APIC Active Pharmaceutical Ingredients Committee

Drug Shortages during COVID-19
Lessons Learned and Forward Look
APIs

EU Steering Group
Wednesday 08-July-2020

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Introduction

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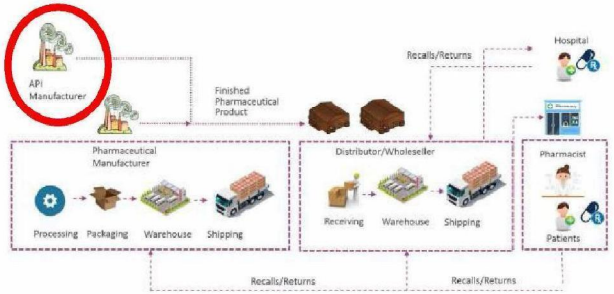
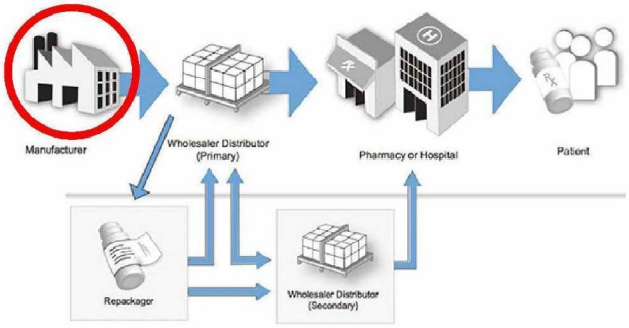
Drug Product Supply





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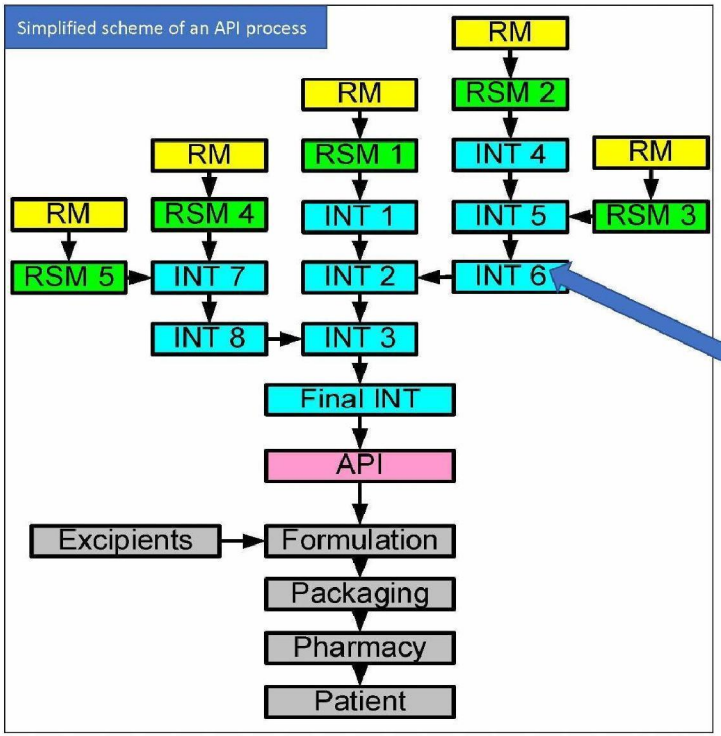
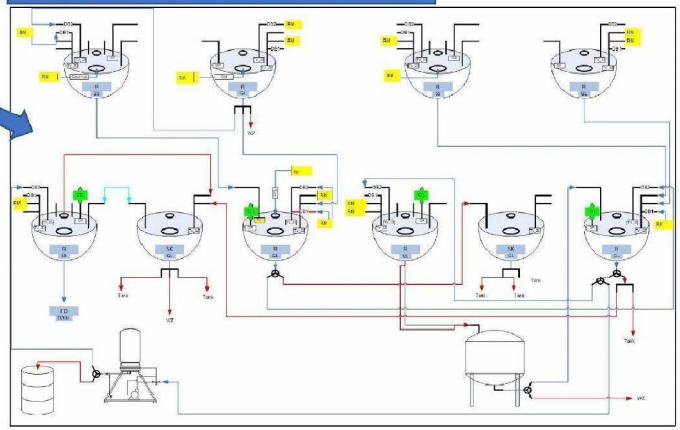
API Process

Simplified scheme of an API process



Additional/Special requirements could be (not limitative)
- Containment facilities
- Unique type of equipment
- Safety (rules for storage of dangerous goods,,...)
- Regulations (REACH, SEVESO,...)
- ...

