Agence nationale de sécurité du médicament et des produits de santé

INSPECTION DIVISION
Starting materials inspection division

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SITUATION REPORT ON THE ACTIVE SUBSTANCE AMOXICILLIN

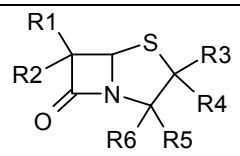
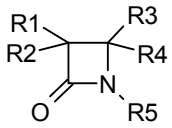
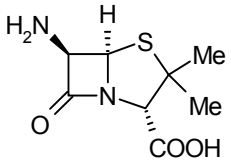
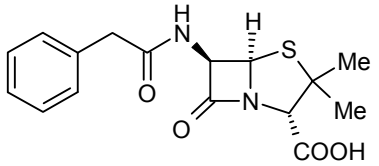
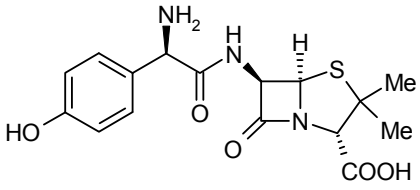
Distribution ☒ ANSM website

I. INTRODUCTION

Amoxicillin is an antibiotic of the beta-lactam family, which includes five structural classes:

- penicillins (e.g., Ampicillin/Amoxicillin/Oxacillin);
- cephalosporins (e.g., Cephalexin/Cefaclor);
- carbapenems (e.g., Imipenem/Meropenem);
- carbacephems (e.g., Loracarbef);
- monobactams (e.g., Aztreonam).

The structure of penicillins derives from the penam core, which comprises an azetidine-2-one ring. 6-aminopenicillanic acid (6-APA) is the basic structure of penicillins. Substitution of the amino function by acylation results in derivatives that differ in their pharmacokinetics, stability, antibiotic spectrum, and resistance to β-lactamases.

	Penam core
	Azetidine-2-one (β lactam)
	6-aminopenicillanic acid (6-APA)
	Penicillin G (PEN G)
	Amoxicillin

Amoxicillin belongs to the group of extended-spectrum penicillins, also called group "A" penicillins (ampicillin and similar). The spectrum of these semi-synthetic penicillins corresponds to that of benzyl-penicillin (PEN G), extended to certain Gram-negative bacilli. The bactericidal effect of penicillins occurs through inhibition of transpeptidation, a necessary step in the development of peptidoglycan, a major polymer of the bacterial wall.
This antibiotic, commonly used since the early 1980s in the treatment of bronchopulmonary, pleural, and ENT infections [amoxicillin: Clamoxyl®; amoxicillin and clavulanic acid (inhibitor of β-lactamases): Augmentin®] is registered in France in several medicinal products (proprietary and many generics). It appears on the WHO List of Essential Medicines.

Depending on the type of proprietary medicinal product, amoxicillin comes in two forms:

- sterile sodium amoxicillin for injectable medicinal products (IM/IV);
- amoxicillin trihydrate for oral medicinal products.

Its dosage may be greater than 2 g/day. The injectable form is indispensable in the management of patients who are unable to take oral forms.

The study published in November 2014 by ANSM and devoted to the evolution of consumption of antibiotics in France between 2000 and 2013[1] stresses that in hospitals or pharmacies, penicillins are the most used class of antibiotics, and their use even increased in pharmacies during the study period. While amoxicillin remains the reference molecule, it is mostly used in association with clavulanic acid. Note that this association is on the list of antibiotics that particularly generate bacterial resistance[2].

Amoxicillin (alone or in combination) was the fifth-highest selling active substance sold in pharmacies in 2013, and the top generic with 39 million boxes of amoxicillin and 18 million boxes of amoxicillin/clavulanic acid[3]. Its availability is therefore a major challenge for the treatment of patients in pathologies of bacterial infections due to germs with antibiotic sensitivity. The full list of medicinal products marketed in 2015 throughout the national territory appears in Appendix 1.

The purpose of this summary is to provide a situation report on the quality and supply of amoxicillin (sodium and trihydrate) used in medical products placed on the domestic market, on the basis of information collected during an investigation conducted with ordering pharmaceutical companies and the results of inspections of manufacturing sites.

II. BACKGROUND

In May 2013, quality issues (non-compliant annual aseptic process simulation test) encountered by a manufacturer of the active substance sterile sodium amoxicillin used in Panpharma's medicinal products led to an inventory shortage for Panpharma amoxicillin 1g, powder for injectable solution, and Panpharma amoxicillin 2g, powder for injectable solution. The massive switch too Clamoxyl®, GSK's powder for injectable solution, led to a further inventory shortage[4].

Furthermore, the inspection of the "Zhuhai United Laboratories Co, Ltd" site conducted from 30 March 2015 to 2 April 2015 by the EDQM and the Romanian authorities led to the recording of a notice of non-compliance in the EudraGMDP database (no. NCF/011/RO) and the decision to suspend CEP 2013-125 concerning the manufacture of sterile sodium amoxicillin[5]. In France, this decision directly impacted Panpharma amoxicillin 1g, powder for injectable solution, and Panpharma amoxicillin 2g, powder for injectable solution. After reviewing all the evidence gathered during the investigation and the provisional measures put in place, and given the essential nature of this active substance in France, Romania, and the UK, a restricted GMP certificate (no. 016/2015/RO)[5] was issued to authorise the use of this AS in the three countries until the qualification of a new supplier by each MA holder.

These incidents highlight the critical nature of the supply of the active ingredient amoxicillin (sodium or trihydrate) on the availability of medicinal products present on the domestic market.

III. APPLICABLE REGULATIONS/GUIDELINES IN FORCE

The standards of good practice, enforceable or not enforceable, applicable to amoxicillin are listed below:

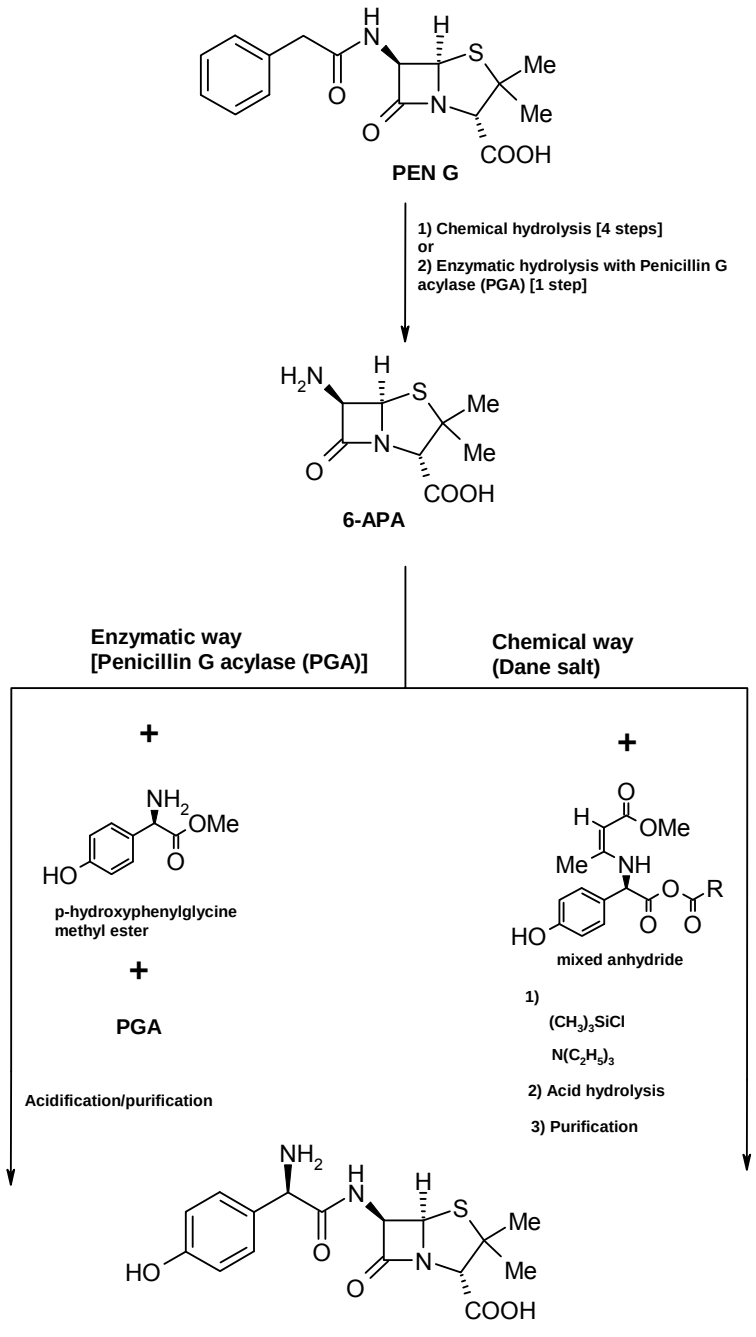
- Part II of the Good Manufacturing Practices for active substances used as starting materials in medicines;
- Guideline 1 of the European Guidelines for Good Manufacturing Practices: Manufacture of sterile medicinal products;
- European pharmacopoeia monograph no. 0577: sodium amoxicillin (semi-synthetic product derived from a fermentation product);
- European pharmacopoeia monograph no. 0260: amoxicillin trihydrate (semi-synthetic product derived from a fermentation product);
- A draft revision of EP monographs no. 0260 and 0577, presented in volume 26.2 of Pharmeuropa of July 2014, is currently under review.

IV. AMOXICILLIN SUPPLY

IV.1. Process for obtaining amoxicillin

In terms of the industrial production described in the literature, the processes for obtaining amoxicillin trihydrate from the key intermediate 6-APA are chemical or enzymatic[6]. The 6-APA is obtained from penicillin G (PEN G/benzyl-penicillin) after breaking the amide bond [-CONH-] through the use of enzymatic or chemical methods.

Examples of processes for obtaining amoxicillin:



The conventional methods for chemically obtaining (using Dane salt) amoxicillin typically involve more than 10 steps, require low-reaction temperatures (-30°C), and use toxic solvents like methylene chloride and silylation reagents. It is reported that the production of one kilogram of amoxicillin generates up to about 70 kg of non-recyclable waste[7].

In contrast, enzymatic methods require far fewer steps, use milder reaction conditions, and generate less waste.

The latter approach is being implemented for industrial production: enzymatic synthesis has been used by DSM since 2006 and will soon be used by GSK at its Singapore site[8].

The literature also describes "one pot" trials for obtaining amoxicillin directly from PEN G[7].

Numerous synthetic routes for sodium amoxicillin from amoxicillin trihydrate are described in the literature (e.g. treatment with sodium hydroxide, sodium 2-ethylhexanoate, or sodium diethyl oxaloacetate)[9].

IV.2. Sources of supply of medicinal product manufacturing sites in France

As part of its mission of surveillance of health products, an investigation was conducted by ANSM in March 2015 with 13 pharmaceutical sites holding marketing authorisations for medicinal products with amoxicillin (trihydrate or sodium) as their active substance in order to draw up an inventory of the manufacturers of the active substance amoxicillin used in medicines placed on the domestic market.

Eleven amoxicillin manufacturers were identified*:

Country	AS manufacturers	AS	Number of pharmaceutical sites supplied
Austria	**Sandoz GmbH** Biochemiestrasse 10 A-6250 KUNDL	Sterile sodium amoxicillin	3
Austria	**Sandoz GmbH** Biochemiestrasse 10 A-6250 KUNDL	Amoxicillin trihydrate	4
Spain	**Deretil, SA** Villaricos, 04618 Cuevas Del Almanzora, Almería	Amoxicillin trihydrate	7
Spain	**Sandoz Industrial Products SA** Ctra Granollers Cardedeu C 251 km 4 Les Franqueses Del Valles 08520 Barcelona	Amoxicillin trihydrate	10
Spain	**Sandoz Industrial Products SA** Poligon Industrial Mas Puigvert E - 08389 Palafolls, Barcelona	Sterile sodium amoxicillin	3
United States	**Teva Pharmaceuticals USA Inc.** 5000 Christopher Drive Mexico, MO 65265	Amoxicillin trihydrate	1
India	**DSM Anti Infectives India Ltd** Bhai Mohan Singh Nagar, District Nawanshahr, Toansa, 144 533 Punjab	Amoxicillin trihydrate	3
People's Republic of China	**Zhuhai United Laboratories Co Ltd** Sanzao Science & Technology Park, National Hi-Tech Zone, Zhuhai,Guandong, 519040	Sterile sodium amoxicillin	1
Singapore	**GSK** 38 Quality Road jurong Industrial estate, Jurong 618809	Amoxicillin trihydrate	4
Oman	**Oman Chemicals** plot n°8186 Buraimi Industrial Area Mahadha Road 512 Al Buraimi	Amoxicillin trihydrate	1

*: The following two manufacturers were not included in the study:

- Ranbaxy Laboratories Ltd, PO Rail Majra, District Nawanshahar India - 144533 Toansa, Punjab (India), whose production has been stopped since January 2013 (last use of 469 kg of amoxicillin trihydrate in 2014; one pharmaceutical client);

