Authorization and GMP Regulation

São Paulo, August 2nd 2014.

Authorization

- Companies need Anvisa authorization (AFE) to begin comercial activities in Brazil related to medicines, pharmaceutical ingredients, cosmetics, toiletries, perfumes, sanitizing and medical devices.

- Comercial activities with controlled drugs need an especial authorization (AE).

- Requirements to get AFE and AE are detailed on Resolution RDC 16, published on D.O.U. 63, April 2nd 2014, page 58 and D.O.U. 64, April 3rd 2014, page 35

Authorization

- Related Legislation:
  - AFE: Law 6.360/1976 and Law 9.782/1999
  - AE: Ordinance 344/1998 and updates
  - AFE and AE: RDC 222/2006 and RDC 76/2008 – request and payment procedures (Anvisa website).

Activities subject to AFE*

1. extract,
2. produce,
3. manufacturing,
4. packing,
5. repack,
6. import,
7. export,
8. store,
9. shipping,
10. transport,
11. sale (retail)
12. distribute;
13. fractionate;
14. purify;
15. synthesize;
16. transform

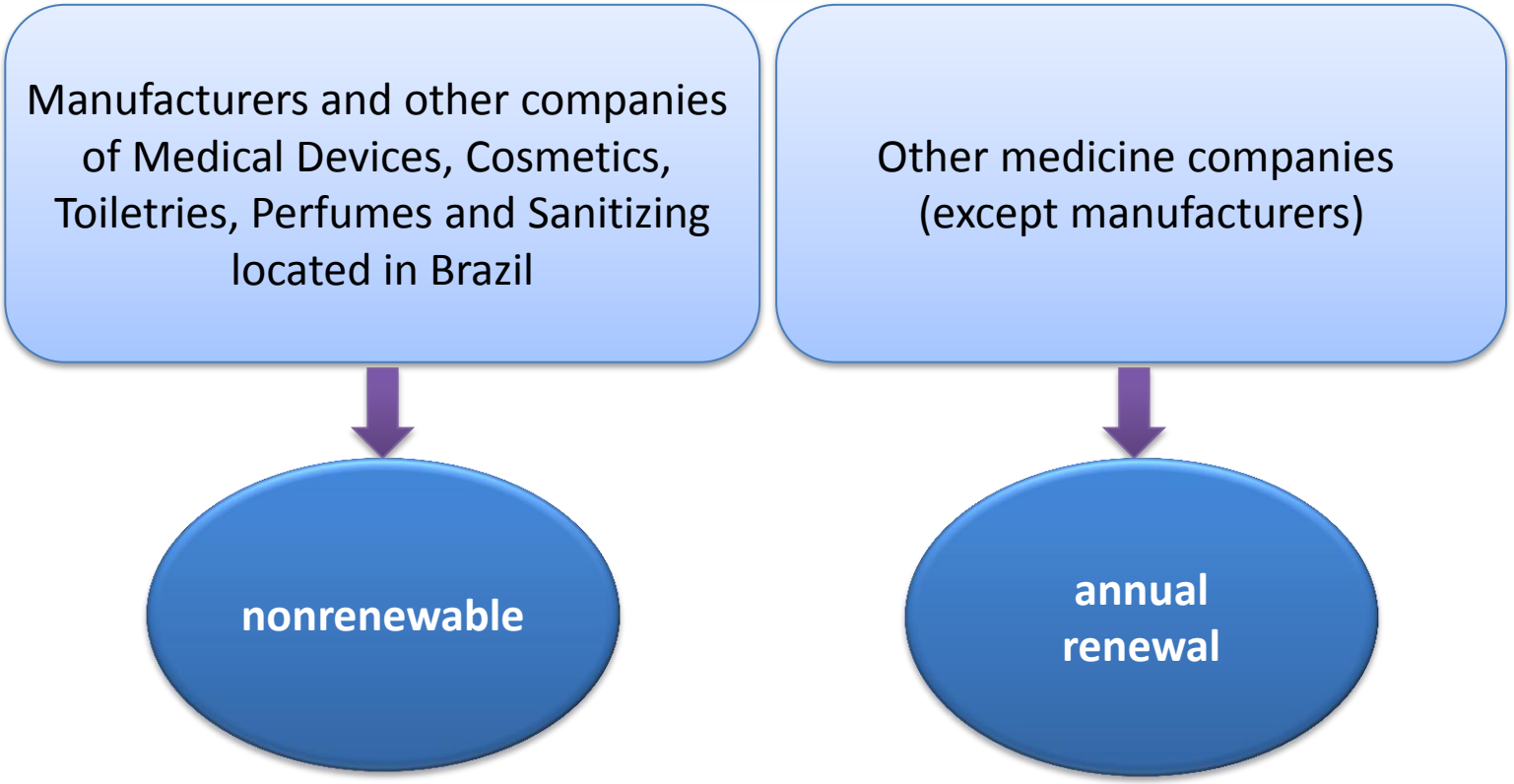
* Law 6.360/1976; Law 9.782/1999 and RDC 16/2014 with changes.

