AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

GMP inspections at ATMP manufacturing sites: recurrent deficiencies

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27/09/2018

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	**X**	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	☐	☐	☐	**X** mandatory
1.3 Employment with a company: other activities	☐	☐	☐	**X** optional
2. Consultancy for a company	**X**	☐	☐	☐ optional
3. Strategic advisory role for a company	**X**	☐	☐	☐ optional
4. Financial interests	**X**	☐	☐	☐ optional
5. Ownership of a patent	**X**	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	**X**	☐	☐	☐ optional
7. Investigator	**X**	☐	☐	☐ optional
8. Grant or other funding	**X**	☐	☐	☐ optional
9. Family members interests	**X**	☐	☐	☐ optional

*Simona Russo, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. I am not receiving any compensation

ATMP MANUFACTURERS_*AIFA EXPERIENCE*

The Italian Medicine Agency (AIFA) is responsible for inspecting the manufacturers of active substances and medicines for human use located within its own territory *(plants currently authorized in Italy ~620: API⇨190, Medicinal products⇨275, Medicinal gases ⇨153)*.

19 ATMPs manufacturers are currently authorized in Italy, among which:

13 ⇨ Hospitals/Academia
6 ⇨ SME/Big Pharma

3 ⇨ Commercial manufacturing *
16 ⇨ IMPs manufacturing
5 ⇨ "Hospital exemption"

14 ⇨ Cell therapy products
7 ⇨ Gene therapy products
2 ⇨ Tissue engineered products

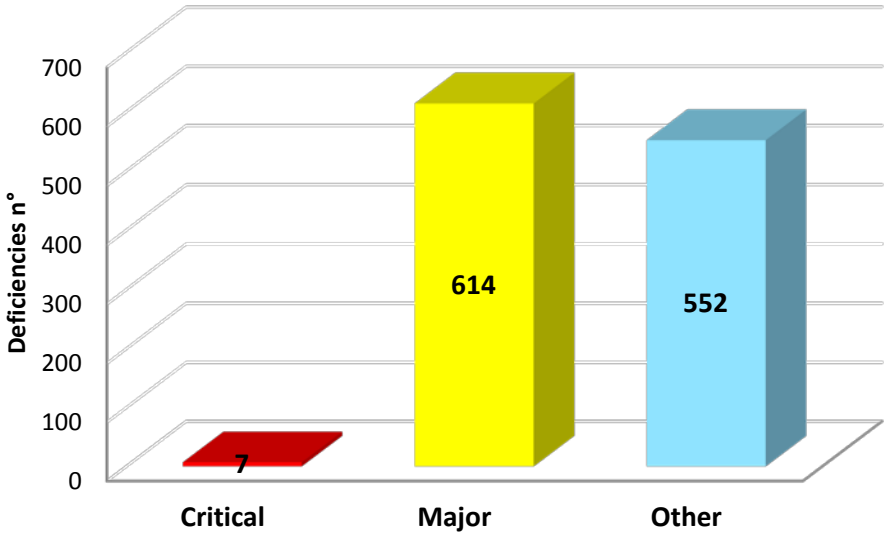
18 ⇨ Starting material➔Finished product
1 ⇨ Bulk API filling only

* *Holoclar, Strimvelis, Zalmoxis*

GMP INSPECTIONS AT ATMPs MANUFACTURING SITES

Overview on GMP inspections carried out at ATMP manufacturing sites in the period 2005-2018 *(August)*:

- Inspected sites: 28 *(uncluding suspended and to be approved plants)*
- GMP inspections performed: 80
- Deficiencies found: 1173
- n° max deficiencies/insp: 41
- n° min deficiencies/insp: 2



(*) *Deficiencies classification in Critical" , "Major" and "Other" is perfomed according to the Compilation of Community Procedures on Inspections and Exchange of Information (EMA/572454/2014 – Rev 17)*

