Major deficiencies 2018

AKTEHOM analysis of US/EU/FR non-compliance issued in 2018

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Analysis Method

An analysis of all the administrative procedures issued in 2018 from the United States (FDA), France (ANSM) & from other Health Authorities within the framework of the EU-GMP non-compliance statement has been conducted by **AKTEHOM**. The details of which are in this presentation.

The purpose of this analysis is to highlight the processes most frequently challenged by these agencies.

The analysis was performed on January 2nd, 2019 following administrative procedures issued from January 1, 2018 to December 31, 2018 :

- FDA Warning letters from the Office of Manufacturing Quality letters (www.fda.gov)
- EU-GMP non compliance statement from drugs manufacturers (http://eudragmdp.ema.europa.eu)
- ANSM Injunctions from all health products excepting Cosmetics and Tattoo products (https://ansm.sante.fr)

A categorization has been performed of every deficiency noted in the inspections and have been grouped together by **AKTEHOM** using the administrative procedures , and are as follows:

- Quality Management System (QMS)
- Production: Non-Conformity
- Data Management
- Process Validation
- Commissioning & Qualification (C&Q)
- Aseptic
- Analytical
- Cleaning Validation

These categories are highlighted as they are the common factor between all the administrative procedures. Therefore, other observations are *not* in the scope of this analysis (specific from a Health Authority).

NB: 483 observations issued by the FDA are published annually at the end of Q1 and are *not* part of this analysis. An update will be done once the data is available.

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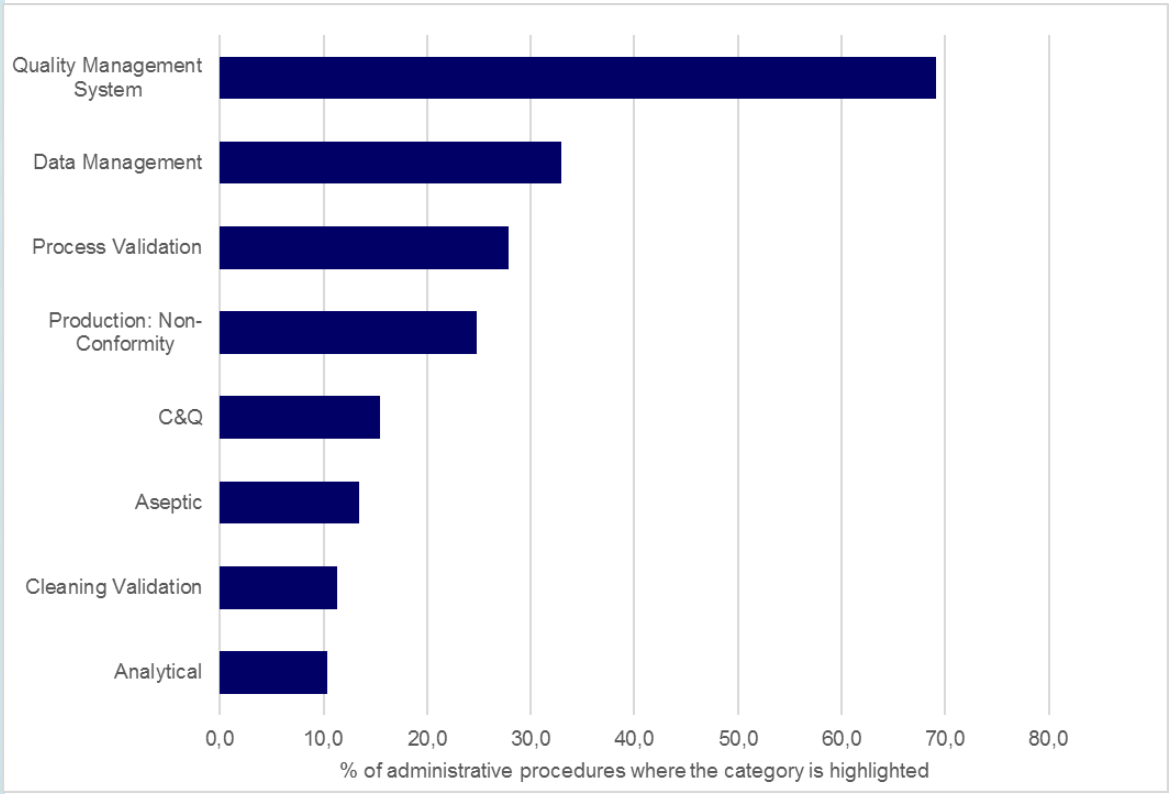
Global analysis 2018