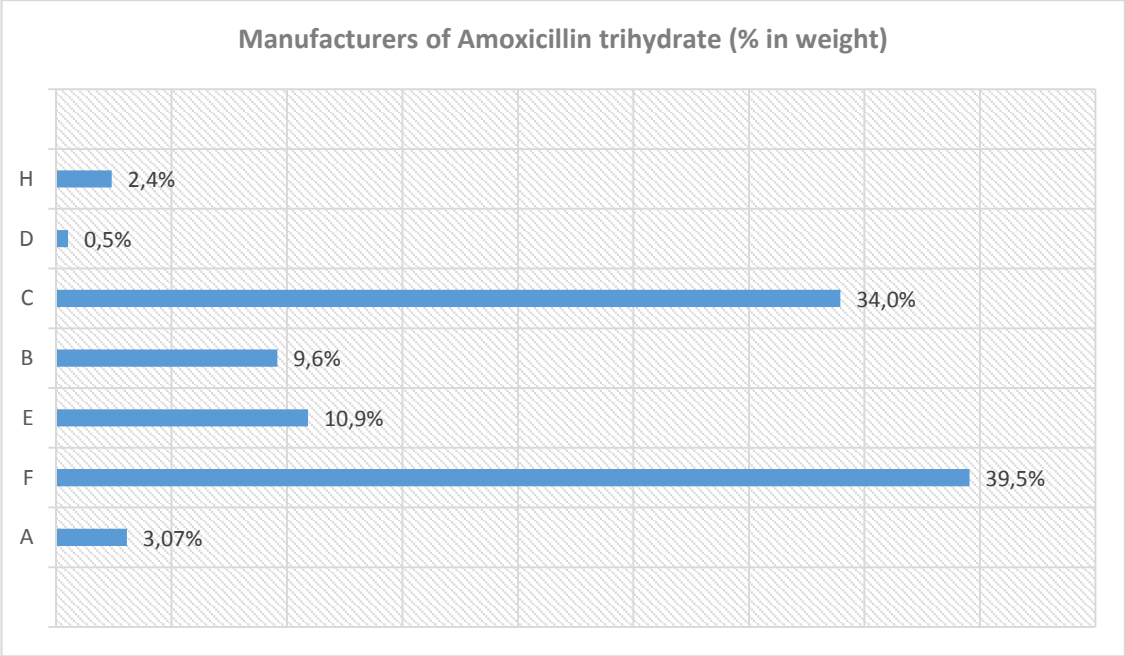
- Antibioticos, avda de Antibioticos 59/61 24009 LEON (Spain), whose production has been stopped since March 2013 (last use of 586 kg of amoxicillin trihydrate in 2012; one pharmaceutical client).

This site, taken over in November 2014 by the "Black Toro Capital" investment fund, recently changed its name: "Antibioticos Leon, S.A.". This is the only site in Europe for obtaining penicillin G (G PEN) with an industrial fermentation capacity of 3070 m^3 (last fermentation operation carried out in July 2011).

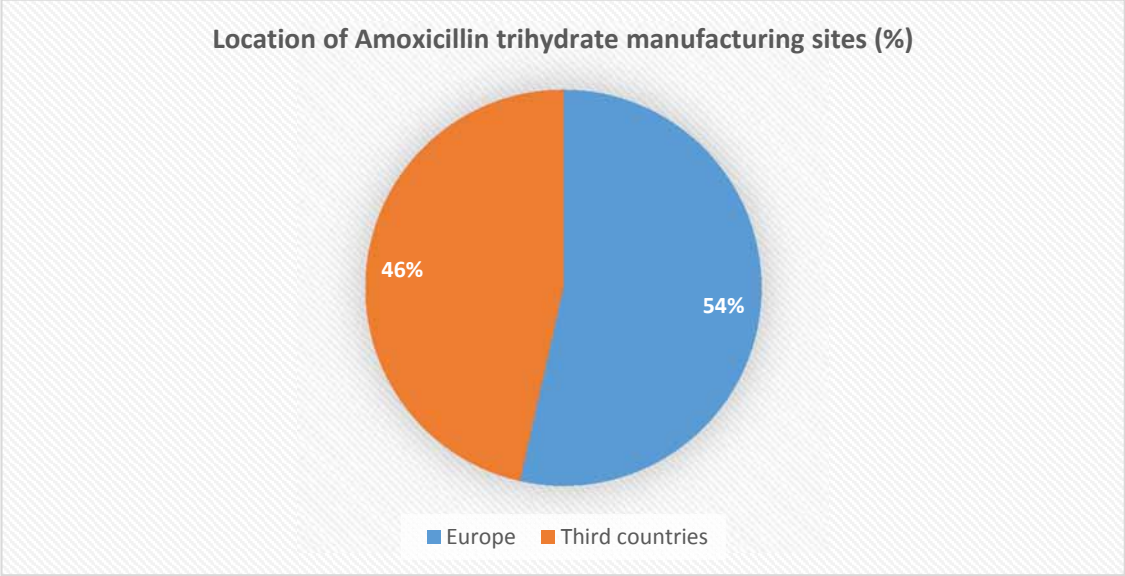
According to the above table, there appears to be a significant European presence of amoxicillin manufacturing companies. However, it must be noted that the production of starting materials upstream of the active substance (PEN G and 6-APA) was carried out in 2015 exclusively in countries outside of Europe, mainly in the People's Republic of China.

Amoxicillin trihydrate:

From the data provided by the operators over a period of three years (2012 to 2014), it appears that around 500 tonnes of amoxicillin trihydrate are used each year to manufacture medicines on the domestic market. Two major manufacturers, **C** and **F**, were highlighted (the names of the establishments have been anonymised for privacy reasons as to the volumes supplied).

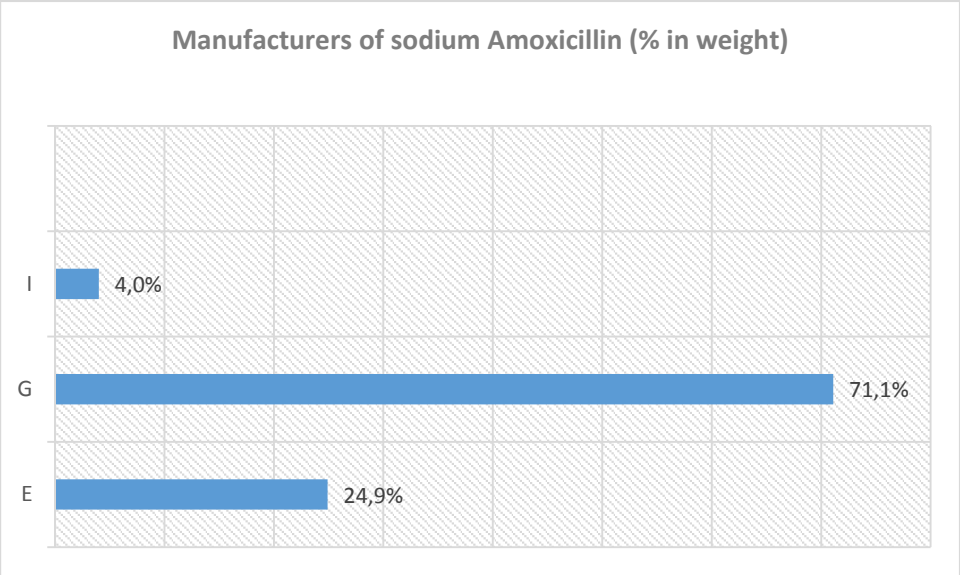


It is noteworthy that 46% of amoxicillin trihydrate comes from countries outside of Europe.

