

WHERE DO OUR ACTIVE PHARMACEUTICAL INGREDIENTS COME FROM? – A WORLD MAP OF API PRODUCTION

Final Report

•••• progenerika

Berlin, September 2020

GLOSSARY

API	Active pharmaceutical ingredient; active ingredient of a drug
ATC Classification	Anatomical Therapeutic Chemical (ATC) Classification; official classification for active pharmaceutical ingredients based on anatomical, therapeutic or chemical / structural characteristics
CEP	Certificate of Suitability of Monographs of the European Pharmacopoeia; proof of active pharmaceutical ingredients quality, used for drug approvals
DDD	Defined daily dose; statistical measure to determine prescribed drug quantity, defined by the World Health Organization (WHO), indicates the assumed average maintenance dose per day for a drug used for its main indication in adults
ROA	Rest of Asia; category used for the analysis to summarize all Asian countries except India and China
ROW	Rest of World; category used for the analysis to summarize all countries which are not explicitly mentioned in the respective depiction

SUMMARY

• Europe's supply of active pharmaceutical ingredients is exposed to various risks

- 2/3 of the currently valid CEPs for APIs are held by Asian manufacturers
- o Indian and Chinese production sites are concentrated in a few provinces
- For 1/6 of the APIs analyzed in this study, there is no European production at all, for more than half of the APIs there are between 1 – 5 CEPs and therefore only very few manufacturers worldwide
- Europe has lost its strong position as an API producer. Looking at new approvals of CEPs between 2000 and 2020, Asia significantly outperformed Europe: Asian manufacturers increased the number of their CEPs from 183 to 2,369, while European manufacturers only grew from 348 to 1,260 CEPs
- Unequal regulatory standards and cost pressure are main reasons for this development. India and China are actively outperfoming European businesses
- Today, European manufacturers focus on specific APIs (e.g. low production volumes, complex production processes), but technical know-how and capacities to increase European API production are (still) available

THE SHIFT OF THE API PRODUCTION TO ASIA MAY IMPACT THE EUROPEAN SUPPLY NEGATIVELY

- 1 Only 33% of CEPs for APIs required in Europe are held by European manufacturers. More than 50% of all CEPs are held by Indian and Chinese manufacturers; Asia as a region holds over 60% of CEPs
- High concentration of API manufacturers within India and China can have negative impact on continuity of supply in Europe in the event of disturbances
- **3** For 93 APIs required in Europe there are no CEPs in Europe
- 4
- For more than half of all APIs there are between 1 5 CEPs worldwide and therefore only a few manufacturers

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EUROPE STARTED FROM A STRONG POSITION, BUT ASIAN MANUFACTURERS CONTINUOUSLY GREW THEIR API PRODUCTION

- 5 Europe started form a dominant position, but strong growth of new CEPs in Asia, mainly in India and China, led to a shift to Asia
- 6 Main reasons for the CEP migration to Asia are price pressure and less rigid regulatory requirements in Asia
- 7 Many of the **trends** were **strongest** in the years **around 2000** and have **weakened since then**. **Today, Europe** is **mainly** a **producer** of **complex**, **smaller-volume APIs**
- 8 A similar development can be observed for API manufacturers. The increasing number of Asian manufacturers and simultaneous stagnation of the number of European manufacturers, led to a clear shift towards Asia
- 9 Although the **trends** in **China** and **India** are **similar**, there are **significant differences** in **growth of CEPs** and **number** of **manufacturers**

EUROPEAN MANUFACTURERS TEND TO HAVE LARGER API PORTFOLIOS WITH SMALLER PRODUCTION VOLUMES; IN ASIA IT IS THE OTHER WAY ROUND

- 10 Many manufacturers in India and China have a relatively small API portfolio, but are constantly expanding
- 11

Manufacturers' product portfolios differ between India and China. Indian manufacturers tend to be larger and more focused on high-volume APIs

SINCE 2000, CEP DATA INDICATES INCREASING ACTIVITY IN ASIA

- 12 Since 2000, API manufacturers in Asia have been more active than European manufacturers especially India and China show strong dynamics
- Growth drivers were similar in Europe and Asia. On the one hand, CEP growth was driven by
 patent expirations and the associated increase of generic APIs; on the other hand, the number of CEPs increased because of newly emerging manufacturers. Both trends are expected to be less dynamic in future



The later an API enters the CEP procedure, the smaller the proportion of European manufacturers from the start. While older APIs were manly produced in Europe after patent expirations, and Asian manufacturers entered the respective market slowly, newer APIs are dominantly produced by Asian manufacturers from the outset