COMPLIANCE OF ATMPs MANUFACTURERS

REGULATORY FRAMEWORK

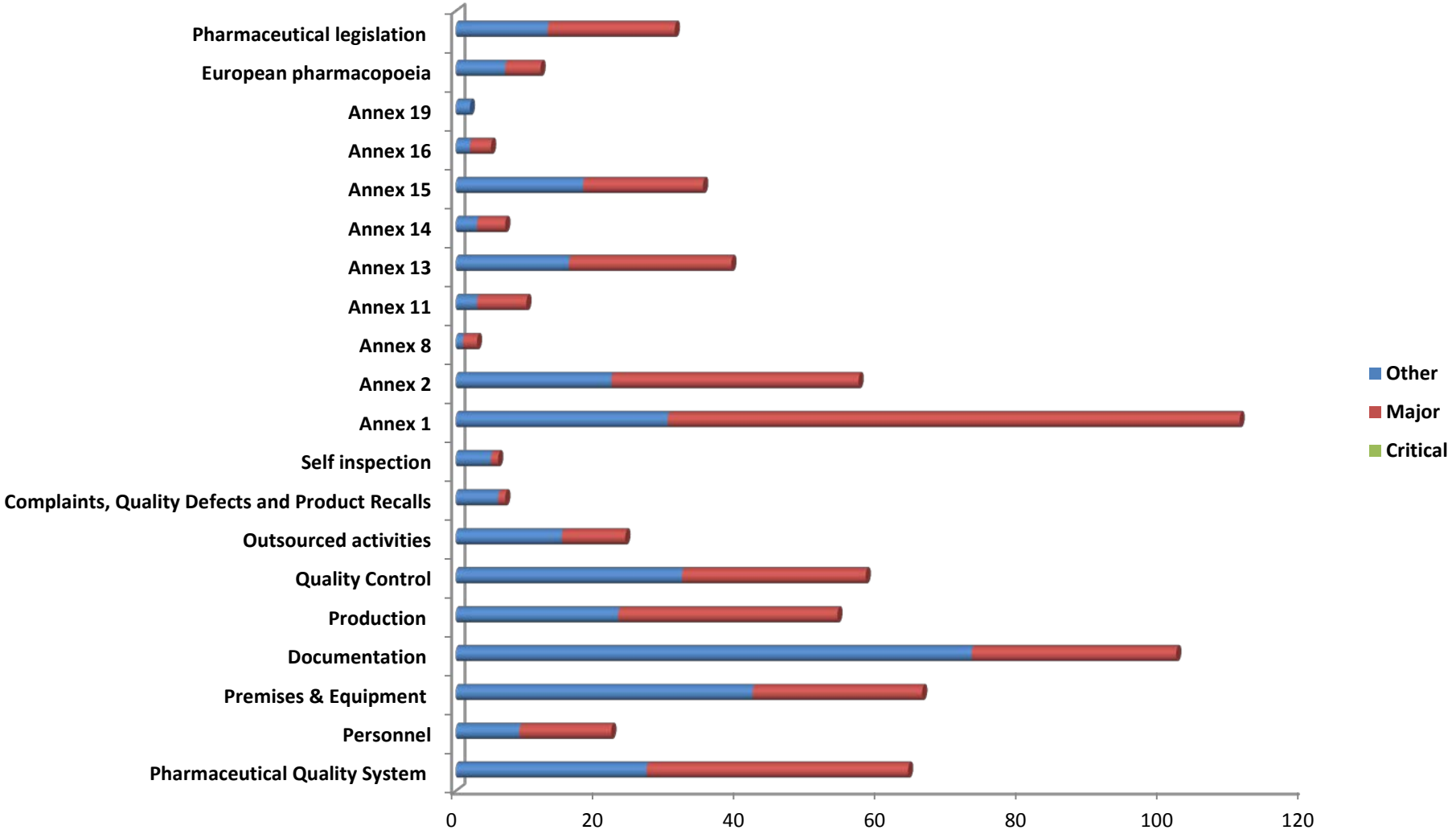
- EudraLex/Vol. 4/Part I+ applicable Annexes - Good Manufacturing Practice (GMP) guidelines *(fully applied until November 21nd, 2017)*
- EudraLex/Vol. 4/Part IV - Guideline on Good Manufacturing Practice for Advanced Therapy Medicinal Products
  (partly applied from November 22nd, 2017; fully applied from May 22nd, 2018)
- Applicable legislation:
  - Regulation (EC) No 1394/2007
  - Directives 2001/83/EC and 2001/20/EC *(as emended)*
  - Directives 2009/120/EC, 2006/17/EC, 2004/23/EC, 2003/94/EC, etc..
- Applicable EP monographs: 2.6.27 "*Microbiological control of cellular products*", 5.2.12 "*Raw materials of biological origin for the production of cell-based and gene therapy medicinal products*", 5.14 "*Gene transfer medicinal products*", *etc.*