Example of simple process for 1 intermediate step
- Only 16 different Raw Materials (RMs)
- Only standard SS/GL/HAST equipment
- No special processing conditions
- No special accomodation conditions



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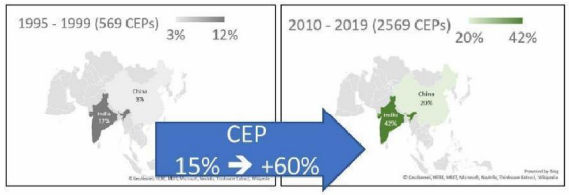
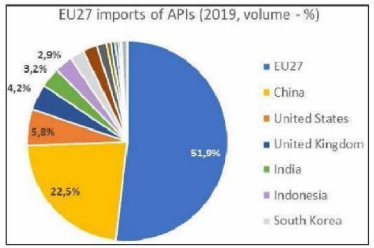
API Supply



Generic API manufacturing locations according to GDUFA (for US market)

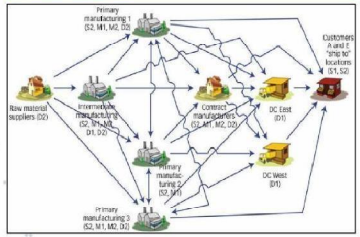
31%
30%
17%
12%
10% ROW



+60% (volume) of RM and RSM for API manufacturing in EU are sourced from China and India

Some APIs start as a plant (which sometimes only grows in one place on earth)

One RSM producer can supply several API manufacturers and dozens of different Finished Dosage Form manufacturers



API · Drug Product · Sponsor · Packaging & Distribution · Intermediates · Primary & Secondary Packaging · Starting Material · Excipients

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Wave 1 – looking back

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Wave 1 – issues encountered

Supply

Disruption in the supply chain, due to unavailability of

- workers and contractors to go on-site, due to travel restrictions
- input (raw) materials, due to manufacturing stops and transport limitation
- solvents, due to increased use, hording and transport limitation

Important note

- though our 70 APIC members are European based companies, the majority of reported issues were related to supply chain issues of raw materials and regulatory starting materials in China and India (... not leading to API unavailability during this first wave ...)

Demand

Unclarity about the API demands

- Due to unclarity about the list of critical medicines, the requests from MAHs to API manufacturers for API volumes were unbalanced and fluctuating
- Health Authorities (EU member states and non-EU) contacted API manufacturers directly
- Hospitals (EU and non-EU) contacted API manufacturers directly

Impact

- Capacity loss: API manufacturers switching production lines (without generating output) and thus resulting in lost manufacturing capacity for other APIs
- Unusable API: eg because of limited stability
- Disruption of the API supply to Drug Product manufacturers due to direct purchasing by the Health Authorities

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Wave 1 – impact actions on supply

Supply in EU

Crucial actions in EU

- the recognition of the full supply chain, from raw material over intermediate to API, as essential
- keeping the EU borders open for goods movements
- extension of the GMP certificates until dec-2021

Impact

- kept the manufacturing facilities in EU operational
- kept the transports in/out of these facilities moving
- continued API supply to the market

Supply outside EU

(10)(2a)

Impact

- in (10)(2a) the full supply chain was recognised as essential
- though it didn't have, and still doesn't have, the same positive effect as in EU

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Wave 1 – impact regulatory flexibility

CEP

- worked well !!!
- these cases were managed efficiently by EDQM !!!
- because single-point-approval