ANALYSES ON THE LEVEL OF ATC CLASSES CONFIRM THESE RESULTS

- 15 Analyses on the level of ATC classes confirm all findings, although there are considerable differences within the ATC classes
- 16

Selected APIs were analyzed in detail; the results confirm the findings for the entire portfolio

- With growing volume of individual products, Asian and especially Indian manufacturers are increasingly coming to the fore
- The analyses of real production volumes for European demand are on average in line with the evaluations based on the number of CEPs. Deviations may occur in individual cases
- It seems that the drivers for production site selection are quite strong: APIs are either produced mainly in Europe or in Asia. For a few APIs there is a balanced Europe to Asia ratio
- Older APIs are historically strong in Europe and show only slow migration to Asia, while younger APIs already have a high proportion of Asian manufacturers when entering the CEP procedure and / or migration to Asia is faster

EUROPE NOW FOCUSES MORE ON "NICHE PRODUCTS", BUT PRODUCTION POTENTIAL AND CAPACITIES ARE STILL AVAILABLE

17 Today, Europe is focused on APIs with low production volumes, technological complex production processes and products with high quality requirements

Study participants made various suggestions for improvements. Besides an improvement of the data situation as a basis for better decisions, changes are proposed for different stages at the value chain. There is also a particularly strong desire for adjustments of both pharmaceutical and reimbursement regulations



Specific measures show possibilities to reduce dependencies on Asia

SCOPE OF THE STUDY, METHODOLOGY AND DATA SOURCES

Scope of the study	 Generic APIs with at least one CEP in the database of the European Directorate for the Quality of Medicines & Healthcare (EDQM) (total: 565 APIs) Sample selection of 21 APIs from the above-mentioned database for in-depth analyses Focus on APIs, no consideration of raw materials and intermediates 						
Methodology	 Creation of a cleansed CEP database, enriched with additional manufacturers' information In-depth analysis of the data from the cleansed CEP database according to various criteria Desk Research for further investigations Interviews with API manufacturers and stakeholders For quantitative estimation of the coverage of European demand for selected APIs To validate the findings and to confirm observed trends and their causes 						
Data sources	 CEPs: From the database of the European Directorate for the Quality of Medicines & Healthcare: https://extranet.edqm.eu/publications/recherches_CEP.shtml Import and export data: QYOBO Market Platform European consumption data: IQVIA Manufacturers' information: Company websites, Pharmaoffer, CPhI, press releases, other websites Trends and volume estimations: Interviews with API manufacturers and stakeholders 						

DISTRIBUTION OF GLOBAL PRODUCTION ANALYZED FOR 565 ACTIVE PHARMACEUTICAL INGREDIENTS

OVERVIEW: API SELECTION FOR OVERALL AND IN-DEPTH ANALYSES

API Selection for Overall Analyses



API Selection for In-Depth Analyses

21 APIs were **selected** and **prioritized for in-depth analyses** through evaluation of all APIs according to following criteria:

- Important representative of the ATC class
- High demand in Europe
- Critical in the treatment of lifethreatening diseases
- Supply shortages in the past
- Economically relevant

*) APIs with following characteristics were excluded: not generic, herbal, biosimilar, vitamin / supplement and APIs from the ATC groups: A01: Stomatological preparations, A11: Vitamins, A12: Mineral supplements, A16: Other alimentary tract and metabolism products, D02: Emollients and protectives, V03: All other therapeutic products, excipients

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

CEP DATABASE¹ USED AS REPRESENTATIVE SOURCE TO ANALYZE GLOBAL ALLOCATION OF API MANUFACTURERS

OVERVIEW ABOUT THE CEP PROCEDURE



¹⁾ Certificates of other authorization procedures, such as the issuance of a DMF, are not included in the analysis

Source: Dr. Helga Blasius, 02.08.2018, Das Valsartan-CEP, https://www.deutsche-apotheker-zeitung.de/daz-az/2018/daz-31-2018/das-valsartan-cep **MUNDICARE** LIFE SCIENCE STRATEGIES

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- For more than half of all APIs there are between 1 5 CEPs worldwide and therefore only a few manufacturers

ASIA CURRENTLY HOLDS ALMOST TWICE AS MANY CEPS AS EUROPE; OTHER REGIONS PLAY A MINOR ROLE

OVERVIEW: GLOBAL DISTRIBUTION OF CURRENTLY VALID CEPS (2020*)¹



 $^{\ast)}$ Data collection: 30.04.2020, applies to all subsequent analyses

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

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WITHIN INDIA AND CHINA, MANUFACTURERS CONCENTRATE IN SPECIFIC PROVINCES

