Quality control in drug distribution in Belgium

Prof. Patrick Herné
University of Liège
Belgium
**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
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).
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