iRACI

SELECTING THE RIGHT SUPPLIER

Suppliers as Critical Assets for Sourcing Decisions

Alternative Sourcing

What if too much is not enough?

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Alternative Sourcing – regulatory perspective

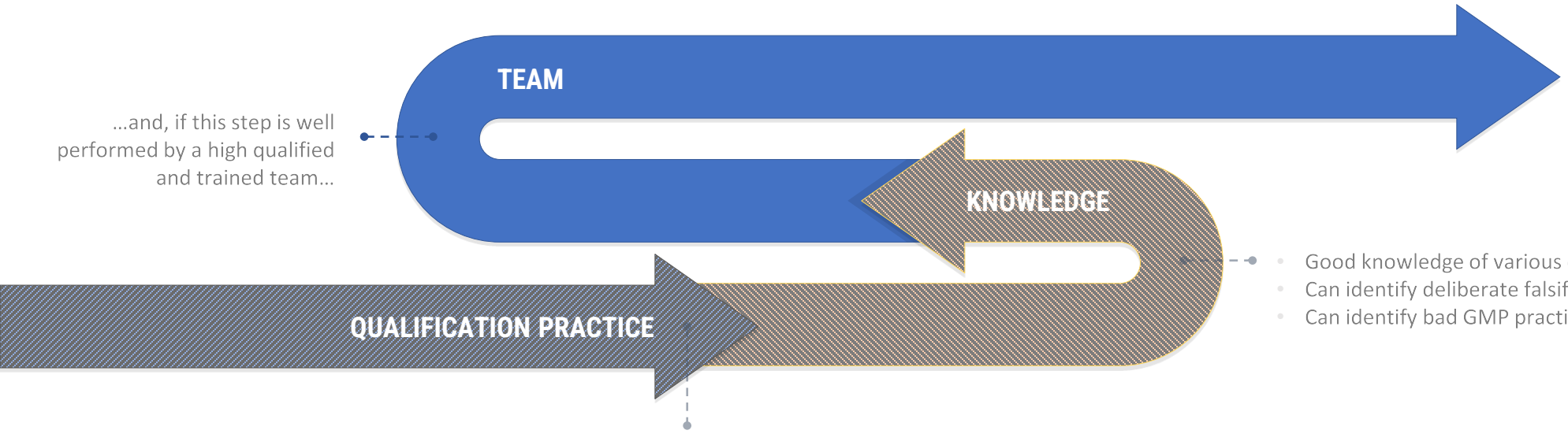
1. Alternative sources – why these need to become the new normal?
2. Regulatory impact of qualification
3. Regulatory harmonization?
4. Impact of having alternative sources in the dossier
5. And… sometimes it is not enough!
6. Future

Alternative sources – why these need to become the new normal?

Permanent Change is the New Normal

- Natural disasters, such earthquakes, hurricanes, wildfires can disrupt the supply chain by damaging manufacturing facilities, transportation infrastructure, and storage facilities;
- Political Instability
- APIs which are only manufactured in some countries e.g. China, India (for example paracetamol outsider the Europe)
- Quality issues
- Regulatory issues, e.g. change in regulations inspections and compliance requirements;
- Pandemics
- Cybersecurity Threats e.g. hackers, data branches
- Cost viability
- Price reductions
- Reference pricing system
- Increased cost of goods (e.g. requirements imposed by FMD systems)
- MA maintenance
- Cessation of supply for non-profitable products

Regulatory impact of qualification



…and, if this step is well performed by a high qualified and trained team…

SUCESS

…the quality of documentation is better, less questions from the authorities and less time for approval!

- Good knowledge of various categories of impurities profile of the API
- Can identify deliberate falsification (e.g. different routes)
- Can identify bad GMP practices (e.g. cross contamination)

A good qualification practice leads to maintain a high level of Quality and safety of the finished products by:

Regulatory harmonization?

