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Quality control in drug distribution in Belgium

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Marketing authorization (A.M.M.)

- **MEDICINES**
  - Medicines cannot be sold without prior registration
    - 4 kinds of registration
      - Centralized European registration: the drug is allowed to be put on the market in all the 28 countries of European Union (European Medicines Agency – EMA)
      - Decentralized European registration: the drug is allowed to be put on the market in some countries of European Union
      - Mutual recognition registration: a drug which is already put on the market in some countries can also be put on the market in some other European countries
      - National registration: valuable in only one European country
    - Registration is materialized by a number, which must be mentioned on the packaging of the drug
  - Tamper evident seal on drugs that are subject to counterfeiting

Notification and CE marking

- **FOODS SUPPLEMENTS**
  - Must be *notified* to the authorities
  - No « authorization », but possibility of withdrawal if considered as« harmful »
  - Receive a « notification number » which
    - must not be mentioned on their packaging but
    - Can be found on a specific website
- **MEDICAL DEVICES**
  - Approved by an independant « notified body »
  - « CE » marking + identification of the manufacturer

Authorizations for manufacture or distribution of drugs

- **Each manufacturer of drug must hold a specific authorization (« manufacturing authorization »)**
  - **Each operation resulting in a transformation of a drug is considered as « manufacture »: including packaging, labeling etc.**
  - **Inspections by Belgian health authorities on a regular basis, when established in Belgium, verifying the respect of Good Manufacturing Practices (GMP)**
  - **Recognition of inspections made in other european countries, because based on the same international requirements**
  - **Pharmaceutical Inspection Convention (PIC): recognition of inspections made by authorities in a lot of non-european countries (but not Vietnam)**

The wholesaler and « wholesaler distributor »

- **Wholesaler distributes in Belgium (or in Europe) *selected* drugs he doesn’t manufacture himself.**
- **Wholesaler distributor (« grossiste –répartiteur ») sells pharmacists all drugs they need (« middlemen » between manufacturers or wholesalers and pharmacists)**
- **Each wholesaler and « wholesaler distributor » must have a specific authorization (« distribution authorization » or « public service authorization ») and is inspected on a regular basis**

The « drug chain »

- Each authorization holder (manufacturer, distributor, wholesaler etc.)
  - can only buy medicines from other authorization holders
  - can only sell medicines to other authorization holders or pharmacies
- Pharmacists (including hospital pharmacists) can only buy medicines from authorization holders
- Each party is responsible for verifying suitability and competence of each other
- Pharmacists can only sell medicines to patients (not to other pharmacists or third parties)
- Consequently, the « drug chain » is locked up from the beginning to the end, what prevent falsifications

Obligations of the « wholesaler distributor »

- Adequate and sufficient supply of drugs (min. 2/3 of all drugs on the market)
- Purchase of medicines only from authorized manufacturers or wholesalers
- Sale of medicines only to hospital or primary care pharmacies
- Respect of delivery time (max. 24 hours, usually 3-4 hours)
- Sufficient personal and means of transportation
- Respect of Good Distribution Practices
- Week-end duties for pharmacists on duty

Good distribution practices (GDP)

- Source: European guideline of 2013
- Applies to all distributors and wholesalers of medicines
- Aim
  - To maintain the quality of each medicine from the manufacturer to the pharmacy (including)
  - To prevent falsified medicines to enter the legal supply chain

Good distribution practices (requirements)

- Management of quality
  - Set up of a quality system in order to meet the aim
  - This quality system has to
    - Ensure the respect of the GDP
    - Identify the respective responsibilities
    - Ensure that products are delivered to the right recipients
    - Document, investigate and correct deviations from established procedures

Good distribution practices (cont.)

- Personnel
  - Responsible (or qualified) person
    - Industry pharmacists at manufacturers and distributors
    - « common » pharmacist at the wholesaler-distributors
  - Other personnel in adequate number, competent and trained (initial and continuing training)
  - Health, hygiene and clothing procedures

Good distribution practices (cont.)

- Premises and equipment
  - Medicinal products stored in segregated and clearly marked areas
  - Narcotics stored separate in a key-locked room
  - Clear separation of the receipt, storage and dispatch areas
  - Premises appropriately cleaned, and protected against intrusion of insects, rodents etc.
  - No food, drink, smoking material or medicinal products for personal
  - Temperature and environment controls
  - Securing of the computerized systems
  - Qualification and validation of the equipment

Good distribution practices (cont.)

- Documentation
  - all written procedures, instructions, contracts, records and data, in paper or in electronic form, have to be documented, approved, dated and signed by the responsible person
  - Tracability of any transaction in medicinal products received, supplied or brokered with
    - quantity received or supplied
    - name and address of the supplier or customer,
    - batch number at least for medicinal product bearing the safety features

Good distribution practices (cont.)

- Operations
  - Qualification of suppliers and customers (see « drug chain »)
  - Investigation of any irregularity in the sales patterns of narcotics, psychotropic substances or other dangerous substances – report to competent authorities
  - Storage
    - In appropriate conditions (temperature, humidity, light etc.)
    - “first expiry, first out”
    - Elimination of the nearly expired medicines, with separate holding and destruction as soon as possible (documented)
    - Prevent mistakes and mix-ups during picking

Good distribution practices (cont.)