GEOGRAPHICAL ALLOCATION OF ASIAN CEPS (2020)¹

India: Geographical Allocation of CEPs by Province

China: Geographical Allocation of CEPs by Province



¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

TODAY, FOR 93 OF THE APIS NEEDED IN EUROPE THERE ARE NO EUROPEAN CEP HOLDERS AT ALL

OVERVIEW: GLOBAL DISTRIBUTION OF API PRODUCTION (2020)¹



¹⁾ Number of all considered APIs with valid CEPs in the respective calendar year (APIs with expired / withdrawn CEPs are already excluded) Quelle: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

FOR MORE THAN HALF OF THE APIS THERE ARE BETWEEN 1 - 5 CEPS WORLDWIDE AND THEREFORE ONLY A FEW MANUFACTURERS

OVERVIEW NUMBER OF API PER GROUP "CEPS PER API" WORLDWIDE (2020)¹



¹⁾ Number of all considered APIs with valid CEPs in the respective calendar year (APIs with expired / withdrawn CEPs are already excluded) Quelle: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

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- 7 Many of the **trends** were **strongest** in the years **around 2000** and have **weakened since then**. **Today, Europe** is **mainly** a **producer** of **complex**, **smaller-volume APIs**
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CONTINUOUS SHIFT TO ASIA FOR 20 YEARS: THE RATIO BETWEEN EUROPE AND ASIA HAS COMPLETELY REVERSED

DEVELOPMENT OF THE NUMBER OF VALID CEPS (2000 – 2020)¹



¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

ASIAN SHARE OF CEP GROWTH OVER THE PAST TEN YEARS WAS AROUND 70 – 80%

SHARE OF GROWTH IN GLOBALLY VALID CEPS (2000 – 2018)^{1,2}



¹⁾ Net growth of all valid CEPs for the APIs considered in the respective timeframe (expired / withdrawn CEPs are already excluded)

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

²⁾ According to current data: decline in 2020, therefore not presentable

IN EUROPE, RATIOS BETWEEN COUNTRIES REMAIN STABLE; WITHIN ASIA, INDIA AND CHINA ARE GROWING FASTER THAN THE REST

DEVELOPMENT OF THE NUMBER OF VALID CEPS (2000 - 2020)¹



¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired/withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

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PRICE PRESSURE AND STRICT REGULATORY REQUIREMENTS IN EUROPE ARE CONSIDERED AS MAIN REASONS FOR MIGRATION TO ASIA

QUOTES ON THE CAUSE OF THE PROBLEM: MIGRATION TO ASIA

"There is **high price pressure** on the generics market **due to discount agreements**. As a result, many **generic companies are forced to buy** active pharmaceutical ingredients **at low prices in Asia**"

"Customers do not accept that it is important to produce in Europe. They are not willing to pay more. Indian prices can never be undercut "

"Some APIs are not produced in Europe, because production costs would be ten times higher than the world market price"

"Some manufacturers are leaving the market because of excessive competitive pressure. The dependence on few manufacturers leads to API shortages" "In Europe, there are very strict safety requirements for setting up a biotechnological plant. This leads to high expenditures of time and costs. Due to high competition, these investments never pay off"

"AOK Tender, the winner takes it all. Asian manufacturer wins everything, although neither forecast planning nor supply chain exist. Supply shortages are pre-programmed"

"Approval process in Europe is too slow, while in India new facilities are being built without problems"

"High cost structure in Europe also due to low production volumes"

"Unfair behavior of China [strong interdependence between state and economy] and strict European regulations give China a competitive advantage"

Source: Supplier Interviews MUNDICARE LIFE SCIENCE STRATEGIES

AROUND 2010, THE NUMBER OF NEWLY ISSUED CEPS REACHED ITS PEAK – IN ASIA AND EUROPE

OVERVIEW OF NEW AND EXPIRED CEPS BY REGION (2000 – 2020)



Number of CEPs

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES 7

MAIN DRIVERS FOR INCREASING NUMBERS OF CEPS WERE NEWLY ADDED APIS – CURRENTLY A PLATEAU IS REACHED

DEVELOPMENT OF THE NUMBER OF APIS WITH VALID CEPS PER REGION (1994 – 2020)¹



¹⁾ Number of all considered APIs with valid CEPs in the respective calendar year (APIs with expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

LARGEST NUMBER OF APIS INCLUDED IN THE CEP PROCEDURE BETWEEN 1996 AND 1998, LATELY MORE EXCLUSIONS

DETAILED ANALYSIS OF NEW AND EXCLUDED APIS (1994 – 2020)



Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

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MANUFACTURERS ARE SIMILARLY ALLOCATED ACROSS THE REGIONS AS CEPS: IN ASIA ALMOST TWICE AS MUCH AS IN EUROPE

