BlueReg
PHARMA CONSULTING

EU Expertise

Webinar

28 APRIL 2021

11AM EDT | 4PM BST | 5PM CEST

Regulatory compliance:

How to accelerate your medicinal product launch in Europe?

Anne-Valérie Faucher

- Associate Director, Regulatory Affairs

Nadia Boehringer

- Vice President, Global Head Regulatory & Scientific Affairs

Welcome
The speakers

Claire RAY
Director, Regulatory Affairs

- **Nadia BOEHRINGER**
  - *Vice-President, Global Operating Unit*
  - *Leads the Global Operating team contributing to global development, registration and maintenance of pharmaceutical products*

- **Anne-Valérie FAUCHER**
  - *Associate Director, Regulatory Affairs*
  - *Broad experience in registration, lifecycle management and regulatory launch*

BlueReg
PHARMA CONSULTING

Welcome
Webinar Agenda

Agenda	Webinar Timings
• Design of the regulatory strategy to prepare the launch sequence for your first medicinal product in Europe • Compliance with the EU and local requirements after a centralised procedure • Coordination and set up of a tailored outsourcing regulatory platform	45 minutes
Q&A session with the BlueReg experts	15 minutes

Please send your questions for the Q&A using the Q&A box at the bottom of your screen

BlueReg
PHARMA CONSULTING

1. Regulatory Strategy

How to prepare the regulatory launch sequence for your first medicinal product in Europe?

BlueReg
PHARMA CONSULTING

EU Marketing Authorisation (MA)

- **A sponsor may have several options to request a marketing authorisation for a new drug in Europe (EU)**

- **Centralised procedure, if eligible**
  - A single marketing authorisation in all EU countries
  - Granted by the European Commission following the scientific assessment of the application by the relevant committees at the European Medicines Agency (EMA)

- **Once the MA is granted, a large number of other national regulatory activities are still required prior to the commercial launch of a medicinal product in every EU country**

BlueReg
PHARMA CONSULTING

Regulatory Strategy Considerations (1/3)

- **Compliance to local national regulations**

- **Implement a regulatory strategy which matches with:**
  - marketing expectations
  - regulatory constraints
  - future geographical roll out in non-EU countries
- **Coordination of all stakeholders at both global and local levels**
- **How to structure local support: no affiliates and/or agents in all EU countries of interest**