- Complaints (of customers)
  - Must be recorded, investigated with appropriate follow-up actions if necessary
- Returned medicinal products (from the pharmacies)
  - Can only be put back in saleable stock if
    - in their unopened and undamaged secondary packaging; in good condition; not expired
    - returned within an acceptable time limit, for example 10 days
    - transported, stored and handled in compliance with their specific storage requirements (especially products requiring specific temperature storage conditions such as low temperature)
    - examined and assessed by a trained and competent person
    - no reason to believe that the product has been falsified

Good distribution practices (end)

- Falsification
  - Wholesale distributors must immediately inform the competent authority and the marketing authorisation holder of any medicinal products they identify as falsified or suspect to be falsified
- Self-inspections are mandatory and have to be documented
- Transportation
  - Must ensure protection of medicinal products against breakage, adulteration and theft
  - Required storage conditions for medicinal products should be maintained during transportation within the defined limits – validation and controls are necessary
  - Deliveries should be made to the address stated on the delivery note, and not somewhere else (i.e. during the closing hours of the pharmacy)
  - Containers must be validated and correctly labeled

Practically for the pharmacist…

- Each pharmacist has 2-3 different wholesalers-distributors
- Each sale of medicine or other product is recorded in the computer, which manages the stock
- When the minimal stock fixed by the pharmacist for a product is reached, the computer suggests recommending the product, in quantity fixed in advance
- The pharmacist orders the drugs and health products he needs from one of his wholesalers
- Daily 3-5 orders (except week-end)
- He receives his order within 2-4 hours (legal maximum 24 hours)
- Returns of drugs from pharmacy to wholesaler are (very) difficult

Traceability of drugs

- Batch number (in coded form) on each drug packaging + expiration date (in clear form)
- CNK (« National Code Number ») = barcode (7 digits)
  - Different for each product (drug, health product, cosmetic, medical device)
  - Avoid mistakes while ordering the product (by scanning the barcode)
- CBU (« Unic barcode »): 16 digits (= CNK + 9 digits)
  - Different for each packaging of drug
  - Scanned at the time of dispensing
  - Allows traceability to the patient
  - Prevents treachery (drugs non dispensed although paid to the pharmacist by social security)
- Safety feature: concerns only several medicines exposed to be falsified
- Compounded drugs are also traceable within the pharmacies, to the patient.

Cold chain

- Manufacturer, distributor and wholesaler: according to GDP, have to
  - store drugs « in appropriate conditions »
  - « in the fridge » = between 2 and 8°C
  - Fridges must be qualified, validated and continuously controlled
- Transport: see GDP above
  - It must be validated and controlled that, during transportation (cars, pickups), temperature in the packaging of the drug doesn't rise above 8°C
  - Use of cool bags is widespread
- Pharmacist
  - Moves the drugs to the fridge upon receipt
  - Has to
    - Validate his fridge (coldest and warmest places)
    - control its internal temperature at least once daily
- After the pharmacist (patient): ??

Internet sales of drugs

- Pharmacy which intend to sale drugs by internet must be notified to the health authorites
- Website strongly regulated
- European safety logo on each page of the website
- Only OTC drugs
- If sale outside of Belgium, only OTC drugs registered in the destination country
- For transportation, the pharmacist has to collaborate with reliable courier companies (responsability for ensuring the quality of the drug during transportation).

« Drug control laboratory » of the pharmacists

- The drug control laboratory (« service de contrôle des médicaments » or SCM) is part of the Belgian Association of Pharmacists (APB)
- Controls on a regular time basis all the drugs authorized on the Belgian market
- Financed by the all the primary care pharmacies: a little part (about 1,5 eurocent) of the sale price of each sold packaging of drug is automatically reassigned to the SCM
- Alerts each pharmacist in case of detected defect
- Collaborates with Health Authorities and pharmaceutical companies to alert pharmacists in case of defects detected by others
- Organizes the recall of the defective medicines from the pharmacies and their return to the companies
- Is organizing a system of regular control of the compounding drugs

Other controls

- Belgian « Federal Agency for Drugs and Health Products »
  - Controls on a regular basis all the distribution chain
    - Directly for authorization holders established in Belgium
    - Recognition of inspections made in the countries being part of the Pharmaceutical Inspection Convention (PIC)
    - Possible joined inspections with local authorities for drugs manufactured outside Belgium (PIC members)
    - Control of all primary care pharmacies
  - Schedules an annual check of all specialized drugs containing some active ingredients
  - Collects randomly other specialities or compounded drugs
  - Makes analyze these samples by approved laboratories
- Belgian « Federal Agency for the Security of the Food Chain »
  - Id. for food supplements, baby milks…

Withdrawal of drugs

- Drugs are withdrawn from market
  - When expired
    - Before selling: destruction by an approved body
    - Returned by patients to the pharmacy: wasting and destruction organized by the Walloon (Belgian) authorities
  - When defective of falsified:
    - R.A.S system in collaboration with European Medicine Agency (EMA) , European national authorities and Non-european authorities
    - Pharmacists are warned by the Federal Agency of Drugs and Healthproducts through professional associations of pharmacists
    - Recall and destruction organized by authorization holders through professional associations of pharmacists