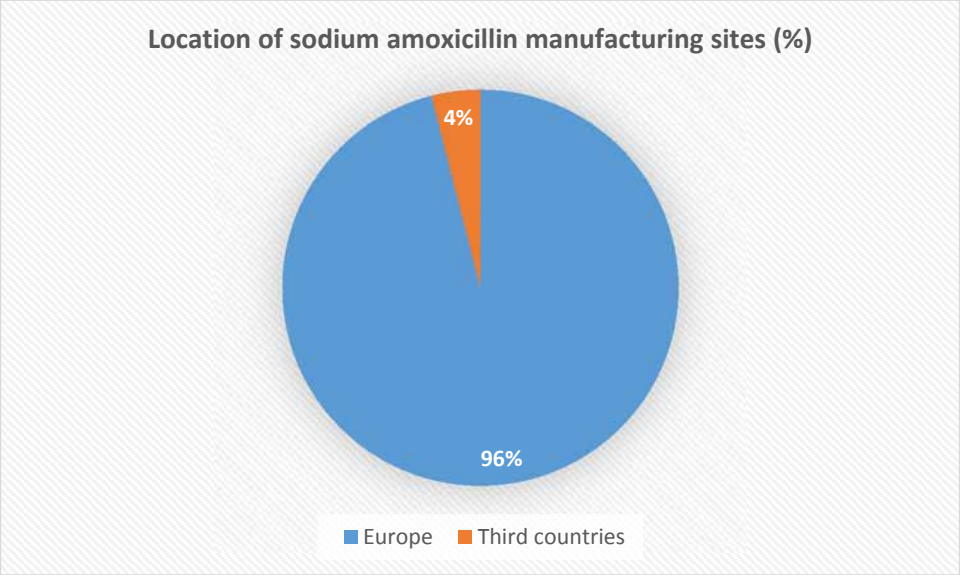


Sterile sodium amoxicillin:

From the data provided by the operators over a period of three years (2012 to 2014), it appears that around 15 tonnes of sterile sodium amoxicillin are used each year to manufacture medicines on the domestic market. Two major manufacturers (**G** and **E**) were highlighted (the names of the establishments have been anonymised for privacy reasons as to the volumes supplied).



In contrast with amoxicillin trihydrate, only 4% of sodium amoxicillin comes from countries outside of Europe.



According to data collected during the investigation, about 515 tonnes of amoxicillin (sodium and trihydrate) are consumed each year for the French market.

This figure is consistent with the national consumption figures for 2014, expressed in Defined Daily Doses (DDD)/1000 inhabitants/day[10].

V. EVALUATION OF AMOXICILLIN MANUFACTURERS BY PHARMACEUTICAL SITE

Amoxicillin (sodium and trihydrate) manufacturing sites located inside or outside of Europe are regularly audited by ordering pharmaceutical sites.

In reviewing the data provided by operators over the last three years, it appears that two intervals for auditing manufacturing sites were defined depending on the criticality of the active substance:

- 2 years for sterile sodium amoxicillin (injectable proprietary medicinal products).
- 3 years for amoxicillin trihydrate (oral proprietary medicinal products).

VI. REVIEW OF RECENT INSPECTIONS

VI.1. Collaboration between competent authorities

The application of the texts is regularly verified during inspections regardless of the category of establishments (manufacturers, distributors, or importers), drug manufacturing sites (France and third countries, knowing that for the territory of the European Union, the relevant competent national authorities are in charge of inspecting sites within their territory), and the category of medications (proprietary and generics).

From a global point of view, the inspections confirm a globalisation of players in the active substance production and distribution chain, particularly in Asia. This dispersion of operators makes their monitoring and control more difficult for both ordering parties through audits and the competent authorities through inspections.

ANSM's action is therefore part of a coordinated framework with the other EU Member States and the EDQM, particularly with regard to inspections in countries outside the EU. This framework is supported by the mandatory nature of the mutual recognition of inspections conducted by other EU Member States and the exchange of information. Therefore, the inspection capacity must be considered not only on just French resources but also those of other Member States and the EDQM as well as those of States that have entered into specific agreements with the EU.

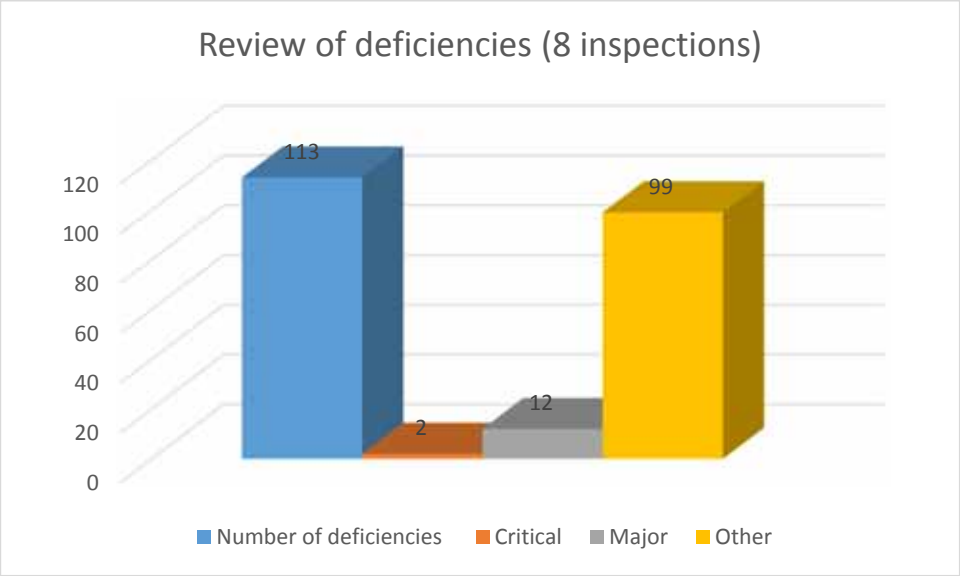
The ANSM and its counterparts in the European and international agencies coordinate their inspection actions accordingly to optimise the monitoring of these activities in third countries. Joint inspections and exchanges concerning the scheduling of inspections, organised in conjunction with the EMA, the EDQM, and the WHO in particular, thus allow remote sites to be covered and information on the results of these inspections to be exchanged. A pooling of inspection results is done within Europe through a database that contains all the certificates of compliance issued by the national regulatory authorities concerned including extra-Community inspections (http://eudragmp.ema.europa.eu/).

This strategy of monitoring by the authorities is established in a regulatory framework harmonised at the Community level in which responsibility for the quality of active substances primarily falls to the drug manufacturers, for which the Qualified Person (*Pharmacien Responsable* in France) is the guarantor.