OVERVIEW: GLOBAL ALLOCATION OF API MANUFACTURERS (2020)¹

Number of Manufacturers

¹⁾ Number of all manufacturers with valid CEPs in the respective calendar year for the considered APIs (Manufacturers with expired or withdrawn CEPs already excluded)

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

AT FIRST, THE NUMBER OF APIS INCREASED ALONG WITH THE NUMBER OF MANUFACTURERS – STAGNATION IN EUROPE ALREADY SINCE 2004

DEVELOPMENT OF THE NUMBER OF ACTIVE MANUFACTURERS (1994 – 2020)¹

¹⁾ Number of all manufacturers with valid CEPs for the considered APIs in the respective calendar year (manufacturers with expired or withdrawn CEPs are already excluded)

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

NET GROWTH OF ASIAN MANUFACTURERS 3 TIMES HIGHER COMPARED TO EUROPE, DUE TO SIGNIFICANTLY MORE MARKET ENTRANTS

OVERVIEW: NEW AND DEFUNCT MANUFACTURERS ASIA AND EUROPE (2000-2020)

Number of Manufacturers

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

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DEVELOPMENT IN CHINA AND INDIA IS SIMILAR, BUT CHINA HOLDS SIGNIFICANTLY FEWER CEPS

INDIA AND CHINA: DEVELOPMENT OF ACTIVE MANUFACTURERS AND VALID CEPS¹

¹⁾ Number of all manufacturers with valid CEPs for the considered APIs in the respective calendar year (Manufacturers with expired or withdrawn CEPs are already excluded)

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

OVER THE PAST YEARS THE NUMBER OF NEW MANUFACTURERS IN CHINA INCREASED CONSISTENTLY STRONGER THAN IN INDIA

INDIA AND CHINA: NUMBER OF NEW AND DEFUNCT MANUFACTURERS (2000 – 2020)

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES 9

EUROPEAN MANUFACTURERS TEND TO HAVE LARGER API PORTFOLIOS WITH SMALLER PRODUCTION VOLUMES; IN ASIA IT IS THE OTHER WAY ROUND

- 10 Many manufacturers in India and China have a relatively small API portfolio, but are constantly expanding
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Manufacturers' product portfolios differ between India and China. Indian manufacturers tend to be larger and more focused on high-volume APIs

10

OVER TIME, MANUFACTURERS IN EUROPE AND ASIA HAVE EXPANDED THEIR PRODUCT PORTFOLIOS AND ARE NOW HOLDING MORE CEPS...

DEVELOPMENT OF CEPS PER MANUFACTUERER (2000 – 2020)¹

¹⁾ All valid CEPs in the respective calendar year for the considered APIs are included (expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

...HOWEVER, AROUND 70% OF MANUFACTURERS STILL HAVE A RELATIVELY SMALL PORTFOLIO WITH ONLY 1 – 3 APIS

DISTRIBUTION OF MANUFACTURERS BY NUMBER OF APIS PER MANUFACTURER (2020)¹

¹⁾ Number of all manufacturers with valid CEPs for the considered APIs in the respective calendar year (Manufacturers with expired or withdrawn CEPs are already excluded) – Manufacturer defined as one production site

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

WITHIN ASIA, INDIAN MANUFACTURERS HAVE LARGER PORTFOLIOS: 35% OF THE INDIAN MANUFACTURERS WITH 6 OR MORE APIS, IN CHINA ONLY 7%

DISTRIBUTION OF APIS PER MANUFACTURER IN INDIA AND CHINA (2020)¹

¹⁾ Number of all manufacturers with valid CEPs for the considered APIs in the respective calendar year (Manufacturers with expired or withdrawn CEPs are already excluded)

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

COMPARED TO CHINA, INDIA IS PARTICULARLY STRONG IN PRODUCING APIS WITH MEDIUM AND HIGH DAILY DOSES

CEP RATIO INDIA TO CHINA BY DAILY DOSES PER API (2020)^{1,2}

Defined Daily Doses per Quarter (in thousand)

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded) ²⁾ All considered APIs with a Defined Daily Dose Q4 2019 > 1 Tsd. DDD in Retail and a combined share of India and China > 0%; n = 337 Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020; Basic List Pro Generika MUNDICARE LIFE SCIENCE STRATEGIES

SINCE 2000, CEP DATA INDICATES INCREASING ACTIVITY IN ASIA

- Since 2000, API manufacturers in Asia have been more active than European manufacturers especially India and China show strong dynamics
- Growth drivers were similar in Europe and Asia. On the one hand, CEP growth was driven by
 patent expirations and the associated increase of generic APIs; on the other hand, the number of CEPs increased because of newly emerging manufacturers. Both trends are expected to be less dynamic in future