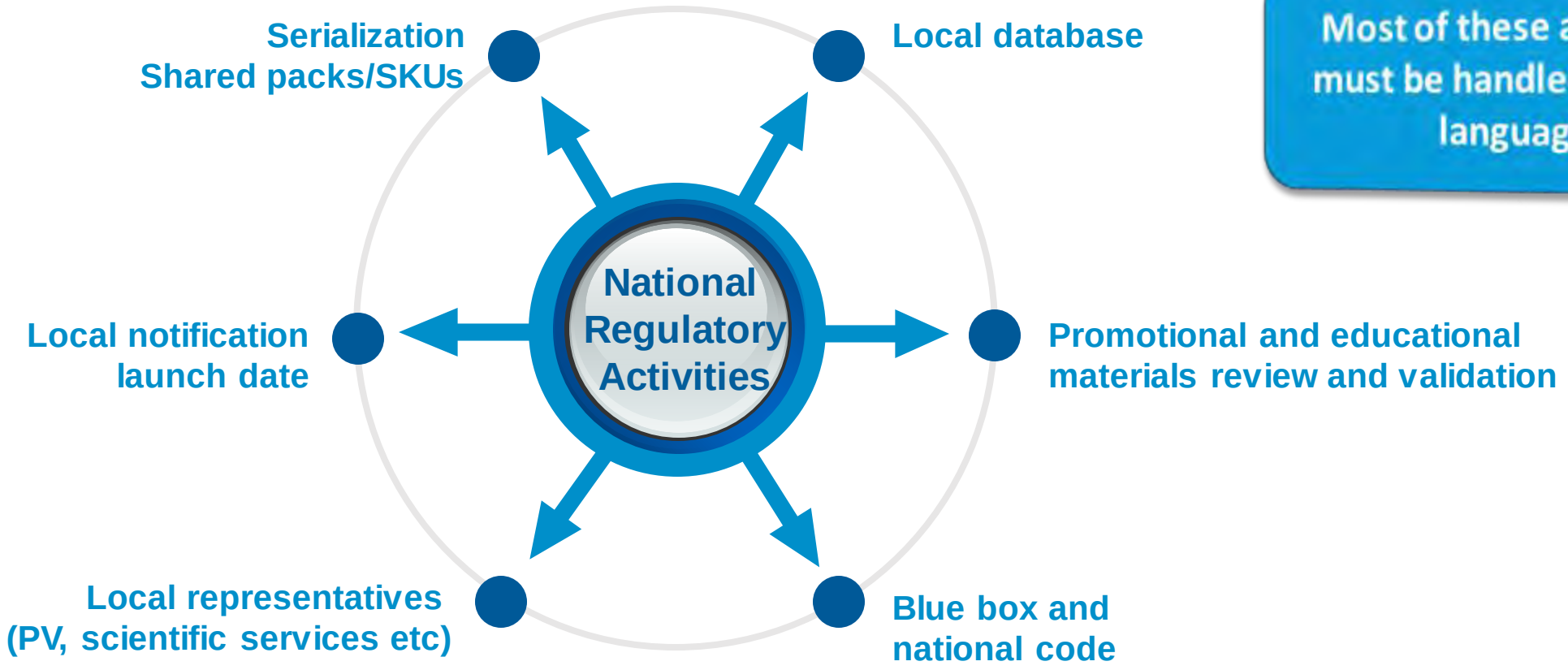
BlueReg
PHARMA CONSULTING

Regulatory Strategy Considerations (2/3)

- **When should commercial launch preparation be initiated?**
- **Consideration of early access program (EAP)?**
  - And if yes, what would be the process to move from an EAP to a commercial launch? What will be the transitional period?
- **How to organise the launch sequence from a regulatory point of view?**
- **Resources/main stakeholders required at global and local levels?**
- **What general local requirements are absolutely mandatory for the launch versus nice to have?**
- **Particular requirements adapted to your product, your distribution and your patients?**
- **Geographical roll out and the impact on future non-EU registration, launches and price?**

BlueReg PHARMA CONSULTING

Regulatory Strategy Considerations (3/3)



Most of these activities must be handled in local language

BlueReg
PHARMA CONSULTING

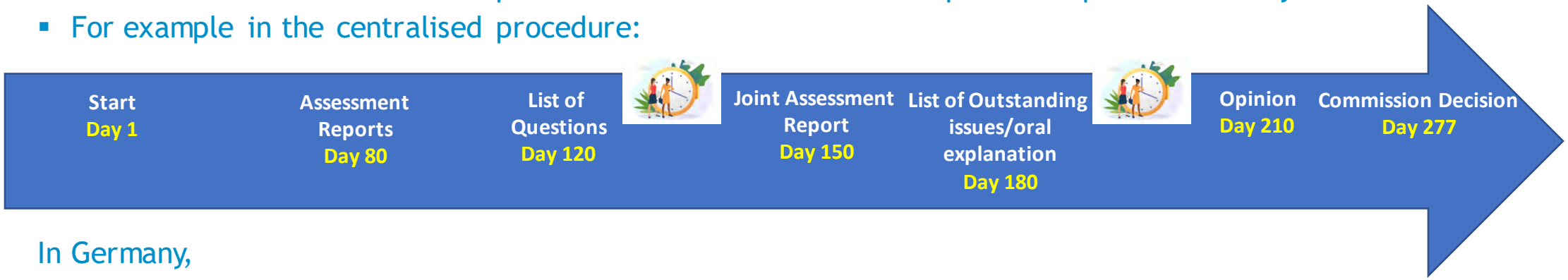
How to Plan the Regulatory Activities of your Medicinal Product Launch?