Positive

- It helps to ensure to have products safe, effective and of high Quality across different countries and regions
- Reduces duplication of efforts and facilitates international trade
- Reduces trade barriers and increase market access
- It can improve the same high standards of safety and efficacy regardless of where they are produced or sold

Negative

- Multiple manufacturing site audits; many different inspectorates, some of them product specific, ‘desk audits’, some countries does not accept them
- Mutual recognition process is to slow
- Requirement to re-test and certify batches from no EU – supply chains more complex
- Variation approval delays and different specific documentation requested

Impact of having alternative sources in the dossier

Active
Product
Ingredient

Excipient

European Certificate of Suitability of monographs of the European Pharmacopoeia (CEPS)

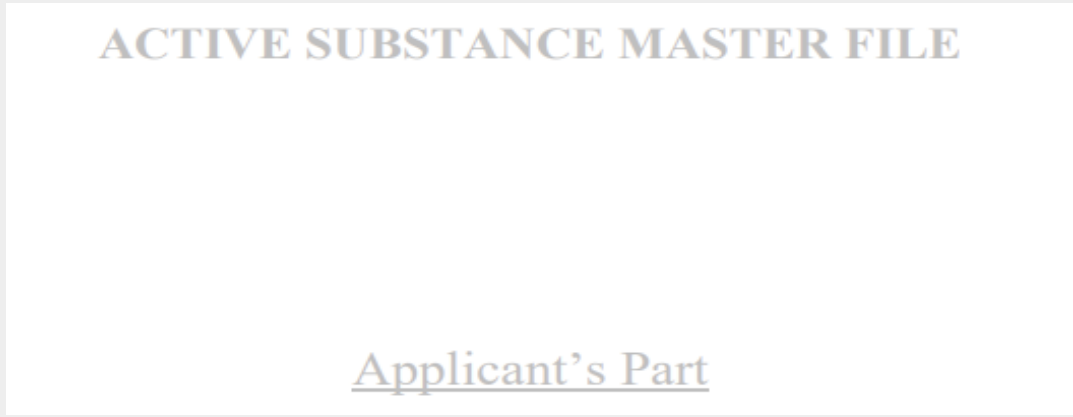

Certification of Substances Department

Certificate of suitability
No. R1-CEP 1996-039-Rev 04

1 *Name of the substance:*
2 **PARACETAMOL**

- Certificate for chemical purity and microbiological quality (“Chemical CEP”)
- Certificate for herbal drugs and herbal drug preparations (“Herbal CEP”)
- TSE Certificate (“TSE CEP”)

Active Substance Master File (ASMF)


ACTIVE SUBSTANCE MASTER FILE

Applicant’s Part

Impact of having alternative sources in the dossier

European Certificate of Suitability of monographs of the European Pharmacopoeia (CEPS)

- Document has been created with the intention of clarifying the information to be concluded from a Certificate of suitability to the Monographs of the European Pharmacopoeia (CEP) for Industry and the Competent Authorities.
- CEPs are normally accepted in all countries which are members of the Ph. Eur. Convention.
- CEPs may be accepted in countries which are not members of the Ph. Eur.
- A CEP does not certify that a specific batch or batches of the substance covered by the CEP from a certain manufacturer complies with the Ph. Eur. monograph and additional tests stated on the respective CEP. CEPs are not equivalent to batch release certificates and shall be complemented by certificates of analysis demonstrating such batch-related compliance.

Impact of having alternative sources in the dossier

European Certificate of Suitability of monographs of the European Pharmacopoeia (CEPS) Variations Guideline

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
For an active substance **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient**			
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
4. Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
5. New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free		**1, 2, 3, 4, 5, 6**	**IB**

Conditions

1. The finished product release and end of shelf life specifications remain the same.
2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5. The active substance/starting material/reagent/intermediate/excipient is not sterile.
6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE
7. For veterinary medicinal products: there has been no change in the source of material.
8. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
9. If Gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should **only** be manufactured in compliance with the relevant country requirements.
10. At least one manufacturer for the same substance remains in the dossier.
11. If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Impact of having alternative sources in the dossier

European Certificate of Suitability of monographs of the European Pharmacopoeia (CEPS)

Documentation

1. Copy of the current (updated) Ph. Eur. Certificate of Suitability.
2. In case of an addition of a manufacturing site, the variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form.
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
4. Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance/excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.

   For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
5. Where applicable, for active substance, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1. The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.

Impact of having alternative sources in the dossier

European Certificate of Suitability of monographs of the European Pharmacopoeia (CEPS)

Approval time:

a) The national competent authority will review the Type IA notification within 30 days following receipt. By Day 30, the national competent authority will inform the holder of the outcome of its review

b) Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder. However, at the latest within 12 months from the date of the implementation, the holder must submit simultaneously to all Member States concerned, to the national competent authority, or to the Agency (as appropriate)

Impact of having alternative sources in the dossier

European Certificate of Suitability of monographs of the European Pharmacopoeia (CEPS)
Part S update in the dossier

Product A | Portugal

Module 3

- 32a-app
- 32p-drug-prod
- 32r-reg-info
- 32s-drug-sub

32s-drug-sub (1)

- 32s1-gen-info
- 32s2-manuf
- 32s3-charac
- 32s4-contr-drug-sub
- 32s5-ref-stand
- 32s6-cont-closure-sys
- 32s7-stab

32s-drug-sub (2)….