Activities subject to AE*
(Medicines and Pharmaceutical Ingredients)

1. extract,
2. produce,
3. manufacturing,
4. improve
5. distribute,
6. carrier,
7. preparing
8. Compounding (pharmacies),
9. fractionate,
10. import,
11. export,
12. transform,
13. packing,
14. repack.

* Ordinance 344/1998 and updates

AFE e AE renewal*



* Law 9.782/1999

AFE is not required in the following companies:

I - that perform the retail sale of medical devices for use directly by the consumer (lay use);
II - affiliates that exclusively perform administrative activities without storage, since the matrix has AFE;
III – that perform the retail sale of cosmetics, toiletries, perfumes and sanitizing;
IV - exclusively engaged in manufacturing, distribution, storage, packaging, export, fractionation, transportation or importation of raw materials, components and supplies activities not subject to special control, which are intended for the manufacture of medical devices, cosmetics, toiletries, perfumes and sanitizing;
V - exclusively perform installation, maintenance and servicing of equipments (medical devices).

* RDC 16/2014, Art. 5º

Technical Documents required for AFE and AE requests*

Type of request	Technical Documents
Initial requests	• **Manufacturers:** Inspection Report • **Other companies:** Inspection Report or equivalent document (ex. Technical Report and others) • **Retail of medical devices:** social contract with object compatible with requested activity
Renewal and Changes	Inspection report or equivalent document or sanitary license from the local authority
All requests for AE	The document must inform that the company meets Ordinance 344/1998 and 6/1999

* RDC 16/2014

Other Requirements

A Brazilian establishment to represent the international company, that needs:

- a national register - CNPJ;
- a sanitary license from the local authority (in Brazil);
- a company register on the Anvisa database;
- payment of fees according to the requests listed on Law 9.782/1999.

GMP Regulation - Medicines

RDC 17/2010* Content	INTERNATIONAL REFERENCE
GMP Principles and Guide – From Article 6 to 318.	Attachment 4 from 37th Report – **WHO** Technical Report Series 908, 2003.
Sterile Products – From Article 319 to 427.	Attachment 6 from 36th Report – **WHO** Technical Report Series 902, 2002.
Biotech Products – From Article 360 to 460.	Attachment 3 from **WHO** Technical Report Series 822, 1992.
Validation – From Article 461 to 526.	Attachment 4 from 40th Report – **WHO** Technical Report Series 937, 2006.
Water for Pharmaceutical Purposes – From Article 527 to 569	Attachment 3 from 39th Report – **WHO** Technical Report Series 929, 2005.
Computerized Systems – From Article 570 to 590	Attachment 11 from **EMEA** GMP Guide and **PIC's** GMP Guide.
Herbal Medicines – From Article 591 to 607.	Attachment 3 from 40th Report – **WHO** Technical Report Series 937, 2006.

* Published in the Brazilian Official Journal on April, 19th, 2010.

GMP Regulation – Medical Devices

RDC 16/13: ISO 13485 and ISO 14971

* Published in the Brazilian Official Journal on April, 19th, 2010.

ANVISA
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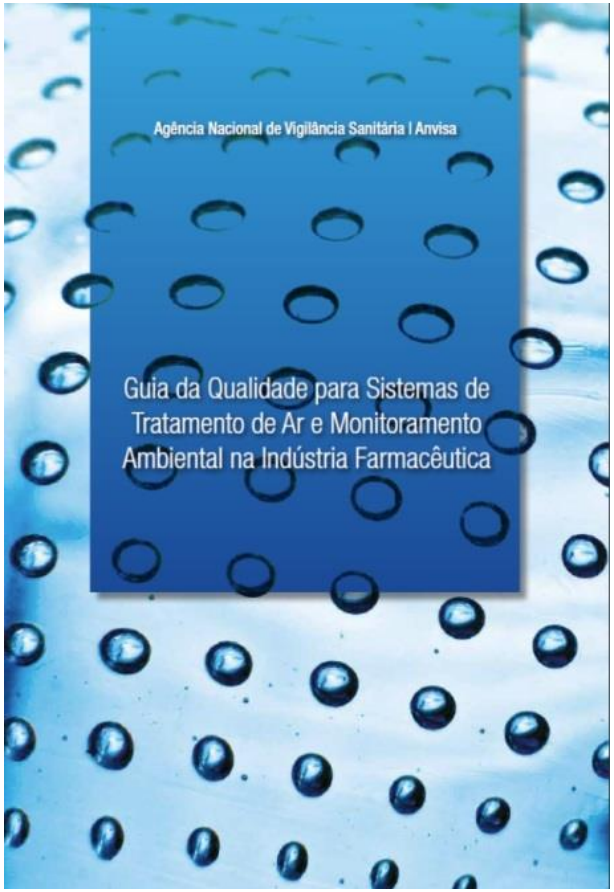
GMP Regulation - API