- **One word: ANTICIPATION!**
- **Plan well in advance what will happen for your future markets**
  - Part of your registration plan
    - ⇒ which countries are prioritised for the launch?
    - ⇒ do you want to set up an EAP in some of these countries?
  - Collate local requirements (regulatory/PV/quality etc) to understand set up priority
  - Put in place a robust project plan allowing for any regulatory hurdles and challenges encountered and ensure all stakeholders are aligned
  - Clearly communicate what is permissible in each market at each stage in terms of promotion etc
  - Assess your internal resources versus the immediate / longer term needs for skill set, local presence etc
  - Ensure adequate budget is in place and put in place contingency planning to fill the gap

BlueReg PHARMA CONSULTING

Planning of Activities for Local Market Launch is Crucial

- **Careful consideration to be given for the timing of each country activity to ensure rate limiting steps and potential delays are minimised**
  - Some activities can commence prior to EC decision but this is dependant upon the country concerned
  - For example in the centralised procedure:



In Germany,

⇒ local number, PZN, can be requested before CHMP opinion to start the serialisation preparation

⇒ educational materials must be translated as CHMP opinion is issued for immediate national submission

In Italy

⇒ Local number, SIS code, can be requested before CHMP opinion and once obtained the appointment of the proxy can be made

⇒ Submission of educational materials will occur post EC decision

BlueReg
PHARMA CONSULTING

2. Compliance with Regulatory Requirements

How to comply with the EU and local requirements after a centralised procedure?

BlueReg
PHARMA CONSULTING

European Definition

- **One pan-European Marketing Authorisation for the EU (30 countries) for which EU guidelines are applicable**
- **The reality is not so straight forward:**
  - 30 local variations due to mandatory local law / guidelines
  - 30 different local Health Agencies in addition to EMA
  - 30 different National Health Systems (NHS)
  - 25 languages

BlueReg PHARMA CONSULTING

Brexit Impact

- **The UK left formally the EU on 31st January 2020**
  - In Practice
    - Great Britain (GB) which represents England, Wales and Scotland
      - EU rules are no longer applicable
      - Medicines and Healthcare products Regulatory Agency (MHRA) guidelines/recommendations must be followed
    - Northern Ireland (NI)
      - EU rules are applicable
      - NI can be considered as a European Member State

Key Requirements to Launch a Product in the EU

BlueReg
PHARMA CONSULTING

Local Representatives (1/3)

- **Local representatives can be mandatory in some countries**
  - Regulatory
    - Responsible for regulatory actions at the local level, such as completion of local databases, obtaining the national code, blue box validation etc
    - Many forms / databases must be completed in local language
    - Qualification of the regulatory representative varies by country
      - Specific qualifications e.g. a pharmacist in France
      - Able to demonstrate the required knowledge to perform the corresponding activities (diploma and CV)
    - Notification to the local competent authority must be completed when required (Germany, France, Spain, Italy etc)

Local Representatives (2/3)

- **Local pharmacovigilance officer**
  - Works in conjunction with the EU Qualified Person Responsible For Pharmacovigilance (QPPV)
  - Responsible for all national PV requirements / actions e.g. adverse event reporting, contact point for local approval of educational material etc
  - Fluent in local language
  - Qualification required varies by country, but generally must be able to demonstrate valid experience
  - Notification to the local competent authority must be undertaken when required

- **Scientific Service**
  - Responsibilities vary per market, but commonly may include responsibility for:
    - Review, approval and submission (when required) for promotional and non promotional materials (in-line with the approved MA)
    - Legal responsibility for some local activities
    - Verification that sales representatives have been adequately trained
  - Required to be fluent in local language
  - Notification to the local competent authority must be undertaken when required

BlueReg PHARMA CONSULTING

Local Representatives (3/3)

Examples of local market representatives required

In green : mandatory
In purple : highly recommended

Country	Regulatory Affairs	Pharmacovigilance	Scientific Services
France	Exploitant (Chief Pharmaceutical Officer (CPO) and deputy)	Local Responsible for PV (LRPV)	Exploitant (Chief Pharmaceutical Officer (CPO) and deputy)
Germany	Information Officer (*Informationdbeauftragter*)	Graduated officer (*Stufenplanbeauftragter*)	Information Officer (Informationdbeauftragter)
Spain	Local contact required	Local PV	Local contact required
UK (NI & GB)	Not required	Local PV (GB)	Not required but require promotional approval signatory
Italy	Local representative (*concessionario*)	Local contact for PV	Local responsible person for Scientific Service (RSS)

BlueReg PHARMA CONSULTING

National Codes (1/2)