- 32s1-gen-info
- 32s2-manuf
- 32s3-charac
- 32s4-contr-drug-sub
- 32s5-ref-stand
- 32s6-cont-closure-sys
- 32s7-stab

32r-reg-info

- certificate-suitability-1stmanufacturer
- certificate-suitability-2ndmanufacturer
- materials-animal-human-origin
- medical-device
- process-val-scheme

Impact of having alternative sources in the dossier

Active Product Ingredient

Excipient

European Certificate of Suitability of monographs of the European Pharmacopoeia (CEPS)


Certification of Substances Department

Certificate of suitability
No. R1-CEP 1996-039-Rev 04

1 Name of the substance:
2 PARACETAMOL

Active Substance Master File (ASMF)

ACTIVE SUBSTANCE MASTER FILE

Applicant's Part

Impact of having alternative sources in the dossier

Manufacturer of the active substance supported by an ASMF (Active substance master file)

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	1, 2, 3	1, 2, 3, 4, 5, 6, 7	IAIN
b) Introduction of a manufacturer of the active substance supported by an ASMF			II

Impact of having alternative sources in the dossier

Manufacturer of the active substance supported by an ASMF (Active substance master file)

Manufacturer:

- Letter-of-Access for DMF (close part)
- Letter-of-Engagement
- EU-GMP (se available)
- List of inspections conducted by European or USA Authorities, in the last 3 years
- Proof-of- Delivery of the Restricted part of DMF to PT-Authority (INFARMED)
- CTD 1.4.1 + 2.3.S sections (quality expert report + signature + CV)
- 2 recent CoA according to applicable Ph.Eur. edition
- existence of an updated EU-DMF version, which version?

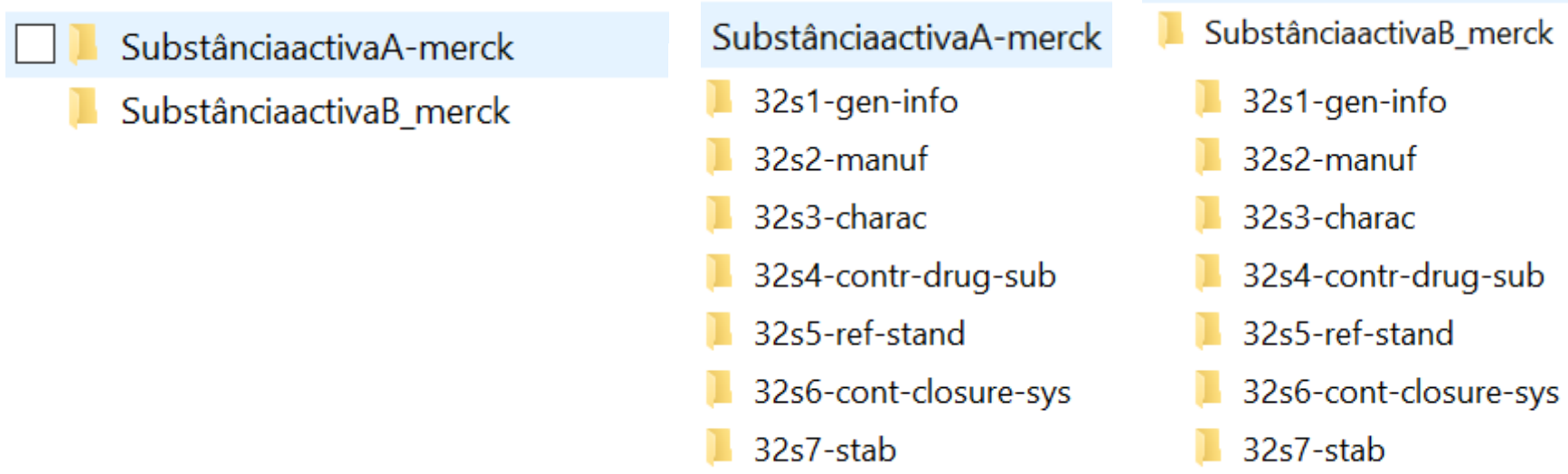
Internal:

- Manufacture of 2 batches (if possible)
- Comparative dissolution profile
- ICH Stability 3M (if possible 6 M)
- QP statement (based on audit))
- Comparative table of specifications (approval vs proposal)
- Comparative table of results (approval vs proposal manufacturer)
- Comparative table of FP results (origin of API fab approved vs proposal)
- Confirmation that FP specifications remain unchangeable

Impact of having alternative sources in the dossier

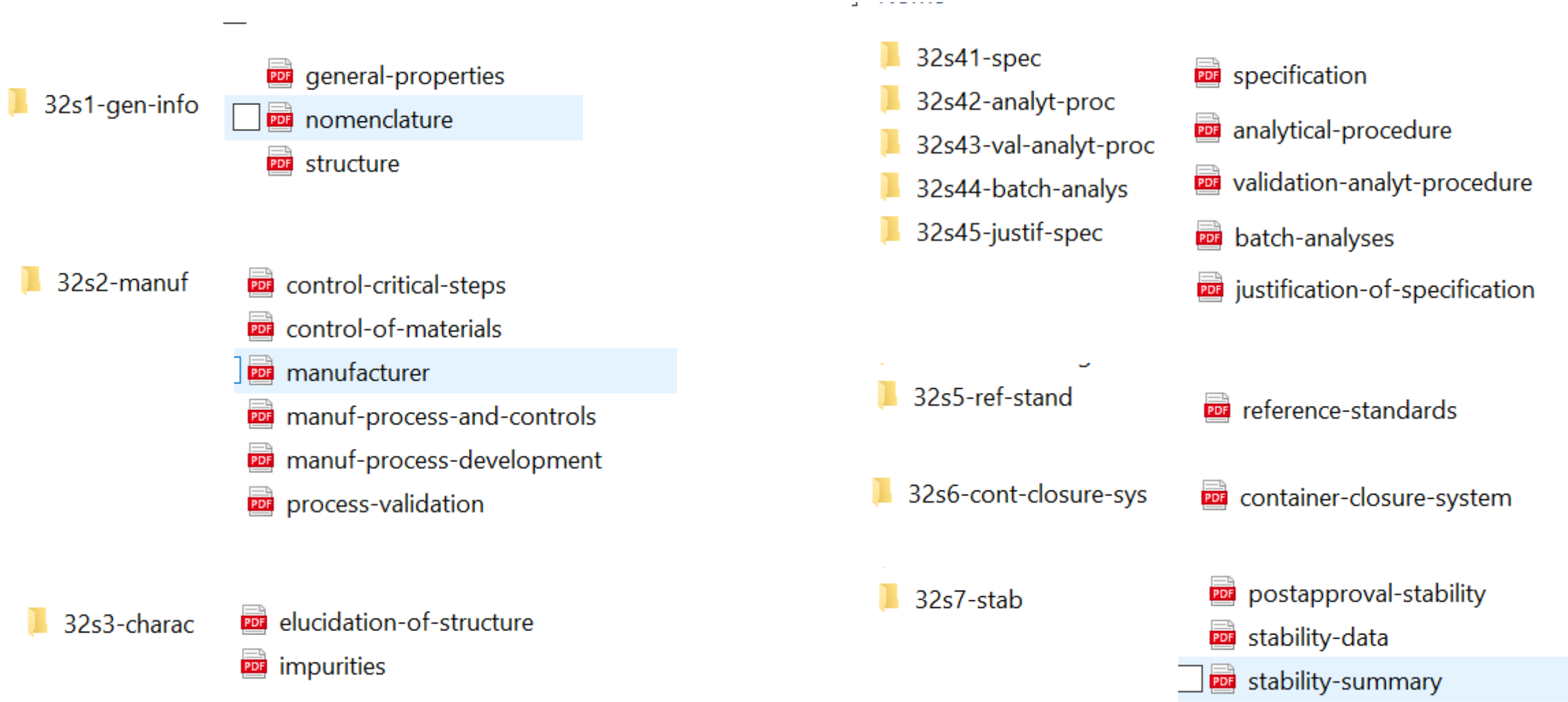
Manufacturer of the active substance supported by an ASMF (Active substance master file)

Product B| Portugal
Module 3



All documentation must be revised!

