Transfer

A technology transfer is required when a pharmaceutical company wants to change from an existing manufacturing site to a new manufacturing site or move from one process of manufacture to another, or one manufacturing facility to another. It is a systematic procedure that is followed to pass the documented knowledge and experience gained during development and or commercialization to another responsible party (the receiving unit) with the demonstrated ability to effectively perform the critical elements of the transferred technology to the satisfaction of all parties and the regulatory bodies. For each change the regulatory bodies require to see all the essential documentation and proof that the new manufacturing site is making the exact same product in the same way. Where changes are needed for the manufacturing site to make the product documentation to support the difference is required.

MAH RESPONSIBILITIES

14. Supply Chain and GDP

It is an essential requirement and obligation of the MAH that they fully understand and can map the entire supply chain all the way from the key raw materials and packing through each stage of the manufacturing and packaging process right through to the end client whilst knowing who handles the product along the way. The GDP regulations are very demanding and tracking all movements of product in detail is required.

Important Note; The IPG fact sheets do not substitute or purport to replace the obligations in the European Commission's Regulations and Guidelines concerning the manufacture and control of Medicines. Any proposed change, or contemplated change to any of the aspects of the MAH Obligations must be fully documented and a clear and non-ambiguous implementation plan approved in the QMS.

MAH RESPONSIBILITIES

Know what you are buying.

Falsified Medicine Check

MAH RESPONSIBILITIES

The WDA holder needs to have systems in place to identify a potential false product.

Are all the protections on the pack, QR code and is it real, tamper seal in place.

Returns cannot always be used, is your quarantine system robust.

If your delivery has not been "supply chain mapped", how do you know if the product has not been switched on route.

Are all the staff that "touch and see the product" properly trained.

Is the container seal the same number you were advised.

We therefore have to approve all new suppliers, audit suppliers, know the suppliers being used, check your customer is permitted to handle human medicines, have Technical Agreements in place, check that supplier's documents are correct, check staff are following the SOPs and trained.

If the delivery is diverted, where has it been, did it get transhipped.

Has the artwork changed.

THE PILLARS OF COMPLIANCE

These essential packages provide sufficient instruction for you to progress your business. All available for purchase. If you are going to proceed with IPG, we will provide you with a Compliance Suite of documented instructions around the following;

The WDA

These packages offers a high standard of service

The MIA

A long-standing popular version or model.

GMP

It was generally perceived as having an unique quality.

GDP

These packages offers a high standard of service

APIA

A long-standing popular version or model.

MAH Guide

An outline of the responsibilities of an MAH holder and the relation to the other essential pillars of compliance.

Specials Approvals

Where a product does not have an MA in the UK/EU.

Named Patient Approvals

Where a pharmacy has script for a product not licensed in the country of the patient.

THE PILLARS OF COMPLIANCE

These essential packages provide sufficient instruction for you to progress your business. All available for purchase. If you are going to proceed with IPG, we will provide you with a Compliance Suite of documented instructions around the following;

QPPV

Responsibilities of the Qualified Person for Pharmaconviglilence.

RP

Responsibilities of the Responsible Person.

RPi

Responsibilities of the Responsible Person for import.

QP

Responsibilities of the Qualified Person.

Auditing

An outline of auditing

QMS

Outline of the Quality Management system.

ABOUT US

Our strategies are built on more than just process and tools. We come to understand your business and growth objectives, and tailor our plans to fit your specific needs.

"Nothing we do is theory"

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.

TIMELINE

OUR HISTORY

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

MILESTONES

1999 — **IPG Founded**

IPG was founded by David Kenneth Bilton in 1999 to source APIs.

2003 — **China**

Started trading finished dose and China operations established

2008 — **Licenses**

First MA in UK market (Enalapril).
MIA and WDA licenses granted

2009 — **Launching**

Opened the Canadian Offices. Launched Generic Licensing

2010 — **Tech Transfers**

China tech transfers started

TIMELINE

2012 — **End to End**

First Full Service Client

2013 — **NHS**

First NHS Tender won for 3 molecules

2014 — **Global Reach**

New Zealand Office Opened. Active Pharmaceutical Ingredient Registration obtained.