The later an API enters the CEP procedure, the smaller the proportion of European manufacturers from the start. While older APIs were manly produced in Europe after patent expirations, and Asian manufacturers entered the respective market slowly, newer APIs are dominantly produced by Asian manufacturers from the outset

THERE ARE MORE CEPS AND MORE MANUFACTURERS IN ASIA, BUT ABOUT THE SAME NUMBER OF APIS AS IN EUROPE

OVERVIEW CEPS, APIS AND MANUFACTURERS BY REGION (2000 - 2020)¹

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded)

²⁾ Mfr. = Manufacturer

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

STRONGEST RELATIVE GROWTH IN CHINA AND LOWEST IN FRANCE OVERVIEW CEPS, APIS AND MANUFACTURERS TOP COUNTRIES (2000 – 2020)¹

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded)

²⁾ Mfr. = Manufacturer

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

MARKET ENTRIES OF NEW MANUFACTURERS AND EXPANSION OF PRODUCT PORTFOLIOS ARE IMPORTANT GROWTH DRIVERS IN ASIA

DRIVERS FOR CEP GROWTH (2000 – 2020)¹

Main Driver

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¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded)

²⁾ Incl. CEPs issued for new production procedures; thereby some manufacturers may hold more than one CEP for specific APIs

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

THE LATER AN API ENTERS THE CEP PROCEDURE, THE LOWER THE SHARE OF EUROPEAN MANUFACTURERS

DEVELOPMENT OF THE SHARE OF ASIAN MANUFACTURERS BY LIFE CYCLE

Until 1999 2000 - 2009 2010 - 2019 2 3 4 5 6 7 0 1 8 9 10 Life Cycle Year > 20 - 40% > 40 - 60% CEP Share Asia: 0 % > 0 - 20% > 60 - 80% > 80 - 100%

First Year of the API in CEP Procedure

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

ANALYSES ON THE LEVEL OF ATC CLASSES CONFIRM THESE RESULTS

- 15 Analyses on the level of ATC classes confirm all findings, although there are considerable differences within the ATC classes
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Selected APIs were analyzed in detail; the results confirm the findings for the entire portfolio

- With growing volume of individual products, Asian and especially Indian manufacturers are increasingly coming to the fore
- The analyses of real production volumes for European demand are on average in line with the evaluations based on the number of CEPs. Deviations may occur in individual cases
- It seems that the drivers for production site selection are quite strong: APIs are either produced mainly in Europe or in Asia. For a few APIs there is a balanced Europe to Asia ratio
- Older APIs are historically strong in Europe and show only slow migration to Asia, while younger APIs already have a high proportion of Asian manufacturers when entering the CEP procedure and / or migration to Asia is faster

CONSPICUITIES WITHIN THE API CLASSES ARE ANALYZED ACCORDING TO ATC CLASSIFICATION

OVERVIEW ATC CLASSIFICATION

Overview ATC Logic

The Anatomical Therapeutic Chemical (ATC) Classification System

Inspired by: WHO, Introduction to Drug Utilization Research, Oslo 2003 and WidO, 2018

Application in Analysis: First ATC Level

- A Alimentary tract and metabolism
- B Blood and blood forming organs
- C Cardiovascular system
- D Dermatologicals
- G Genito urinary system and sex hormones
- H Systemic hormonal preparations, excl. sex hormones and insulins
- J Antiinfectives for systemic use
- L Antineoplastic and immunomodulating agents
- M Musculo-skeletal System
- N Nervous system
- P Antiparasitic products, insecticides and repellents
- R Respiratory system
- S Sensory organs

Source: https://www.wido.de/fileadmin/Dateien/Bilder/Publikationen_Produkte/Arzneimittel-Klassifikation/wido_arz_atc_klassifikation.jpg, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

DETAILED ANALYSIS OF THE APIS PER ATC CLASS REVEALS SIGNIFICANT DIFFERENCES: RISK OF KNOWHOW LOSS ESPECIALLY IN C, J, L AND P

GLOBAL DISTRIBUTION OF VALID CEPS PER ATC* CLASS (2020)¹

*) A – Alimentary tract and metabolism; B – Blood and blood forming organs; C – Cardiovascular system; D – Dermatologicals; G – Genito urinary system and sex hormones; H - Systemical hormonal preparations, excl. sex hormones and insulins; J – Antiinfectives for systemic use; L – Antineoplastic and immunomodulating agents; M – Muscolo-skeletal system; N – Nervous system; P – Antiparasitic products, insecticides and repellents; R – Respiratory system; S – Sensory organs