VI.2. Monitoring of amoxicillin (sodium or trihydrate) manufacturing sites by international authorities since 2010

AS manufacturers	AS	Inspections by international authorities	compliance with the GMP
Sandoz GmbH Biochemiestrasse 10 A-6250 KUNDL (Austria)	Sterile sodium amoxicillin Amoxicillin trihydrate	- US-FDA [02/04/2015] - BASG / AGES [06/02/2013; 22/07/2013; 19/11/2013]	**Yes**
Deretil, SA Villaricos, 04618 Cuevas Del Almanzora, Almería (Spain)	Amoxicillin trihydrate	- US-FDA [23/09/2013] - AEMPS [07/05/2013] - US-FDA [28/06/2010]	**Yes**
Sandoz Industrial Products SA Ctra Granollers Cardedeu C 251 km 4 Les franqueses Del Valles 08520 Barcelona (Spain)	Amoxicillin trihydrate	- CRA-CAT [20/04/2015] - US-FDA [08/07/2013] - AEMPS/DEQM [18/10/2011]	**Yes**
Sandoz Industrial Products SA Poligon Industrial Mas Puigvert E - 08389 Palafolls, Barcelona (Spain)	Sterile sodium amoxicillin	- AEMPS [04/05/2015] - CRA-CAT [04/03/2015] - US-FDA [18/09/2013] - CRA-CAT [23/01/2012] - AEMPS [26/09/2011]	**Yes**
Teva Pharmaceuticals USA Inc. 5000 Christopher Drive Mexico, MO 65265 (United States)	Amoxicillin trihydrate	- US-FDA [02/2015] - US-FDA [02/2012]	**Yes**
DSM Anti Infectives India Ltd Bhai Mohan Singh Nagar, District Nawanshahr, Toansa, 144 533 Punjab (India)	Amoxicillin trihydrate	- TGA [05/12/2012]	**Yes**
Zhuhai United Laboratories Co Ltd Sanzao Science & Technology Park, National Hi-Tech Zone, Zhuhai,Guandong, 519040 (People's Republic of China)	Sterile sodium amoxicillin	- NAMMD/DEQM [30/03/2015] - BGV (Germany) [21/10/2013] - BGV (Germany) [24/11/2011] - NAMMD (Romania) [24/10/2011]	- restricted GMP certificate no. 016/2015/RO [15/06/2015] - "**Notice of non-compliance**": NCF/011/RO [15/06/2015]
GSK 38 Quality Road jurong Industrial estate, Jurong 618809 (Singapore)	Amoxicillin trihydrate	- US-FDA [20/01/2014] - ANSM [01/11/2015]	**Yes**
Oman Chemicals plot n°8186 Buraimi Industrial Area Mahadha Road 512 Al Buraimi (Oman)	Amoxicillin trihydrate	- AEMPS/DEQM (05/02/2015) - LANUV (Germany) [06/02/2012]	**Yes**

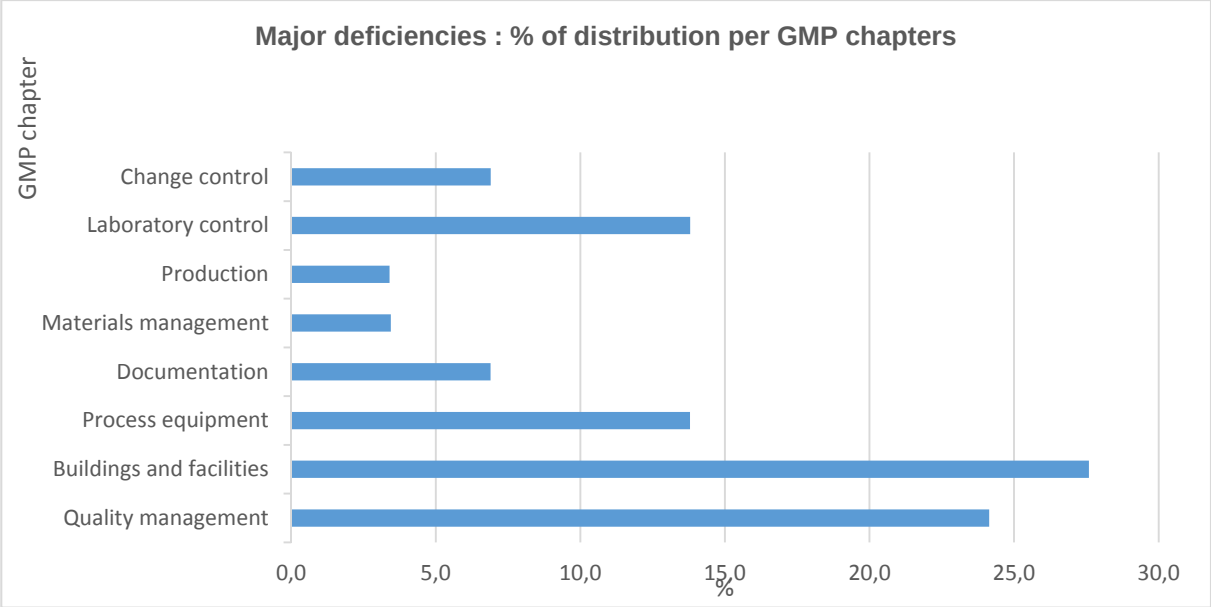
All sites are regularly inspected by international authorities. The investigation revealed that the GSK site in Singapore, although already regularly supervised by the USFDA (last inspection in 2014), had never been inspected by a European authority. An inspection was therefore conducted by ANSM starting in November 2015 and resulted in the issuance of a certificate of compliance with good practices.
A review of recent inspections conducted by the European authorities or the TGA (part II of the GMP/appendix 1 for sterile sodium amoxicillin) at eight sites was conducted. These inspections resulted in a finding of 113 deviations from the GMP, including 12 major and 2 critical. The number of findings per inspection varies from 2 to 36.
The two critical findings occurred during the inspection of the "Zhuhai United Laboratories" site.

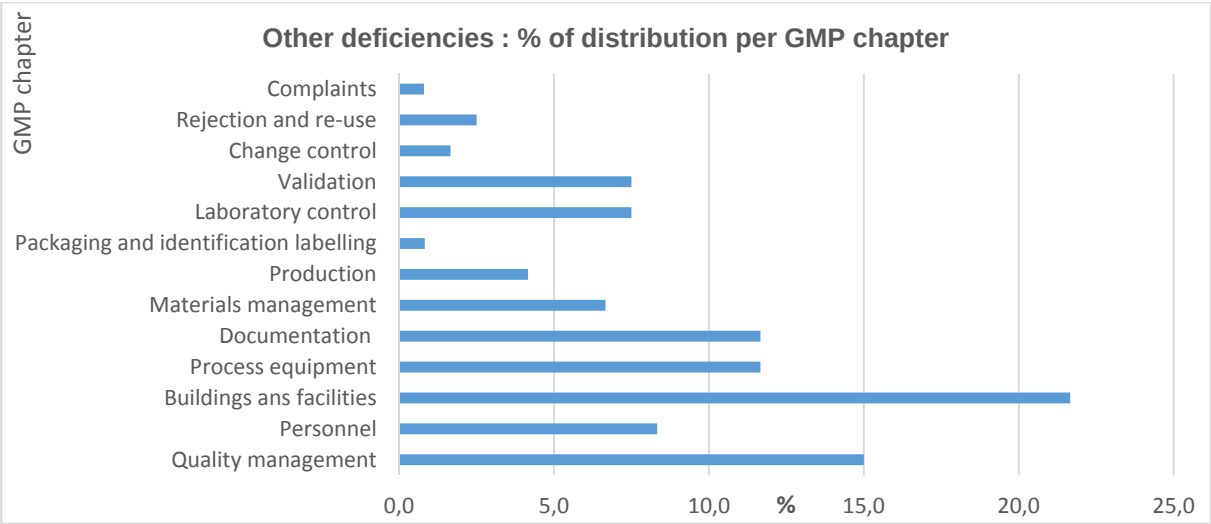


The critical and major findings[11] related to the following themes:

Critical findings
Non-compliance concerning aseptic working conditions in relation to the requirements of Appendix 1 of the GMP
Non-compliance on the quality system and its implementation
Major findings
Failure on identifying storage areas for starting materials
Failure on quality risk management
Failure on representative sampling of starting materials
Failure on batch control before mixing
Failure on means of control to prevent any access or modification of data of the HPLC systems
Failure on computerised system management
Failure on performing system suitability tests of chromatographic systems
Failure on recording of analytical controls
Failure on control of risk of contamination of production areas by beta-lactams
Failure on design of installations for control of risk of contamination
Failure on management of internal audits
Failure on design and maintenance of buildings and installations

The detailed analysis of the findings by each GMP chapter shows that the non-compliances relating to "quality management" and "buildings and installations" are preponderant, whether with regard to "major" findings or the "other" findings:




Other deficiencies : % of distribution per GMP chapter
GMP chapter
Complaints
Rejection and re-use
Change control
Validation
Laboratory control
Packaging and identification labelling
Production
Materials management
Documentation
Process equipment
Buildings ans facilities
Personnel
Quality management
0,0
5,0
10,0
%
15,0
20,0
25,0

VII. CONCLUSION

The investigation of 13 pharmaceutical sites holding marketing authorisations for medicinal products placed on the domestic market with amoxicillin (in sodium or trihydrate form) as their active substance permitted the production of a complete inventory of AS procurement sources as well as the amounts used.

Eleven amoxicillin manufacturers located inside or outside of Europe were identified. Around 500 tonnes are used each year to manufacture medicinal products placed on the French market.

Over the 2012-2014 period, two major players were identified for each of the two forms:

- Amoxicillin trihydrate:
  - establishment **F** [39%];
  - establishment **C** [34%].

- Sodium amoxicillin:
  - establishment **G** [71%];
  - establishment **E** [25%].

Approximately 46% of amoxicillin trihydrate and 96% of sodium amoxicillin used in medicines placed on the domestic market came from European countries over the 2012-2014 period.
In the particular case of sodium amoxicillin, which is used for injectable forms, it is noteworthy that in June 2015, the Chinese manufacturer "Zhuhai United Laboratories" was the subject of a CEP suspension decision by the EDQM, and a notice of non-compliance was recorded in the EudraGMDP Community database. Note that this manufacturer is not one of the major players listed above.

Although at first glance there appears to be a significant European presence of amoxicillin manufacturing establishments (46% [trihydrate] and 96% [sterile sodium] to supply the French market), the fact that 6-amino penicillanic acid (6-APA), a key starting material for the manufacture of amoxicillin, is manufactured in countries outside of Europe must be taken into consideration. Relocating these players further up the production line is therefore a real challenge in terms of control and dependence for the pharmaceutical industry.

The investigation also permitted a review of the quality level of the production sites used:

- the ordering pharmaceutical sites supervise the amoxicillin manufacturing sites through regular audits;
- the 11 manufacturing sites are regularly inspected by international authorities and, with the exception of "Zhuhai United Laboratories" (People's Republic of China), present an acceptable level of compliance with good manufacturing practices.

Furthermore, this study sheds light on the fragile nature of the sodium amoxicillin supply chain, causing inventory shortages (May 2013/June 2015; see paragraph II).

The four pharmaceutical sites producing injectable medicinal products are supplied by three manufacturers, including one located in a country outside of Europe.

Given the small number of players, any quality/production problem encountered by a sodium amoxicillin manufacturer immediately affects the availability of injectable pharmaceutical products manufactured by the pharmaceutical sites.

As a second step, the plan is to propose that the other European authorities engage in collaborative work to expand this type of public study to other active substances presenting major therapeutic challenges and/or high prescription levels.

VIII. LIST OF REFERENCES

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Reference 2: - ANSM report: "Caractérisation des antibiotiques considérés comme «critiques»" [Characterisation of "critical" antibiotics], November 2013.
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Reference 3: - ANSM report "Analyse des ventes de médicaments en France en 2013" [Analysis of drug sales in France in 2013], June 2014.
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Reference 4: - "Amoxicilline : risque de rupture de stock de toutes les formes injectables de ces médicaments – Point d'Information" [Amoxicillin: risk of inventory shortages of all injectable forms of these medications – Point of Information, 23/05/2013
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Reference 7: - "Enzymatic synthesis of Amoxicillin via one-pot enzymatic hydrolysis and condensation cascade process in the presence of organic co-solvents", Qi Wu et al., *Appl Biochem Biotechnol*, 160:2026-2035, (2010).

Reference 8: - Chimie Pharma Hebdo N°742, "GSK investit à Singapour" [GSK invests in Singapore], Monday, 13 July 2015;
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- Chimie Pharma Hebdo N°317, "Antibiotiques : des investissements en Inde pour DSM" [Antibiotics: investments in India for DSM], 14 November 2005.
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Reference 9: - Patent EP 0009845 B2 "Process for the manufacture of sodium amoxicillin preparations" (filed 11 November 1979);

- Brevet EP 0220925 A1 "A process for the preparation of sodium amoxicillin" (filed 21 October 1986);

- Patent WO 1997015579 A1 "Production of a crystalline salt of amoxicillin" (filed 28 October 1996).

Reference 10: - InVS and ANSM report "Consommation d'antibiotiques et résistance aux antibiotiques en France : nécessité d'une mobilisation déterminée et durable ; Bilan des données de surveillance" [Consumption of antibiotics and resistance to antibiotics in France: need for determined and sustainable mobilisation; Review of monitoring data], 17 November 2015.
http://ansm.sante.fr/var/ansm_site/storage/original/application/8cca0ffcbe1b15d4ee3e1d34ed5e7a40.pdf

Reference 11: Critical Deficiency:

A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

Major Deficiency:

A non-critical deficiency:

- which has produced or may produce a product, which does not comply with its marketing authorisation;

- or which indicates a major deviation from EU Good Manufacturing Practice;

- or (within EU) which indicates a major deviation from the terms of the manufacturing authorisation;

- or which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;

- or a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such;

Other Deficiency:

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

(A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as a major or critical).

IX. ACRONYMS

AEMPS
Agencia espanola de medicamentos y productos sanitarios (French competent authority)

ANSM
Agence nationale de sécurité des médicaments et des produits de santé (French competent authority)

6-APA
6-aminopenicillanic acid

AS
Active substance

BASG / AGES
Bundesamt für sicherheit im gesundheitswesen ; Institut inspektionen mediznprodukte & hämovigilanz (Austrian competent authority)

BGV
Behörde für gesundheit und verbraucherschutz der freien und hansestadt hamburg (German competent authority, federal states of Hamburg)

CEP
Certificate of compliance with the European Pharmacopoeia

CRA-CAT
Competent regional authority. Direccion de regulation, planificacion y recursos sanitarios. Departamento de salud. Generalitat de catalunya (regional competent authority of Catalonia)

DDD
Defined daily doses

DSM
De StaatsMijnen

EDQM
European Directorate for the Quality of Medicines

EMA
European Medicines Agency

EP
European Pharmacopoeia

EU
European Union

GMP
Good manufacturing practices

GSK
GlaxoSmithKline

IM
Intra muscular

IV
Intra venous

LANUV
Landesamt für natur umwelt und verbraucherschutz nordrhein westfalen (German competent authority, federal states of North Rhine-Westphalia)