2017 — **Supply Chain**

Complex supply chain first project

2018 — **Africa**

1 st supply TB & PPE products to Africa

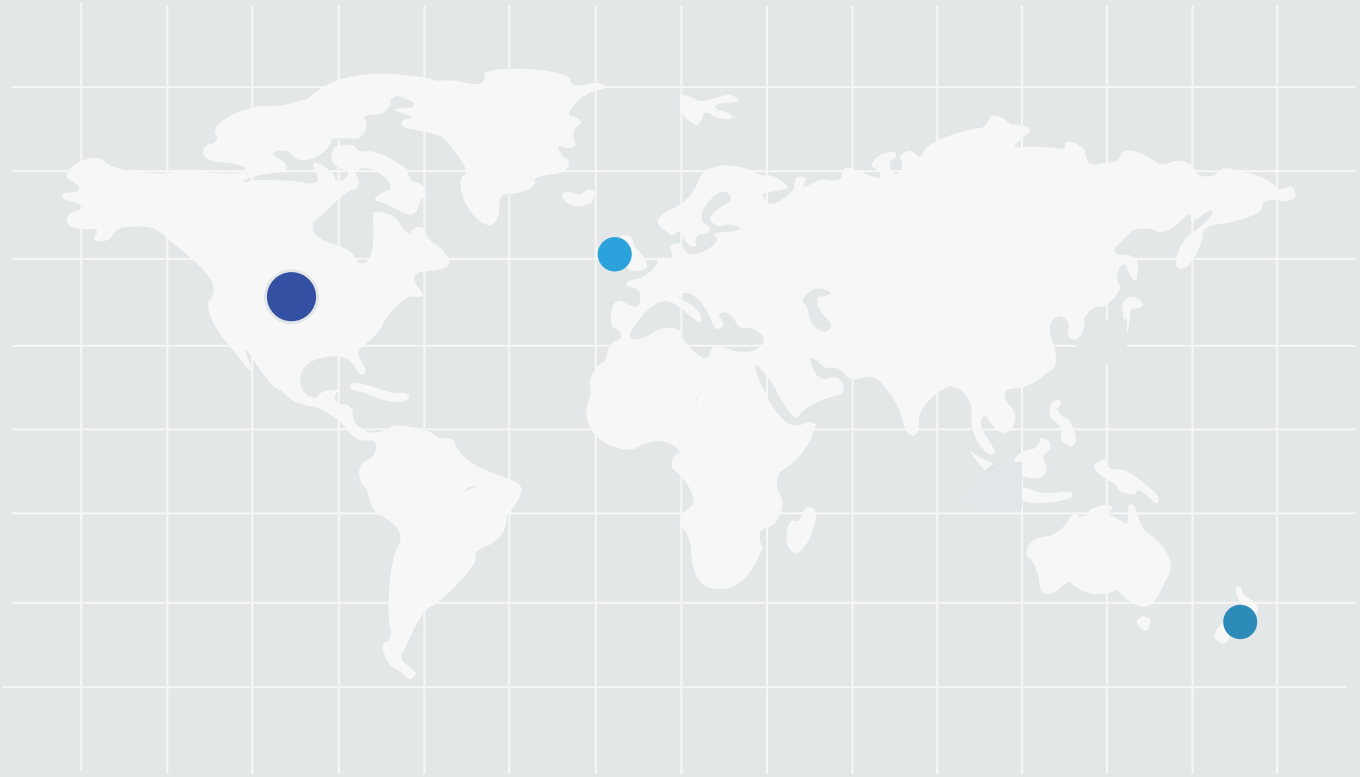
2019 — **New Business Launch**

Launched men’s telehealth program

ipg
ice pharma group

GLOBAL REACH

We have offices in the UK, New Zealand and Canada. We operate mainly within the EU, Middle Eastern, and Far Eastern Markets, we have been operating in China since 2005 and in America since 1999.



Expertise

Our expertise is built on over 20 years of industry knowledge and experience. Our core staff bring a wealth of industry know how. We have worked on a large variety of projects from sourcing novel APIs to getting new workshops GMP approved, to large complex projects that encompass sourcing product licenses, gaining 120 EU marketing authorisations and commercial supply across 18 EU countries, as well as delivering hundreds of products into struggling developing nations and large-scale supplies of personal protective products across the world. With an extensive network our reach is global

Our core capabilities include:

- Supply chain management
- Complex projects
- Regulatory and compliance
- Sourcing and supply

ice pharma group

COMPLIANCE
GOVERNANCE

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