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

EVEN WITHIN ASIA, THERE ARE SIGNIFICANT DIFFERENCES IN THE DISTRIBUTION OF VALID CEPS

DISTRIBUTION OF VALID CEPS IN ASIA PER ATC* CLASS (2020)¹

Number of CEPs (and their distribution in Asia (in %))

*) A – Alimentary tract and metabolism; B – Blood and blood forming organs; C – Cardiovascular system; D – Dermatologicals; G – Genito urinary system and sex hormones; H - Systemical hormonal preparations, excl. sex hormones and insulins; J – Antiinfectives for systemic use; L – Antineoplastic and immunomodulating agents; M – Muscolo-skeletal system; N – Nervous system; P – Antiparasitic products, insecticides and repellents; R – Respiratory system; S – Sensory organs

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FOR EVERY 6TH API, EUROPE'S DEPENDENCE ON ASIAN SUPPLIERS IS EXTREMELY CRITICAL (NO CEPS IN EUROPE)

SHARE OF EUROPEAN API MANUFACTURERS BY ATC CLASS (2020)¹

Proportion of APIs with x% Manufacturers in Europe

¹⁾ Number of all considered APIs with valid CEPs in the respective calendar year (APIs with already expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

THE LATER AN API ENTERS THE CEP PROCEDURE, THE HIGHER THE ASIAN SHARE FROM THE BEGINNING

DEVELOPMENT OF THE SHARE OF ASIAN MANUFACTURERS BY LIFE CYCLE

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

21 APIS SELECTED FOR IN-DEPTH ANALYSES

SAMPLE SELECTION

THE HIGHER THE VOLUME OF AN API, THE HIGHER THE PROPORTION OF ASIAN CEP HOLDERS

SELECTED APIS: CEP SHARE ASIA IN RELATION TO DEFINED DAILY DOSES (2020)^{1,2}

Defined Daily Dose (DDD) per Quarter (in million)

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded) ²⁾ API sample selected by defined daily dose Q4 2019 > 1 million DDD in retail (exclusion of: Piperacillin, Benserazide, Levodopa); n = 18 Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020; Basic List Pro Generika MUNDICARE LIFE SCIENCE STRATEGIES

... THE SAME CORRELATION APPLIES WITHIN ASIA FOR THE INDIAN CEP SHARE

SELECTED APIS: CEP SHARE INDIA IN RELATION TO DEFINED DAILY DOSES (2020)^{1,2}

Defined Daily Dose DDD per Quarter (in million)

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired/withdrawn CEPs are already excluded) ²⁾ API sample selected by defined daily dose Q4 2019 > 1 million DDD in retail (exclusion of: Piperacillin, Benserazide, Levodopa); n = 18 Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020; Basic List Pro Generika MUNDICARE LIFE SCIENCE STRATEGIES

Estimation

MOST APIS ARE EITHER PRODUCED MAINLY IN EUROPE OR ASIA -FEW APIS WITH BALANCED EUROPE TO ASIA RATIO

ESTIMATED SHARE OF SUPPLY FOR EUROPEAN DEMAND BY REGIONS

Share of Supply in % (above the pillar: total European demand in tons)

India China Europe

*) Estimation, Data basis limited; **) API mainly in combination with Tazobactam (exclusively produced in Asia). Source: Supplier Interviews, Import Data Analysis QYOBO Market Platform, CEP Database, Pharmaoffer; IQVIA MUNDICARE LIFE SCIENCE STRATEGIES

THE LIFE CYCLE ANALYSIS OF SELECTED APIS ALSO REVEALS A SHIFT OF PRODUCTION TO ASIA

API SELECTION: DEVELOPMENT OF SHARE OF ASIAN MANUFACTURERS BY LIFE CYCLE

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

API Selection with first CEP between 1992 and 2001

API Selection with first CEP between 2001 and 2014

EUROPE NOW FOCUSES MORE ON "NICHE PRODUCTS", BUT PRODUCTION POTENTIAL AND CAPACITIES ARE STILL AVAILABLE

- Today, Europe is focused on APIs with low production volumes, technological complex production processes and products with high quality requirements
- Study participants made various suggestions for improvements. Besides an improvement of the data situation as a basis for better decisions, changes are proposed for different stages at the value chain. There is also a particularly strong desire for adjustments of both pharmaceutical and reimbursement regulations
- 19
- Specific measures show possibilities to reduce dependencies on Asia

TODAY, EUROPE IS FOCUSED ON "NICHE PRODUCTS"; POTENTIAL FOR PRODUCTION EXPANSION STILL EXISTS

SHARE OF VALID CEPS BY REGION (2020)¹

¹⁾ Number of all valid CEPs (expired / withdrawn CEPs are already excluded)

Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020; Supplier Interviews **MUNDICARE** LIFE SCIENCE STRATEGIES

INTERVIEWEES MADE SUGGESTIONS FOR IMPROVEMENTS

"Scattergun approach does not work. First, clarify which APIs and drugs are relevant for patients in Europe"

"Statutory health insurances must be persuaded by politicians that not only the price but also the manufacturing location plays a role in the selection of refundable drugs"

"Approvals in Europe too slow, while new capacities are easily built in India"

"Registration requirements (for new and old) should be adjusted:
Pharmaceutical manufacturers must prove that supply shortages due to outage of Asian manufacturers can be backed by European API suppliers, so that European demand is secured"

"European API manufacturers would have to make costly improvements within production processes to reduce their prices"

> "Everybody has to contribute. Especially customers must accept higher prices if APIs should be produced in Europe"

Source: Supplier Interviews MUNDICARE LIFE SCIENCE STRATEGIES

SPECIFIC MEASURES SHALL REDUCE DEPENDENCE ON ASIA

The focus is on strengthening the European network – Example Kundl (Novartis/Sandoz)

- Kundl plant is the last remaining, fully integrated antibiotics production site in the western world
- Novartis and Austrian government secure long-term production of key antibiotics in Europe
- Planned joint investment of more than EUR 150 million - Austrian government contributes EUR 50 million

Special attention on supply-critical APIs for Europe – Example Sanofi

SANOFI 🎝

- Major initiative by Sanofi to found an independent company for API production in France
- · Goals of the initiative:
 - Second largest API manufacturer with ~ 1Mrd. € turnover
 - Strengthening the API production in Europe
 - Close the current gaps in European API supply
 - o Reduce dependence on Asian API imports

DR. ANDREAS MEISER PARTNER

MUNDICARE benefits from Andrea's extensive experience in academic research, strategy consulting, and the setting up and management of biotech start-ups. He works at the interface between science and industry and drives the implementation of new solutions in the biotech environment. Prior to his partnership at MUNDICARE, he was responsible for research and development in various companies and led interdisciplinary consulting projects with large teams.

FOCUS

- < Strategy: business development, innovation, market assessment and market entry strategies
- < Implementation: Implementation of projects, PMOs in various industries
- < Regional experience: Germany, Europe, Asia

MUNDI CARE LIFE SCIENCE STRATEGIES

MILESTONES

Partner at MUNDICARE

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Numerous consulting projects with a broad industry portfolio focusing on business development, implementation of new technologies and the planning/implementation of PMOs \clubsuit

Interim management R&D in a medium-sized pharmaceutical company: Development of new production methods to increase efficiency

Setting up biotechnology start-ups: development and marketing of new technologies in the field of blue (algae) biotechnology

McKinsey & Company: After initially working in a wide range of process industries, he joined the chemical practice as an industry specialist. Afterwards he was a project manager with a portfolio of engagements in the areas of chemicals, climate change and biotechnology. As an industry expert, he supported teams worldwide in biochemicals and bioenergy. Andreas has a global client portfolio with relocation to Asia, is an author of publications and lectures at various international congresses \uparrow

Longer research stays in Russia and Latin America

PhD in biotechnology: Commercial production of active pharmaceutical ingredients using a biotechnological approach

Scientific activity at Fraunhofer Gesellschaft

↑ Study of microbiology/biotechnology

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Intensive engagement in chemistry, National Team Chemistry Olympiad

GREAT BY EXPERIENCE: THREE BRAINS, ONE TEAM, ONE NETWORK

Specialists and team players, forward and lateral thinkers, problem solvers and troubleshooters, analysts and doers - each partner is an expert, the whole team a bridge across the entire value chain. MundiCare combines diversity and multitasking, health industry and management consultancy, consulting approaches and reality.

DR. ANDREAS MEISER – DR. MICHAEL MEHLMANN – BJÖRN KOMISCHKE

WE LOOK FORWARD TO YOUR INQUIRY

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BACKUP

STRONG DEPENDENCE ON ASIA FOR HIGH-VOLUME APIS RAMIPRIL AND SIMVASTATIN ALREADY A FEW YEARS AFTER THE FIRST CEP WAS ISSUED

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020 MUNDICARE LIFE SCIENCE STRATEGIES

HIGHER EXPIRATION RATE OF ASIAN CEPS IS BALANCED BY A SIGNIFICANTLY STRONGER INCREASE IN NEW CEP APPROVALS

DEVELOPMENT OF THE NUMBER OF VALID API CERTIFICATES (2000 – 2020)¹

- Number of new CEPs within the last 10 years decreased by 45% in Europe (7% increase in Asia) compared to previous period)
- In Europe, 18% of CEPs expired between 2010 and 2020 (Asia: 27%)
- Ratio of expiring CEPs to new CEPs in Europe significantly worse than in Asia (Europe: 1 to 2.2 vs. Asia: 1 to 3.5)