MA
Marketing authorisation

NAMMD
National agency for medicines and medical devices (Romanian competent authority)

NCS
Notice of GMP non-compliance

PGA
Penicillin G acylase

TGA
Therapeutic goods administration (Australian competent authority)

US FDA
Food and Drug Administration (US competent authority)

WHO
World Health Organisation

X. APPENDICES

X.1. Appendix 1: List of pharmaceutical sites and proprietary medicinal products

Pharmaceutical Sites	Proprietary Medicinal Products
Actavis France*	- Actavis amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for children, powder for oral suspension in vial - Actavis amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for infants, powder for oral suspension in vial - Actavis amoxicillin/clavulanic acid 500 mg/62.5 mg for adults, coated tablets - Actavis amoxicillin/clavulanic acid 1 g/125 mg for adults, powder for oral suspension in single-dose packet
Arrow Génériques	- Arrow amoxicillin 500 mg 12 capsules - Arrow amoxicillin 1 g 6 dispersible coated tablets - Arrow amoxicillin 1 g 14 dispersible coated tablets - Arrow amoxicillin 125 mg/5 ml 60 ml powder for oral suspension - Arrow amoxicillin 250 mg/5 ml 60 ml powder for oral suspension - Arrow amoxicillin 500 mg/5 ml 60 ml powder for oral suspension - Arrow amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for infants 30 ml powder for oral suspension - Arrow amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for children 60 ml powder for oral suspension - Arrow amoxicillin/clavulanic acid 500 mg/62.5 mg for adults 16 coated tablets - Arrow amoxicillin/clavulanic acid 500 mg/62.5 mg for adults 24 coated tablets - Arrow amoxicillin/clavulanic acid 1g/125 mg for adults 8 packets of powder for oral suspension - Arrow amoxicillin/clavulanic acid 1g/125 mg for adults 12 packets of powder for oral suspension
Biogaran	- Almus amoxicillin 500mg, box of 12 capsules - Almus amoxicillin 1 g, dispersible coated tablets - Almus amoxicillin 500 mg/5 ml powder for suspension - 60 ml glass vial - Almus amoxicillin 250 mg/5 ml powder for suspension - 60 ml glass vial - Biogaran amoxicillin 1g, box of 6 dispersible tablets - Biogaran amoxicillin 1g, box of 14 dispersible tablets - Biogaran amoxicillin 125 mg/5 ml powder for oral suspension - Biogaran amoxicillin 250 mg/5 ml powder for oral suspension - Biogaran amoxicillin 500 mg/5 ml powder for oral suspension - Biogaran amoxicillin 1g, box of 6 dispersible tablets - Biogaran amoxicillin 1g, box of 14 dispersible tablets - Biogaran amoxicillin 125 mg/5 ml powder for oral suspension - Biogaran amoxicillin 250 mg/5 ml powder for oral suspension - Biogaran amoxicillin 500 mg/5 ml powder for oral suspension - Biogaran amoxicillin 500 mg, box of 12 capsules
Cristers	- Cristers amoxicillin 125 mg/5 ml, powder for oral suspension - Cristers amoxicillin 250 mg/5 ml, powder for oral suspension - Cristers amoxicillin 500 mg, capsules - Cristers amoxicillin 500 mg/5 ml, powder for oral suspension - Cristers amoxicillin/clavulanic acid 1 g/125 mg for adults, powder for oral suspension in single-dose packet (amoxicillin/clavulanic acid ratio: 8/1) - Cristers amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for children, powder for oral suspension in vial (amoxicillin/clavulanic acid ratio: 8/1) - Cristers amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for infants, powder for oral suspension in vial (amoxicillin/clavulanic acid ratio: 8/1) - Cristers amoxicillin/clavulanic acid 500 mg/62.5 mg for adults, coated tablets (amoxicillin/clavulanic acid ratio: 8/1)
EG Labo	- EG amoxicillin/clavulanic acid 100mg/12.5mg, 30ml vial - EG amoxicillin/clavulanic acid 100mg/12.5mg, 60ml vial - EG amoxicillin/clavulanic acid 1g/125mg, 12 packets - EG amoxicillin/clavulanic acid 1g/125mg, 8 packets - EG amoxicillin/clavulanic acid 500mg/62.5mg, 16 coated tables - EG amoxicillin/clavulanic acid 500mg/62.5mg, 24 coated tables - EG amoxicillin 125mg/5ml, powder for oral suspension, 60 ml vial - EG amoxicillin 250mg/5ml, powder for oral suspension, 60 ml vial - EG amoxicillin 500mg/5ml, powder for oral suspension, 60 ml vial - EG amoxicillin 1g, 6 dispersible tablets - EG amoxicillin 1g, 14 dispersible tablets - EG amoxicillin 500mg, 12 capsules
Laboratoire GSK	- Clamoxyl 1g dispersible tablets - Clamoxyl 125 mg/5 ml, powder for oral suspension - Clamoxyl 250 mg/5 ml, powder for oral suspension - Clamoxyl 500 mg, capsules - Clamoxyl 500 mg/5 ml, powder for oral suspension - Augmentin 1 g/125 mg for adults, powder for oral suspension in single-dose packet (amoxicillin/clavulanic acid ratio: 8/1) - Augmentin 100 mg/12.50 mg per ml for children, powder for oral suspension in vial (amoxicillin/clavulanic acid ratio: 8/1) - Augmentin 100 mg/12.50 mg per ml for infants, powder for oral suspension (amoxicillin/clavulanic acid ratio: 8/1) - Augmentin 500 mg/62.5 mg for adults, coated tablets (amoxicillin/clavulanic acid ratio: 8/1)