Impact of having alternative sources in the dossier



Impact of having alternative sources in the dossier

Manufacturer of the active substance supported by an ASMF (Active substance master file)

Approval time:

- As a rule, for major variations of Type II, a 60-day evaluation period will apply. However, in practice this period can increase until 6 months…

Impact of having alternative sources in the dossier

So far its easy:

- 2 different documentation types
- A lot documents
- Huge organization
- Long approval times
- A lot of relation and communication with NCA

BUT…

What if, …

instead of one Dossier with manufacturer A and B, **you have more than 100 dossiers in multiple countries around the world???**

Impact of having alternative sources in the dossier

RA Management Impact

Increased control over dossier versions and status of change

Consequences of different timeframe approvals: e.g. If you have 5 MAs updated and 8 not yet updated (sometimes because different requirements from the local's agencies), it can take more than 8-10 months for a full harmonized dossier portfolio!

In the meantime, production is made with two different manufacturers

Supply Impact

Some orders can be produced with manufacturer A and others with manufacturer B

Manufacturing process Impact

In order to meet compliance standards its mandatory to closely monitor the process, in order to avoid:

1. **Potential destruction if do not receive regulatory approval; or**
2. **Loss of shelf life if delayed regulatory approval**

Strong impact in supply and in the plant which obliges to have a **strong quality system**

Impact of having alternative sources in the dossier

And... the plot thickens even further

Lets suppose you want to register a Dossier with 3 manufactures A, B and C in a new country, but in the meantime your supply stopped buying from Manufacturer A for commercial reasons (price, supply problems, quality problems):

	Impacts
a) When requesting updated documentation from all suppliers (e.g. CEP), supplier A will not give you the required Regulatory Documentation as no orders of API are coming in. Thus the dossier cannot be updated with such information.	**Stall the submission process!!!**
b) If Manufacturer A happens to be the backbone of the Dossier, and you need do remove it, then the dossier has to be "rebuilt" (process validation, stability and so on) using Manufacturer B or C Information	**Additional costs** **Additional time to register** **Different versions of the dossier to manage across the portfolio**

And… sometimes it is not enough!

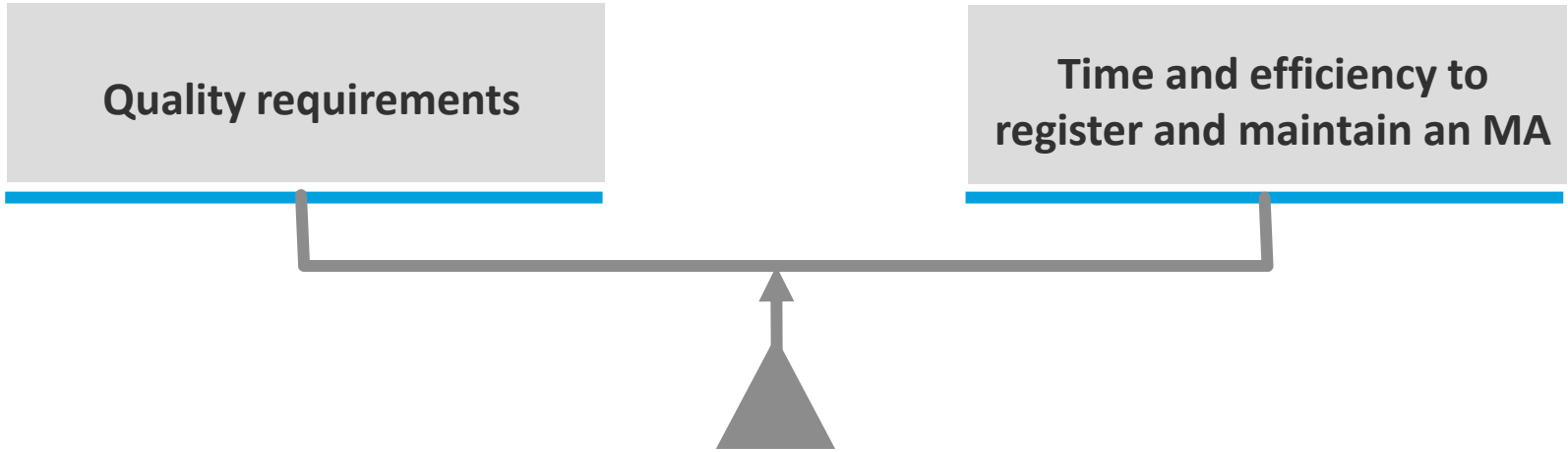
After the company has look for the best cost effectiveness and available manufacturer, it has to deal with regulators that increase the challenges (for instance):

- Only accept to register 1 manufacturer (when sometimes there are 4 manufacturers registered)

- Only accept to register manufacturers that have US-DMF, when the trend is having a manufacturer with a CEP!

Future

For RA operations:



For National Competent Authorities:

- Simplify the variation system
- Faster variation approvals