- **Varying rules across Europe**
  - Can be obtained after the CHMP positive opinion or after the EC decision (sometimes with the blue box validation)
    - To be requested at local level, using different forms / websites all in local language
    - Timelines vary significantly between markets
  - Number of digits is defined by individual countries which enable identification of the product by the packaging
  - Can be linked to the National Health System
  - Different local names (PZN, CIP code, PL number etc)
  - Must be printed in the blue box when defined in the local regulations / laws
    - Sometimes required in a specific area of the blue box e.g. Spanish national code must be printed in the upper right hand corner

BlueReg PHARMA CONSULTING

National Codes (2/2)

- **Example in Germany:**
  - The MAH must first obtain the national numbers:
    - PNR ("Pharmazeutischer Unternehmernummer" – Pharmaceutical company number)
    - ENR ("Eingangsnummer beim BfArM" – BfArM submission number)
    - The PNR and ENR are obtained in less than 1 week
  - Then the PZN (*Pharmazentralnummer)* forms must be completed in German (PNR and ENR are included in the forms)
    - The PZN is obtained in few days. Just before the commercialization, the PZN must be activated, a new submission has to be completed by the local representative in a defined time frame

PharmNet.Bund Recherche der pharmazeutischen Unternehmer- und Eingangsnummer 3/7

3 Eingangsnummer (ENR)

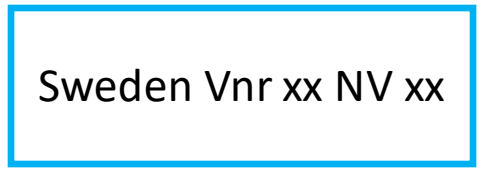
Als zweite Nummer wird eine ENR für eines Ihrer Produkte benötigt. Diese kann, wie nachfolgend beschrieben, bei Kenntnis der PNR über PharmNet.Bund einfach und kostenfrei recherchiert werden.

Rufen Sie hierfür die Webseite www.pharmnet-bund.de auf und klicken Sie auf das Feld „Arzneimittel-Informationssystem".
Wählen Sie die Option „Recherche für Fachkreise. Nach Anklicken erscheint ein Disclaimer der drei Zulassungsbehörden. Die Bedingungen werden durch anklicken der Schaltfläche „akzeptieren" angenommen.

Nun befinden Sie sich in der Rechercheumgebung. Um die jeweilige PNR zu ermitteln wählen Sie im obersten Auswahlmenü die Option „Pharmazeutischer Unternehmer-Nr." aus.

Blue Box

- **The information specific to a Member State should be accommodated on the label in a single blue boxed area (the so-called 'blue box') to appear on one side of the pack**
  - In compliance with "Guideline On The Packaging Information Of Medicinal Products For Human Use Authorised By The Union", version 14.4 dated December 2016
  - Presented in local language / languages of each country
  - 1 box specific per country with different information stipulated
    - At a minimum country + local national code
      - Nordics, Germany, Austria, Northern Ireland
    - Acronyms, legal status, symbols can also be required
      - France, Spain



Conducción: ver prospecto

BlueReg
PHARMA CONSULTING

Serialisation (1/3)

- **Falsified Medicines Directive (FMD) 2011/62/EU came into force in February 2019**
  - For all medicinal products subject to prescription which are not included in the list set out in Annex I to the directive
  - Characterised by
    - Unique Identifier (UI)
      - Alphanumerical code enabling the identification and authentication of individual packs
      - Depending on the country the national code may need to be embedded in the UI
    - Anti-Tampering Device (ATD)
      - Device allowing the verification of whether a pack has been opened/tampered with
      - Vary from stickers to glued end flaps with perforations to bottle caps which have plastic seals
  - All EU countries except Greece and Italy have until 2025 to implement the directive
    - For Italy: Bollino is already in place in line with local regulation
    - For Greece: EOF code is in place in line with local regulation

BlueReg PHARMA CONSULTING

Serialisation (2/3)

- **The Unique Identifier (UI) is defined through four data lines and is also represented using the data matrix:**
  - The product code
    - In countries where the national code is mandatory (AT, DE, ES, FR and Nordics), the NTIN (National Trade Item Number) can be used. The national code is embedded in the product code
      - To create a shared pack, some countries allow the NTIN to be replaced by the Global Trade Item Number (GTIN) e.g. Germany
    - In countries where the national code is not mandatory, the GTIN is used. This number is assigned by (Global Standards 1) GS1
  - The serial number is assigned by the finished product manufacturer
  - Batch number
  - Expiry date