	- Clamoxyl 1 g, powder and solvent for injectable solution (i.m.) - Clamoxyl 1 g, powder for injectable solution (i.m.-i.v.) - Clamoxyl 2 g, powder for injectable solution (i.v.) - Clamoxyl 500 mg, powder for injectable solution (i.m., i.v.) - Augmentin 1 g/200 mg for adults, powder and solvent for injectable solution (i.v.) - Augmentin 1 g/200 mg for adults, powder for injectable solution (i.v.) - Augmentin 2 g/200 mg for adults, powder for injectable solution (i.v.) - Augmentin 500 mg/50 mg for infants and for children, powder for injectable solution (i.v.)
Mylan France	- Mylan amoxicillin 1 g, 14 dispersible tablets - Mylan amoxicillin 1 g, 6 dispersible tablets - Mylan amoxicillin 125/5 mg/ml 1 vial powder for oral suspension - Mylan amoxicillin 250/5 mg/ml 1 vial powder for oral suspension - Mylan amoxicillin 500 mg, 12 capsules - Mylan amoxicillin 500/5 mg/ml 1 powder for oral suspension - Mylan amoxicillin/clavulanic acid for adults 1/200 g/mg 10 vials powder for injectable solution - Mylan amoxicillin/clavulanic acid for adults 2/200 g/mg 10 vials powder for injectable solution - Mylan amoxicillin/clavulanic acid for children 1/100 g/mg 10 vials powder for injectable solution - Mylan amoxicillin/clavulanic acid for children 500/50 mg/mg 10 vials powder for injectable solution
Panpharma	- Panpharma amoxicillin 500 mg, capsules - Panpharma amoxicillin/clavulanic acid 500 mg/100 mg for adults, powder for injectable solution (i.v.) - Panpharma amoxicillin 1 g, powder for injectable solution - Panpharma amoxicillin 1 g/5 ml, powder and solution for injectable solution (im) - Panpharma amoxicillin 2 g, powder for injectable solution - Panpharma amoxicillin 500 mg, powder for injectable solution - Panpharma amoxicillin/clavulanic acid 1 g/100 mg for children, powder for injectable solution (i.v.) - Panpharma amoxicillin/clavulanic acid 1 g/200 mg for adults, powder for injectable solution - Panpharma amoxicillin/clavulanic acid 2 g/200 mg for adults, powder for injectable solution - Panpharma amoxicillin/clavulanic acid 500 mg/50 mg for infants and for children, powder for injectable solution (i.v.)
Sandoz SAS	- Sandoz Amoxicillin 1 g, dispersible tablets nl 34834 - Sandoz amoxicillin 125 mg/5 ml, powder for oral suspension nl 21556 - Sandoz amoxicillin 250 mg/5 ml, powder for oral suspension nl 21557 - Sandoz amoxicillin 500 mg, capsules nl 21558 - Sandoz amoxicillin 500 mg/5 ml, powder for oral suspension nl 21712 - Almus amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for children, powder for oral suspension nl 27152 - Almus amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for infants, powder for oral suspension nl 27153 - Almus amoxicillin/clavulanic acid 500 mg/62.5 mg for adults, coated tablets nl 27597 - Sandoz amoxicillin/clavulanic acid 1 g/125 mg for adults, powder for oral suspension in single-dose packet nl 27926 - Sandoz amoxicillin/clavulanic acid 500 mg/62.5 mg for adults, coated tablets nl 27595 - Sandoz amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for children, powder for oral suspension in vial nl 27099 - Sandoz amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for infants, powder for oral suspension in vial nl 27100 - Sandoz amoxicillin/clavulanic acid 2 g/200 mg for adults, powder for infusion solution nl 31932 - Sandoz amoxicillin/clavulanic acid 500 mg/50 mg for infants and for children, powder for infusion solution (iv) nl 33534 - Sandoz amoxicillin/clavulanic acid 1 g/200 mg for adults, powder for injectable solution nl 31931
Sanofi	- Zentiva amoxicillin 1 g, dispersible coated tablets - Cristers amoxicillin 250mg/5ml powder for oral suspension - Zentiva amoxicillin 500 mg, capsules - Cristers amoxicillin 500 mg/5ml powder for oral suspension - Zentiva amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for children, powder for oral suspension - Zentiva amoxicillin/clavulanic acid 100 mg/12.5 mg per ml for infants, powder for oral suspension - Zentiva amoxicillin/clavulanic acid 500 mg/62.5 mg for adults, coated tablets
Sun Pharma (Ranbaxy Pharmacie Générique)	- Ranbaxy amoxicillin/clavulanic acid 100 mg/12.5 mg for children, powder for oral suspension (60ml) - Ranbaxy amoxicillin/clavulanic acid 100 mg/12.5 mg for infants, powder for oral suspension (30ml) - Ranbaxy amoxicillin/clavulanic acid 1g/125 mg for adults, powder for oral suspension, packet (x 8 & 12) - Ranbaxy amoxicillin/clavulanic acid 500 mg/62.5 mg for adults, coated tablets (x 16 & 24) - Rpg amoxicillin/clavulanic acid 100 mg/12.5 mg for children, powder for oral suspension (60ml) - (GSK holder) - Rpg amoxicillin/clavulanic acid 100 mg/12.5 mg for infants, powder for oral suspension (30 ml) - (GSK holder)

	- Rpg amoxicillin/clavulanic acid 1g/125mg packets (x 8 and x 12) - (GSK holder) - Rpg amoxicillin/clavulanic acid 500 mg/62.5 mg coated tables (x 16 and x 24) - (GSK holder) - Rpg amoxicillin 250mg/5ml, powder for oral suspension, vial (60 ml) - Rpg amoxicillin 500mg/5ml, powder for oral suspension, vial (60 ml) - Ranbaxy amoxicillin 1g, dispersible tablets (x 6 & x 14) - Ranbaxy amoxicillin 500mg, capsules (x 12)
Teva Santé	- Amoxicillin/clavulanic acid ratio 1 g/125 mg for adults, powder for oral suspension in single-dose packet - Amoxicillin/clavulanic acid ratio 500 mg/62.5 mg for adults, coated tablets - Amoxicillin/clavulanic acid ratio 100 mg/12.5 mg per ml for children, powder for oral suspension in vial - Amoxicillin/clavulanic acid ratio 100 mg/12.5 mg per ml for infants, powder for oral suspension in vial - Teva Santé amoxicillin/clavulanic acid 1 g/125 mg for adults, powder for oral suspension in single-dose packet - Teva Santé amoxicillin/clavulanic acid 500 mg/62.5 mg for adults, coated tablets - Teva Santé amoxicillin/clavulanic acid 100 mg/12.50 mg per ml for children, powder for oral suspension in vial - Teva Santé amoxicillin/clavulanic acid 100 mg/12.50 mg per ml for infants, powder for oral suspension in vial - Ratiopharm amoxicillin 500 mg, capsules - Teva amoxicillin 1 g, dispersible tablets - Teva amoxicillin 125 mg/5 ml powder for oral suspension - Teva amoxicillin 250 mg/5 ml powder for oral suspension - Teva amoxicillin 500 mg, capsules - Teva amoxicillin 500 mg/5 ml powder for oral suspension - Teva Santé amoxicillin 1 g, oro-dispersible tablets - Teva Santé amoxicillin 125 mg/5 ml powder for oral suspension - Teva Santé amoxicillin 250 mg/5 ml powder for oral suspension - Teva Santé amoxicillin 500 mg/5 ml powder for oral suspension
Zydus France	- Zydus amoxicillin/clavulanic acid 500 mg/62.5 mg, film-coated tablets - Zydus amoxicillin/clavulanic acid 100mg/12.5 mg, 30 ml bottle for infants - Zydus amoxicillin/clavulanic acid 100mg/12.5 mg, 60 ml bottle for children - Zydus amoxicillin 125mg/5ml 60ml pos fr - Zydus amoxicillin 250mg/5ml 60ml pos fr - Zydus amoxicillin 500mg/5ml 60ml pos fr - Zydus amoxicillin 500mg 12hgc fr - Zydus amoxicillin 1000mg 6dt fr - Zydus amoxicillin 1000mg 614dt fr - Zydus amoxicillin/clavulanic acid 1g/125mg 12 pos fr - Zydus amoxicillin/clavulanic acid 1g/125mg 8 pos fr

* Actavis France's proprietary medicinal products have not been on the market since May 2014.
End of factory output in early 2013.