After the analysis of all administrative procedures (98 in total), regardless of the competent Health Authority, the 4 most frequent inspection deficiencies highlighted are:

- Quality Management System
- Data Management
- Process Validation
- Production Non-Conformity

Overview: ANSM Injunctions / EU-GMP non-compliance / FDA Warning Letters



FDA

52 FDA - Warning Letters

ansm

33 ANSM Injunctions

13 EU-GMP NC statements

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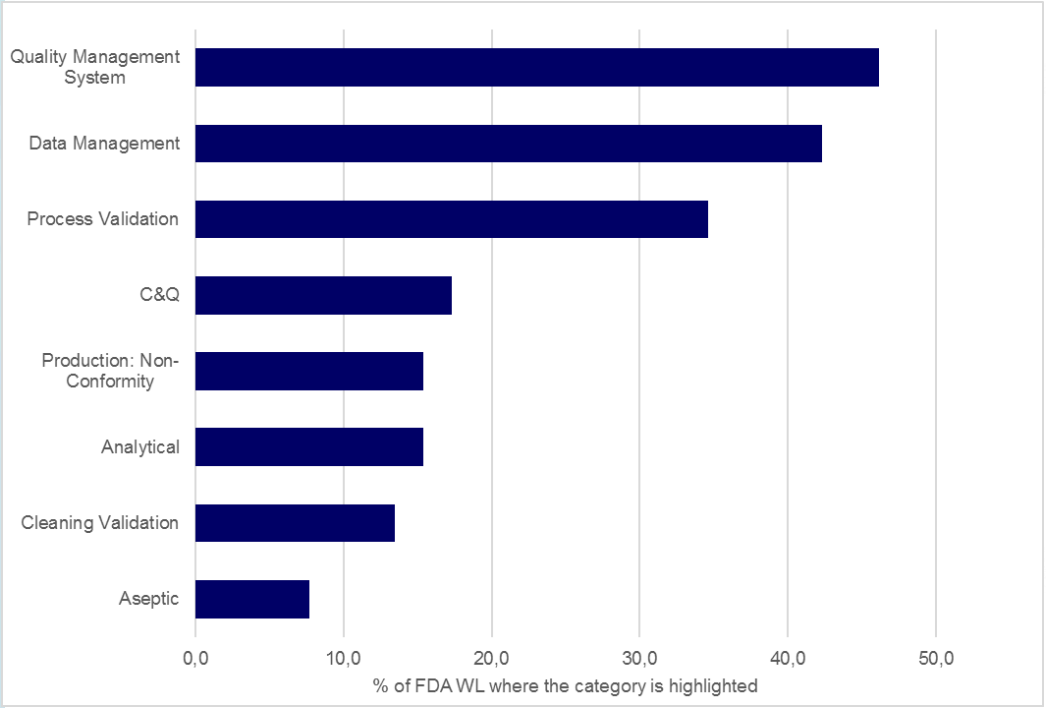
United States analysis 2018

The most frequent inspection deficiencies mentioned in the FDA Warning Letters (WL) are:
- Quality Management System
- Data Management
- Process Validation

Data management is mentioned more frequently WL, as compared to the other Health Authorities.
As shown on the map, the FDA inspects manufacturing sites around the world and more than 75% of WL issued relate to sites located in Asia.