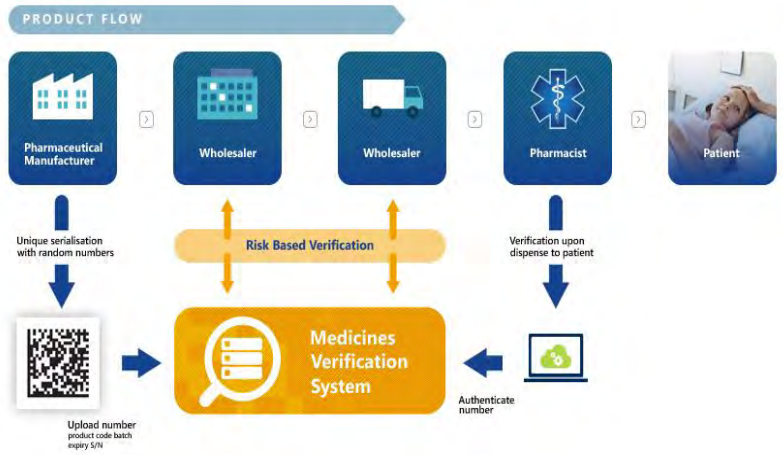
Data Matrix

(01) Product code (e.g. GTIN/NTIN/PPN)
(21) Serial Number
(10) Batch/Lot Number
(17) Expiry Date
National reimbursement number
(applicable to DE, FR, BR, ES, PT,)

BlueReg PHARMA CONSULTING

Serialisation (3/3)

- **EU MAH to be registered in the EU Hub (EMVS European Medicines Verification System)**
  - Contract and fees to be paid only at the time of registration
- **EU MAH to be registered in each EU country where a local launch is planned (NMVS National Medicines Verification System)**
  - Contract and fees at local level to be paid
    - Fee due initially at registration
    - Then annually based on turnover
- **For the EMVS and NMVS, all submissions must be performed by someone from the MAH (with an email address linked to the MAH)**
  - Timelines are variable and careful planning required



Source: https://emvo-medicines.eu/mission/emvs/

Local Databases

- **Accessible to Healthcare professionals (HCPs) and sometimes also to patients**
- **Key points to consider:**
  - All the databases are in local language
  - Different routes of registration
    - Automatic – Without MAH action
      - France: Public database at ANSM level
      - UK: Public database at MHRA level
    - Mandatory – With MAH action
      - Spain: *Raefar*
      - Sweden : *Liiv*
    - Recommended – With MAH action and fees
      - Germany: *Rote Liste* & *FachinfoService*
      - France: *Vidal*
      - Sweden: *Fass*

Local Launch Date Notification

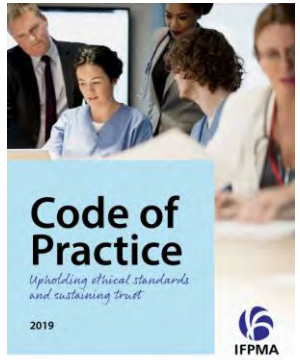
- **The European marketing status must be submitted to the EMA and in addition local actions may be required**
  - Mandatory : Simple notification in the database (in local language):
    - Sweden: to be completed 1 working day before the launch date
    - Spain: to be undertaken a minimum of 15 days before the product commercialization
  - Mandatory: Declaration to be submitted (in local language):
    - France: form to be completed and submitted to the local Agency
    - Germany: form to be completed and submitted to the local Agency approximately 3 weeks before the expected launch date

BlueReg PHARMA CONSULTING

Promotional Materials (1/2)

- **International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)**
  - Global standards for the ethical promotion of pharmaceutical products to HCPs

- **European Federation of Pharmaceutical Industries and Associations (EFPIA)**
  - European ethics rules for promotion of medicinal products to HCPs
    - Advertising of prescription-only medicines is limited to healthcare professionals
    - Materials must be compliant with approved Summary of Product Characteristics
    - Information must be accurate, up to date and verifiable
    - Product must be presented objectively and without exaggerating its properties



Promotional Materials (2/2)