ASMF

- not applied
- changes require approvals of all MAHs
- too complex to obtain all approvals

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Wave 1 – conclusion

Because all parties worked shoulder to shoulder through this crisis

→

together we achieved to avoid critical shortages negatively affecting COVID patients (in EU)

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Wave 2 - prepare

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Wave 2 – pre-note - ROW

Though in EU the first wave might be "under control" …
- in the rest of the world the first wave is still growing
- and second "outbreaks" are already emerging

This means that
1) API and Drug Product demand worldwide will continue to increase
2) the supply from these areas to EU might come under stress (~due to lockdowns, limited transport,…)

In addition
3) the manufacturing capacity used for increased volumes of COVID APIs is not available for other APIs
4) as the worldwide pressure remains … it will be difficult to re-build the (buffer) stock

This could result in less API and Drug Product being available for EU patients

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Wave 2 – proposed actions

Supply Chain

1) SUPPLY

➔ Allow materials, equipment and people required for the manufacture of APIs to move

- Keep the recognition of the full supply chain, from raw material over intermediate to API, as essential
- Keep the EU borders open for goods movements and essential workstaff
- Continue talks with Chinese/Indian governments to implement the same strategy

2) DEMAND

➔ Have clear and transparent picture on the forecasted API demand

- eg a central reliable list with crucial medicines
- eg implement digital telematics (as presented/requested by FDF manufacturers)

Regulatory

Ease the regulatory processes to implement "emergency" changes at API manufacturers

- eg move to a "central single-point one-step" change approval for the API manufacturer (without MAHs requiring to get secondary approvals)
- Apply this for all impacted APIs (not only for COVID ICU medicines)

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The future

resilient API supply

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Future → resilient API supply

Risk identification

Know/understand the risk in the supply chain

- not only from the perspective of one API / Drug Product manufacturer
- but, from a holistic point of view (~ total picture for a single Drug Product)
- to discover "critical points" in the supply, eg
  - Only one manufacturer of an RSM
  - Only one intermediate manufacturer, requiring one specific piece of equipment

Potential approach

- Digitalise the data available in the submitted registration dossiers
- Analyses the data for finding the "critical points"

Risk mitigation

Help industry to mitigate the "critical points", eg

- by making these "critical points" visible for industry
- agile regulatory processes to implement mitigation actions, by eg implementing a "central single-point one-step" change approvel process (... increase the central role of EDQM ... ?)

Help industry to implement resilient supply, eg

- ensuring the "level playing field", by making sure that whatever is imported in the EU has to comply with the same level of standards (eg wrt quality, environment,...)
- have incentives (eg market awards, financial,...) to overcome the additional investments and costs of making the supply chain more resilient

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Thank you !!!

MAHs' specific points on APIs

1st wave	• Demand surge for FDFs destabilised demand for APIs • Direct purchasing of APIs by governments was disruptive for FDF manufacturers
2nd wave	• Clarity on demand for FDFs will stabilise demand for APIs
Resilient API supply	• Holistic policy to incentivise the MAHs to diversify risk in API supply

Future: resilient API supply

- Political Agenda: shortages prevention
  - Expectation from MAHs to multiply API sources in the dossier
  - Less dependence from third countries
- Regulatory large scale processes/reviews currently lead to optimisation of portfolio and withdrawal of MAs (e.g. FMD, Brexit, nitrosamines)
  - Maintenance of multiple API suppliers - engage resources (human and financial)
    - Qualification of suppliers/ audits/ variations (costs and staff)
    - Contractual challenges (obligation to buy)
  - To procure goods (APIs) at similar price levels as in 3rd countries
- What is needed:
  - Incentives to MAHs to build resilience in the supply chain like EU based manufactured products
  - Recognition of additional effort by MAHs to qualify alternative API sources (e.g. criteria in P&R, tender)
  - Simplification of the API maintenance process from a regulatory perspective (digitalisation / easy variations/ no duplication of assessment due to multiple users/ MAHs of the same API)