¹⁾ Number of all valid CEPs in the respective calendar year 2000; 2010; 2020 for the considered APIs (expired / withdrawn CEPs are already excluded) Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020

TREND STILL VISIBLE WHEN CONSIDERING A LARGER NUMBER OF ACTIVE PHARMACEUTICAL INGREDIENTS, BUT LESS OBVIOUS

CEP SHARE ASIA IN DEPENDENCE ON DDD PER API (2020)^{1,2}

Defined Daily Dose (DDD) per Quarter (in thousand)

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired / withdrawn CEPs are already excluded) ²⁾ Shown are all APIs with a daily dose Q4 2019 > 1 thousand DDD in the retail sector; n = 410Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020; Basic List Pro Generika

CHINA'S SHARE OF CEPS FOR HIGH-VOLUME APIS IS SLIGHTLY LOWER THAN INDIA'S

SELECTED APIS: CEP SHARE CHINA FOR DEFINED DAILY DOSES (2020)^{1.2}

Defined Daily Dose (DDD) per Quarter (in million)

¹⁾ Number of all valid CEPs in the respective calendar year for the APIs under consideration (expired/withdrawn CEPs are already excluded) ²⁾ API selected by DDD Q4 2019 > 1 million DDD in retail (Exclusion of: Piperacillin, Benserazide, Levodopa); n = 18 Source: Certificate Database, European Directorate for the Quality of Medicine & Healthcare, Date: 30.04.2020; Basic List Pro Generika MUNDICARE LIFE SCIENCE STRATEGIES

SHARE OF EUROPEAN MANUFACTURERS OF EU SUPPLY ON AVERAGE COMPARABLE TO SHARE OF CEPS – DIFFERENCES FOR INDIVIDUAL APIS

COMPARISON OF SHARE OF EU SUPPLY VS. SHARE OF CEPS

			EU-Supply			CEP Distribution ¹		
API	In CEP Procedure Since	#CEPs Total	Europe	China	India	Europe	China	India
Benserazide	2010	2	100,00%	0,00%	0,00%	100,00%	0,00%	0,00%
Propofol	2001	6	100,00%	0,00%	0,00%	60,00%	0,00%	40,00%
Methotrexate	1996	4	95,00%	5,00%	0,00%	75,00%	25,00%	0,00%
Levothyroxine	1998	7	95,00%	0,00%	5,00%	57,14%	0,00%	42,86%
Tamoxifen	1995	4	95,00%	0,00%	5,00%	100,00%	0,00%	0,00%
Oxycodone	2005	10	90,00%	0,00%	10,00%	100,00%	0,00%	0,00%
Formoterol	2005	14	85,00%	0,00%	15,00%	46,15%	0,00%	53,85%
Levodopa	1998	9	60,00%	30,00%	10,00%	0,00%	66,67%	33,33%
Amoxicillin	1994	25	30,00%	65,00%	5,00%	47,83%	34,78%	17,39%
Quetiapine	2014	30	30,00%	10,00%	60,00%	27,59%	10,34%	62,07%
Metamizole	2000	5	20,00%	80,00%	0,00%	20,00%	80,00%	0,00%
Azithromycin	2002	17	20,00%	65,00%	15,00%	25,00%	43,75%	31,25%
Metformin	1997	25	20,00%	5,00%	75,00%	13,04%	4,35%	82,61%
Piperacillin	1998	10	15,00%	85,00%	0,00%	55,56%	33,33%	11,11%
Prednisolone	1992	14	10,00%	80,00%	10,00%	23,08%	53,85%	23,08%
Levetiracetam	2010	21	10,00%	45,00%	45,00%	4,76%	38,10%	57,14%
Ramipril	2001	17	10,00%	10,00%	80,00%	17,65%	17,65%	64,71%
Diclofenac	1997	12	10,00%	5,00%	85,00%	30,00%	30,00%	40,00%
Venlafaxine	2005	34	10,00%	5,00%	85,00%	15,63%	12,50%	71,88%
Candesartan	2011	14	5,00%	90,00%	5,00%	15,38%	30,77%	53,85%
Simvastatin	2001	22	0,00%	40,00%	60,00%	0,00%	33,33%	66,67%
Average			43%	30%	27%	40%	24%	36%

¹⁾ Weighting between Europe, China, India; CEPs from ROA and ROW not included

Source: Supplier Interviews, Import Data Analysis QYOBO Market Platform, CEP Database, Pharmaoffer; IQVIA Demand Analysis