- **Local code / laws applicable per country**

	Germany	France	UK (GB and NI)
Local law	Law on Advertising in the Health Sector (*Heilmittelwerbegesetz - HWG*), Law on the Trade in Medicinal Products (*Arzneimittelgesetz - AMG*) Act against Unfair Competition (*Gesetz gegen den unlauteren Wettbewerb - UWG*) which contains more general advertising rules	Consumer Code (*Code de la Consommation*) Public Health Code (*Code de la Santé Publique - CSP*)	Blue Guide "Advertising and Promotion of Medicines in the UK" For prescription medicines: Code of Practice of the Association of the British Pharmaceutical Industry" (ABPI)
Signatory	Information officer	Responsible Pharmacist / Chief Pharmaceutical Officer	Qualified signatories to certify advertising material
Submission to the Authority	Not applicable	A "Visa" must be obtained from French Agency before any use. Careful planning required as only four submission slots per year	Not required unless requested by MHRA ("Vetting") for an agreed period / until notified no longer required

Educational Materials

- **Educational materials can be requested by the EMA (as part of the RMP) during the assessment**
  - EMA approves the English version
- **All the national competent authorities must approve the local version prior to dissemination**
  - Must be translated into local language
  - Some additional local requirements must be added (blue hands for Germany)
  - Submissions managed locally
    - Must be submitted by local PV representative in some countries (such as CZ and SK)
  - Timelines are country dependent
    - Approval timelines vary from 1 month to 1 year, with an average approval received in approximately 4 to 6 months

BlueReg
PHARMA CONSULTING

Local Wholesale Distribution Authorization (WDA)

- **European WDA is required to distribute the product within the EU**
- **A local WDA may also be required in some EU countries**
  - France – under the "*Exploitant*" responsibility
  - Hungary
  - Sweden if there is a local warehouse
  - UK

BlueReg PHARMA CONSULTING

Shared Pack and Stock Keeping Unit (SKUs)

- **Shared packs permitted to rationalize European SKUs**
- **There is no specific guideline / law regarding the shared packs and SKUs**
  - The layout of the outer packaging is validated by EMA during the registration procedure
  - All the required information in local language (including the blue box) must be printed on the outer packaging
  - All the serialization requirements must be followed
  - Consideration to be given to the outer packaging size for the readability for the patients / HCPs
- **Typically, the main shared packs in Europe are often:**
  - BeNeLux
  - Austria and Germany
  - Iberia (Spain and Portugal)
  - Baltics (Estonia, Lithuania and Latvia)
  - Nordics (Sweden, Finland and Denmark or Sweden, Finland and Norway)

BlueReg PHARMA CONSULTING

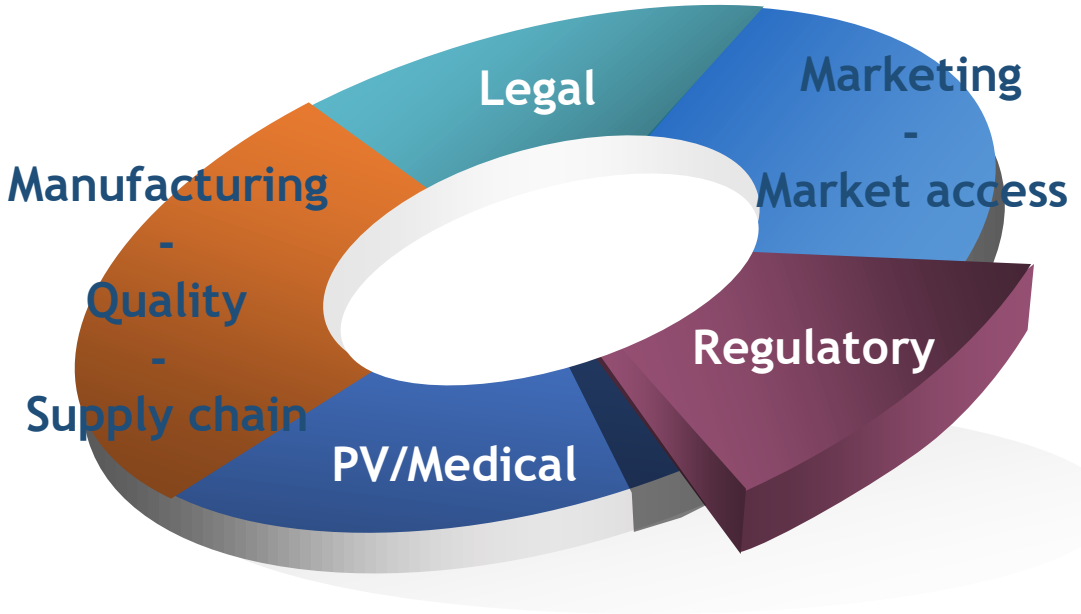
Why use a tailored outsourcing regulatory platform?