(*) *According to national legislation (Italian MoH Decree dated January 16th, 2015)*
GMP apply also to ATMPs prepared on a non-routine basis

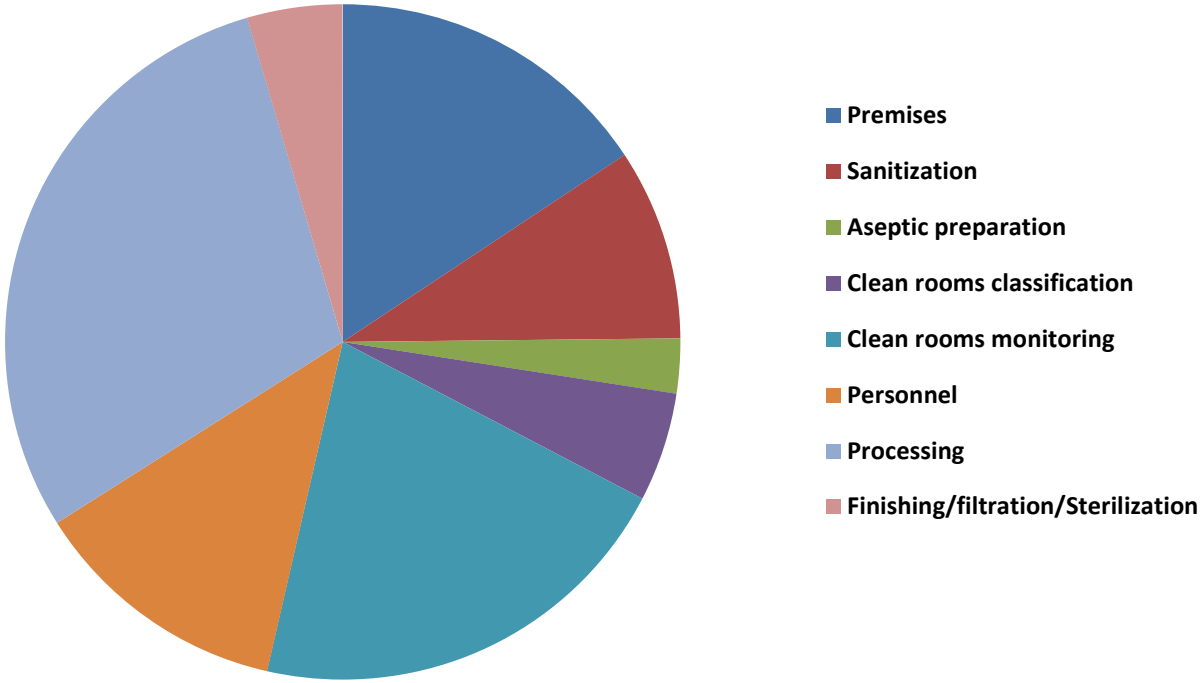
RECURRENT DEFICIENCIES ASSESSEMENT: *ADOPTED METHOD*

- Type of inspection: PERIODIC *(no pre-approval/for cause inspections)*
- Assessed period : 2010 ⇨ 2018 (*August*)
- Sample size *(n° of manufacturing sites)*: 16
- Inspection reports reviewed: 41