FDA Warning Letters



source: fda.gov

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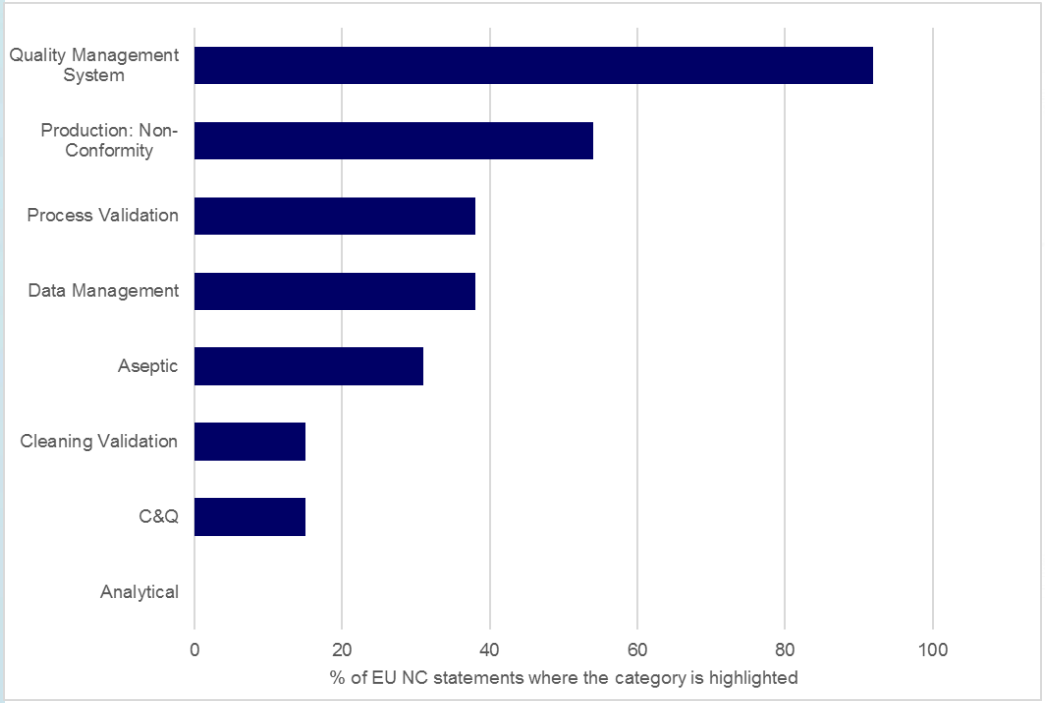
European analysis 2018

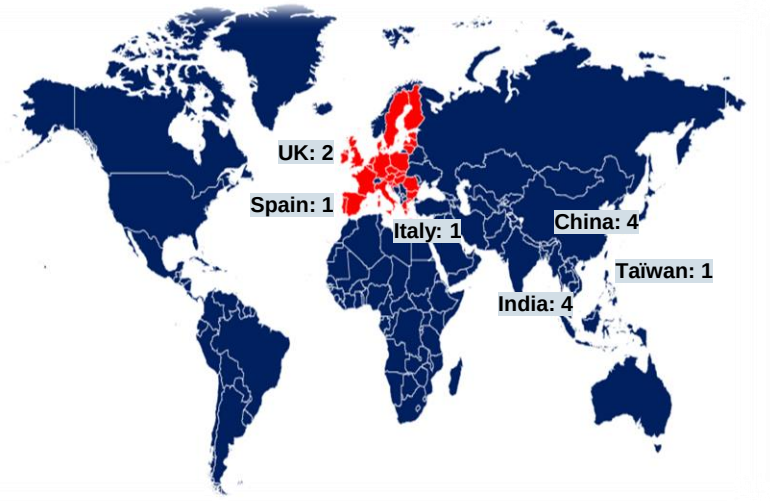
EU-GMP Non-Compliance Statements are delivered by Health Authorities from every EU country.

The Quality Management System deficiencies are highlighted in all (except 1) EU-GMP Non-Compliance Statements. Which is then followed by: Production Non-Conformity, Process Validation, Data Management and Aseptic. These are the most frequent inspection deficiencies highlighted in this administrative procedure.
As shown on the map, EU-GMP Non-Compliance Statements issued concerns only European and Asian countries.

EU-GMP Non-Compliance Statements



source: eudragmdp.ema.europa.eu



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France analysis 2018

The Quality Management System is the most frequent category mentioned into ANSM Injunctions (more than 70% of Injunctions). This category can be separated into 2 groups:

- QMS : Deviations/CAPA/Change Control ➔ 27%
- QMS : Others (Third-Party Management, Quality Policy,…) ➔ 46%