3. A tailored outsourcing regulatory platform

BlueReg
PHARMA CONSULTING

Outsourcing Platform to Support EU Local Market Launch (1/4)

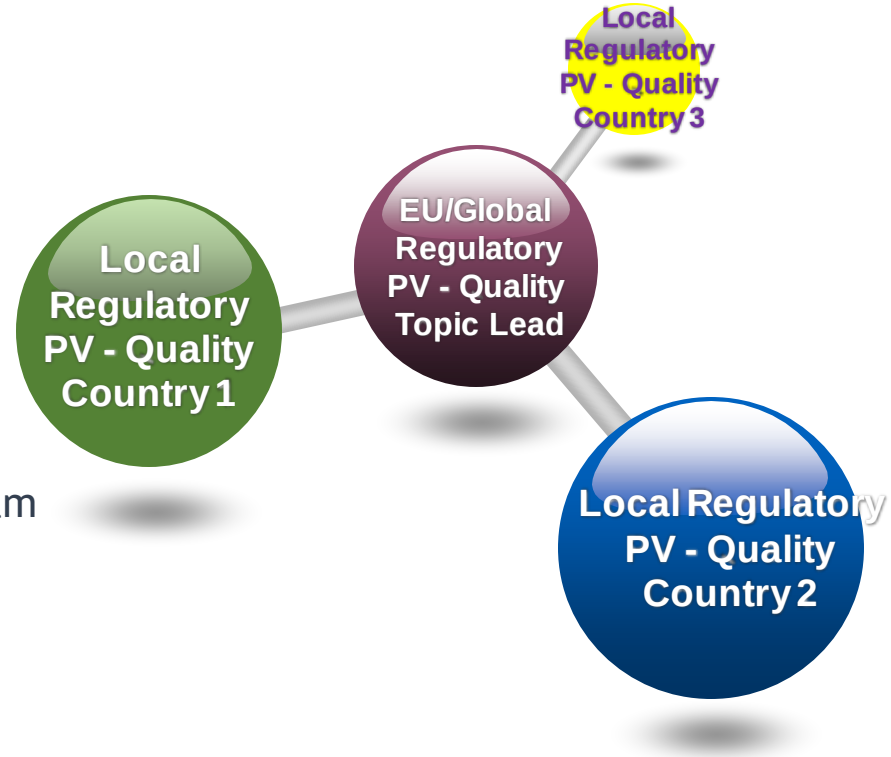
- **Market launch is complex and it is essential it is well planned early in your submission process**
- **Global launch team organisation**
  - All main stakeholders to be involved in the launch planning
  - Critical to include regulatory representative
    - Provide EU regulatory input
    - Represent all local regulatory markets
  - Oversight of the launch strategy
- **Specific local launch team**
  - Similar functions to address particular local challenges, with possibly the corresponding GM
- **Key challenge**
  - Not able to fulfil all the roles at local or even global levels at the start of the launch planning
    - recruitment may be on going
    - requirements may not be clear enough to commence recruitment
    - required roles may not require a full resource until subsequent products are launched
    - many specialities may be required which often may not be covered by one resource



BlueReg PHARMA CONSULTING

Outsourcing Platform to Support EU Local Market Launch (2/4)