DEFICIENCIES DISTRIBUTION (*GMP Part I+Annexes*)



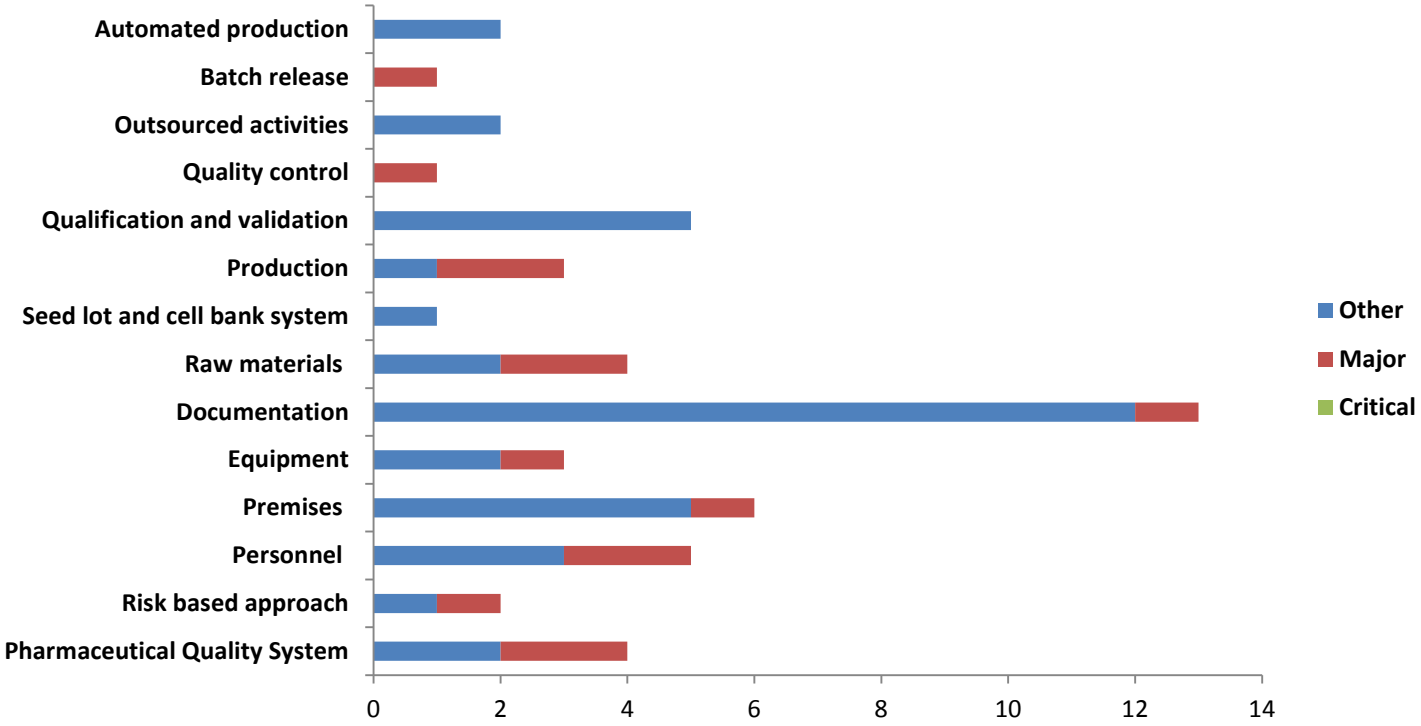
DEFICIENCIES DISTRIBUTION_ Annex 1



(*) Processing issues mainly refer to validation of aseptic process (media-fill) and flow of components/containers/etc...intended to be used in the aseptic area

DEFICIENCIES DISTRIBUTION (*GMP Part IV*)

- Assessed period: *November 22nd, 2017* ⟹ *today*
- Sample size: 6



RECURRENT DEFICIENCIES_ANNEX 1

1) Aseptic process validation (media-fill) resulted not adequate in that:

- Only one process simulation test per shift and process is repeated yearly;
- The process simulation is not representative of the different manufacturing processes performed at the site;
- A detailed media-fill protocol is not available;
- The media-fill protocol does not challenge worst case interventions or the maximum number of operators allowed during aseptic manipulations;
- In the media-fill BR, the operators' access is not registered nor is provided a scheme for particle and microbiological monitoring sampling points.