RDC 249/05: ICH Q7a

* Published in the Brazilian Official Journal on April, 19th, 2010.

Publications



DECENTRALIZATION: NATIONAL SYSTEM OF SANITARY SURVEILLANCE RESPONSABILITIES

Anvisa (high complexity activities) →

- Regulation (ex. GMP guidelines elaboration)
- Coordination of National System of Sanitary Surveillance
- Activities Execution (ex. borders control, counterfeiting products combat, local inspection when requested by States or Municipalities)
- Companies Authorization, Marketing Authorization, GMP certification, etc.

States and Federal District (medium complexity activities) →

- Activities Execution (Ex. GMP inspections)
- Complementary regulation
- Coordination of state activities

Municipalities (basic health services) →

- Activities Execution (Ex. GMP inspections)
- Complementary regulation
- Coordination of local activities
- Companies Licensing

GMP INSPECTION

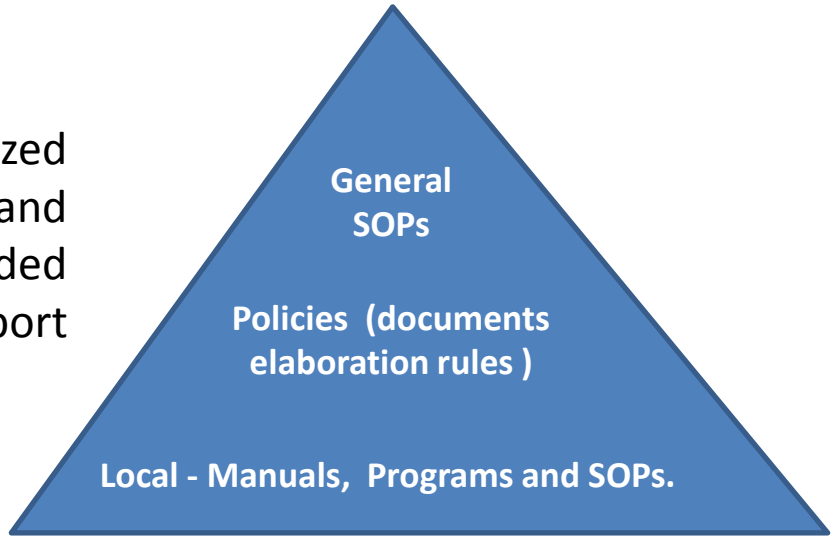
- **BRAZIL**
  Performed by States and Municipalities;
  Sometimes with Anvisa's collaboration

- **MERCOSUR**
  Member joint Inspections;
  Independent Anvisa's Inspection, only if authorized by the state member;
  Exchange of GMP inspection report (not GMP certificate recognition)

- **OUTSITE MERCOSUR**
  Independent Inspection

NATIONAL SYSTEM OF SANITARY SURVEILLANCE: DOCUMENTS AND GMP CERTIFICATION

Documents are harmonized among Anvisa, States and Municipalities. It is included inspections procedures and report contents.



ANVISA is responsible for issuing GMP certification, but States and Municipalities are responsible for the inspection. Thus, Anvisa receives all inspection reports, which are assessed internally. The main objective is to maintain an updated database and identify local needs, such as training.

GMP CERTIFICATE RENEWAL

- GMP certificate is valid for 2 year.
- Before expiration, the renewal has to request to ANVISA.
- Based on a risk assessment, ANVISA decides if another inspection will be necessary. It is take into account:
  - GMP compliance history
  - Time elapsed since the last inspection
  - If there are new products/lines
  - Marketing complaints
  - Annual product review information (for medicines)

GMP CERTIFICATE

- Situations in which the GMP certificate is necessary:
  - Marketing authorization and post-marketing changing requests;
  - Marketing in general.

SANCTIONS

- Are defined by law (6.437/77) some other sanctions in case of serious GMP deviation:
    - Marketing Authorization cancelation;
    - Production Authorization and License revoking
    - Recalls and Products interdiction
    - Warnings and Fees
    - Cancellation of advertising

Thank you!

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