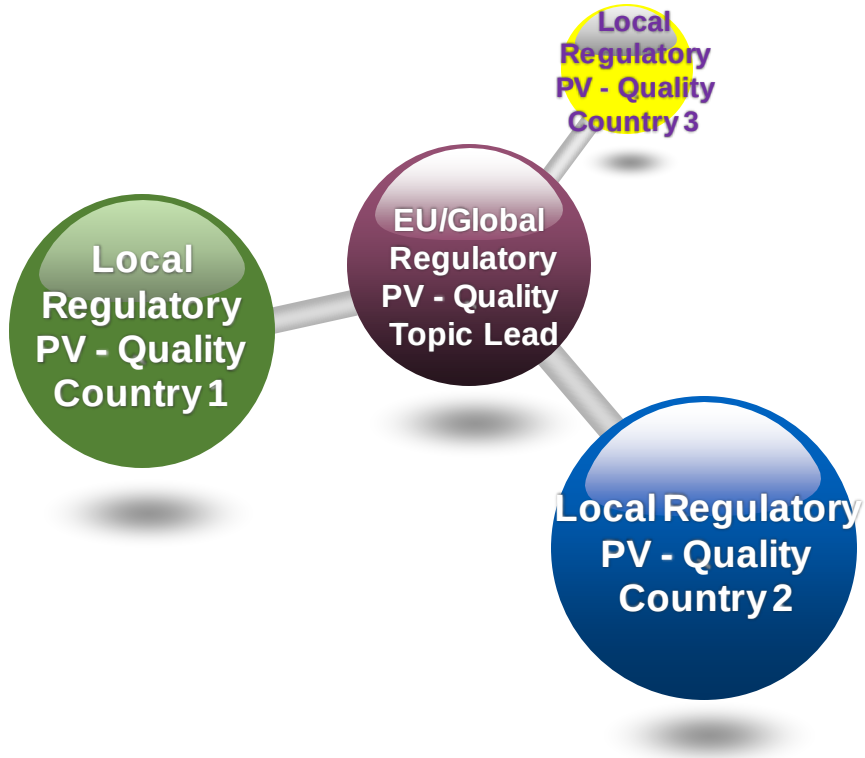
- **BlueReg recommends**
  - Initially externalising the regulatory resources to collect the local requirements for the launch and beyond
  - Assess the gap and address issues by sourcing internally or delegate responsibilities to third party
  - This third party can:
    - project manage the entire process in conjunction with your team or can provide support to your team
    - fulfil all local national roles and provide all local regulatory support for successful market launch and beyond



BlueReg PHARMA CONSULTING

Outsourcing Platform to Support EU Local Market Launch (3/4)

- **BlueReg recommends**
  - At the EU level
    - Select appropriate local resources (can be a combination of your internal staff and third party resources)
    - Centrally coordinate local partners / company staff and ensure high a quality of support
    - Align action plans versus timelines with all stakeholders
    - Propose corrective actions
  - At the country level
    - Set up the strategy per country as per appropriate timeline
    - Develop corresponding SOPs, tracking tools and RACI tables
    - With the support of local partners / company staff
      - Prepare/review local documents in local languages
      - Submit locally and interact with local agencies as required
      - Be your local representative as required



BlueReg PHARMA CONSULTING

Outsourcing Platform to Support EU Local Market Launch (4/4)

Flexible operational outsourcing platform is key for the success of your launch in Europe

- **Strong governance and project management to ensure quality and adherence of timelines**
- **Various skills and profiles will be required at different steps of your launch**
  - demonstrate agility in terms of workload capacity and resource planning
  - require team spirit and cohesion between all stakeholders
- **Establish a strong and long-term relationship between the pharmaceutical company and the chosen partners**
  - trust and loyalty from both sides are required
- **Governance should be set up at global level**
- **Local plan must be determined at country level**

BlueReg
PHARMA CONSULTING

Conclusions

- **All EU and local requirements must be fulfilled country by country**
- **Complexities of local regulation and language barrier**
- **Exemptions can be negotiated in very rare occasions, mainly on labelling languages**
- **Local support is required for all functions with strong governance of all stakeholders**
- **Launch sequence should be established as early as possible taking into account Early Access Programs or equivalent**

ANTICIPATION of your launch is key…..

….. But in addition: your TEAM should be WELL PREPARED and WITH A CLEAR UNDERSTANDING of the REQUIREMENTS

BlueReg
PHARMA CONSULTING

Q & A Session

BlueReg
PHARMA CONSULTING

Let’s stay in touch

Yasmine GARNIER
Marketing & Communication Project Manager at BlueReg

- **Visit our website:** www.blue-reg.com
- **Follow us on LinkedIn :** www.linkedin.com/company/bluereg-group
- **Follow us on Twitter :** https://twitter.com/BlueregGroup
- **Send Yasmine an email :** garnier.yasmine@blue-reg.com

BlueReg
PHARMA CONSULTING

Thank you

BlueReg
PHARMA CONSULTING