RECURRENT DEFICIENCIES_ANNEX 1

2) Materials flow in classified areas resulted not adequate in that:

- Apheresis bags are introduced in grade A/B areas without any sanitization step;
- Disposable materials and reagents used in grade A/B areas have only one protective bag or are lacking any protection. They are introduced from the pass-through to the biosafety cabinets by means of disinfection procedures that have not been validated;
- The procedure to introduce the materials in classified areas does not expect a step of sanitizing surfaces with a sporicide;
- At the end of manufacturing operations, partially used packages of sterile disposables, inadequately sealed, can be transferred to the grade C warehouse and reused in grade A areas for subsequent processing activities.

RECURRENT DEFICIENCIES_ANNEX 1

3) Environmental monitoring of clean rooms resulted not adequate in that:

- The sampling points for the environmental monitoring are not representative of either the lay-out or the manufacturing activities;
- Pass-boxes never undergo particle and microbiological monitoring;
- Microbiological monitoring in Grade A/B areas is performed by active air sampling only;
- Alert limits for particle and microbiological monitoring are not established.

RECURRENT DEFICIENCIES_ANNEX 1

4) Clean rooms qualification and management resulted not adequate in that:

- After HVAC system shut-down, Grade B areas are released for manufacturing following extensive cleaning only;
- During clean rooms qualification, the clean-up time of Grade B personnel and materials airlocks has not been defined, therefore the personnel flow in the airlocks is not regulated accordingly;
- Several personnel and materials airlocks have no functional interlocks and the periodic check of interlocks is not included in the preventive maintenance plan;
- In grade B manufacturing rooms there are ceiling tiles damaged or with unsealed gaps, not guaranteeing the cleanliness of the aseptic area;
- In grade B manufacturing rooms there are non-coplanar ceiling lamps, not coplanar electrical outlets and exposed electric wires, not easy to clean;
- In grade B manufacturing rooms there are thermostatic baths filled with unsterilized PW changed on a weekly basis.

RECURRENT DEFICIENCIES_ANNEX 1

5) The periodic qualification/re-qualification of operators enabled to perform aseptic manipulations does not expect media-fill participation or microbiological monitoring of garments.

6) The initial gowning worn in the not classified locker is maintained until the grade B airlock; moreover, not always gloves worn by grade A/B operators undergo microbiological monitoring at the end of critical activities.

7) Clean rooms cleaning/sanitization procedures resulted not adequate in that:

- Cleaning and disinfection procedures are not validated;
- Not suitable tools are used to clean grade B rooms (*e.g. not autoclaved reusable items, vacuum aspirators, etc.*);
- Disinfectants bottles found in the aseptic areas are expired or not sterile.

RECURRENT DEFICIENCIES_ANNEX 2/Chapter 5

1) The risk of plant contamination by infectious agents was not properly under control:

- The starting material (*biopsy*) is manipulated in the manufacturing areas, lacking of a segregated area for infectious materials handling, prior to receive donor serological results;
- Donors serologic screening prior to biopsy entry in the manufacturing plant does not adequately consider anamnestic data related to infectious agents *(e.g. geographical origin, sexual habits, travel, other risk factors)*;
- The operator who carried out the first processing step on potentially infected biopsy can move to other manufacturing rooms without obligation of gloves and garments change;
- Gene therapy products manufactured by using infected and uninfected starting materials can be performed in the same manufacturing area;
- In case of infected material handling, there is no specific cleaning/sanitizing procedures in place.