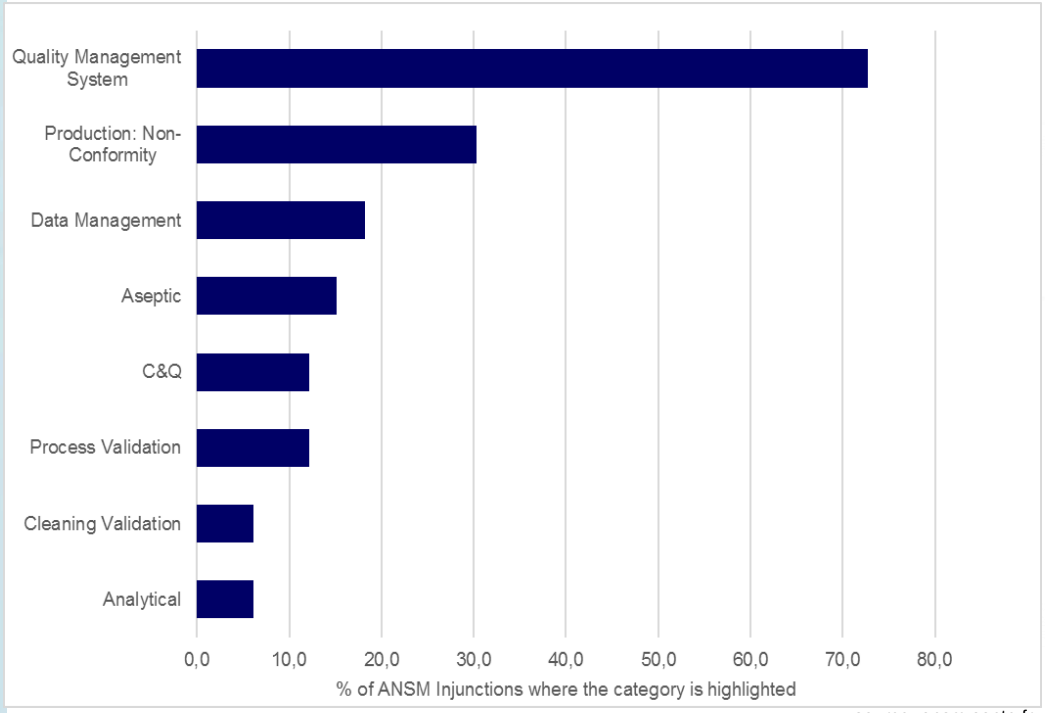
The QMS is followed by: Production Non-Conformity, Data Management and Aseptic. These are the most frequent observations highlighted in this administrative procedures.

Injunctions issued by ANSM concerns only manufacturing site based in France.

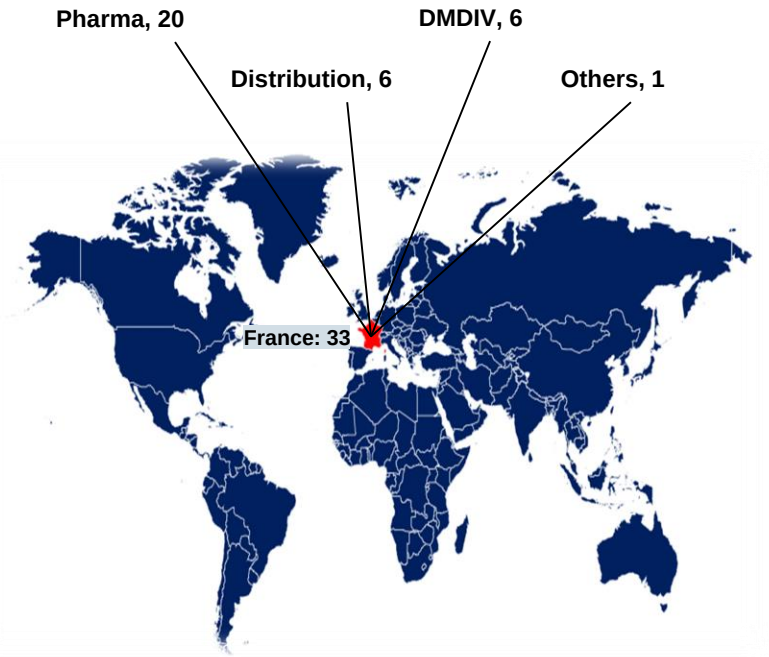
Currently on 36 different sites there are on-going open injunction proceedings that cover Pharma, DMDIV, Distribution & others.

5 of which are on-going since 2017 and a further 31 injunctions procedures since 2018.

ANSM Injunctions



source: ansm.sante.fr



To remember

The most frequent categories that are the subject of administrative procedures in 2018, in order of importance are:

- Quality Management System
- Data Management and Production Non-Conformity
- Process Validation

Within the QMS category, Deviations, CAPA and Change Control processes are highlighted in approximately 23% of all administrative procedures, even though these processes have been in place for a long time.

Asia is the area where Europe and US Health Authorities highlight the most non-compliance with regulations. Unlike the injunctions issued by the ANSM which only affect one European country, the FDA's WLs have a worldwide scope.