(*) *More flexible approach for infected materials is foreseen by EU GMP Part IV. Segregated areas not mandatory for infected donors (required for infectious viral vector only).*

RECURRENT DEFICIENCIES_ANNEX 2/Chapter 5

2) The risks of contamination/cross-contamination were not adequately under control in that:

- The same operator can manipulate two different batches under the same hood and during the same shift only after having sanitized the hood shelf and, therefore, in absence of an accurate change over procedure;

  (*e.g. garments/gloves change, removal of exhausted media or other materials used during previous processing, centrifuges sanitization, etc*...)*;*

- Incubators can be used for 3-5 different batches at the same time, in the absence of an effective physical separation.

(*) *More flexible approach is foreseen by EU GMP Part IV _ incubation of distinct cell cultures in closed vessels is considered a suitable separation.*

RECURRENT DEFICIENCIES_ANNEX 2/Chapter 5

3) Most of the raw materials used in the manufacturing process were not pharmaceutical/clinical grade and did not undergo analytical and/or functional testing prior to acceptance.

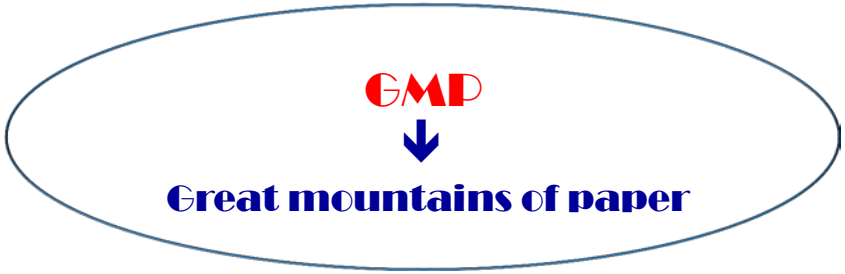
4) The procedures for ensuring traceability were not adequate in that:

- Donor and recipient are not identified by a unique code, but by first and last name/date of birth;
- Donor and recipient are identified by a code that differs by only one letter; such code is transcribed manually several times during the process with risk of error;
- The label of the apheresis bag is not attached to the BR. The data it contains are transcribed manually by the operator, in absence of a double-check from an independent operator, with risk of error;
- It's not available a technical agreement with the hospital pharmacy, provider of the blood products used for ATMP production, regulating the exchange of information to ensure the traceability and look-back procedures foreseen for blood products.

(*) *No longer possible to rely on Annex 14 to support such deficiency*

RECURRENT DEFICIENCIES_Chapter 4

"DOCUMENTATION "



1) Manufacturing and quality control activities recorded in the BR did not fully comply with the activities described in the IMPD approved by the competent authorities.
2) Maintenance and cleaning activities of premises/equipment were not adequately registered in the logbooks.
3) Records of manufacturing and analytical activities were not made or completed at the time each action is taken.
4) Specifications for critical raw and packaging materials were not available.

RECURRENT DEFICIENCIES_Chapter 4
"DOCUMENTATION "

5) The registration of in process controls was carried out with poor accuracy and the reconciliation of different manufacturing steps was not complete and traceable.
6) SOP poorly detailed or unavailable for critical activities.
7) There was no system of documentation review, nor a procedure for reviewing, updating and distributing SOP, templates, work-sheets.
8) It was not available a validation protocol defining objectives and methods and the results of the validation exercise were not properly registered or documented *(Ch. 4/Annex 15*)

RECURRENT DEFICIENCIES_Chapter 1
"*PHARMACEUTICAL QUALITY SYSTEM*"

1) Change control management resulted not adequate because the regulatory impact is not always correctly addressed.
2) Some of the QC testings required for batch certification were carried out at external laboratories not GMP certified.

   (*) *EU GMP Part IV allows such scenario in exceptional circumstances*

3) Qualification of critical materials suppliers was not accurate *(e.g. acceptance specifications not available, QC testing not performed, audit not performed, quality agreement not available, etc.)*;
4) For materials of human or animal origin that are used in the manufacturing process, a risk assessment related to viral safety issues was not available.

Thanks for your attention

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