ZSMU Pharmacology Department

Lecture N1:

SYSTEM OF PHARMACOVIGILANCE IN UKRAINE. CONCEPT OF SIDE EFFECTS OF DRUGS

WHO's Requirements for Drugs:

- Effectiveness
- Safety
- Availability for Patients

Task of Pharmacotherapy

- ✔ Reducing Mortality
- ✔ Improving the Quality of Life

Mortality from Side Effects (SEs) of Drugs (excluding Medical Errors and Misusages) takes the **5 place after**:

- Cardiovascular diseases
- Cancer
- Respiratory organs diseases
- Traumas

SEs as the reason for hospitalization: 4.2 – 6%

Frequency of SEs in hospitalized patients: 5-35%

CAUSES of FATAL COMPLICATIONs

Gastrointestinal Bleedings:

NSAIDs, Anticoagulants, Glucocorticoids, et al.

Bleedings from other organs:

Cytostatics, *Anticoagulants*

Aplastic anemia: *Phenylbutazone* (*Butadion*), C*ytostatics*

Chloramphenicol - *Levomicetin*, *Gold* preparations

Acute and Chronic Liver Damage:

Chlorpromazine (*Aminazine*), *Isoniazid*, *Tetracyclines*

Kidney Damage:

NSAIDs, *Aminoglycosides*: *Gentamicin*, *Neomycin* et al.

Decrease in Resistance to Infections:

Cytostatics, Corticosteroids

Allergic reaction: Penicillins, Local Anesthetics, et al.

Drugs known for their side effects

Drug	Date	Side effect	Outcome
Streptocid	1937	Liver Damage	Solvent was changed
Thalidomide	1961	Phocomelia	Forbidden
Levomicetin	1966	Blood Dyscrasia	Restricted Use
Klioquinol	1975	Myopathic Neuropathy	Forbidden
Benoxaprophen	1982	Liver Damage	Forbidden
Indoprophen	1984	GI bleedings, perforations	Forbidden
Osmozine	1984	GI bleedings, perforations	Forbidden
Butadion	1984	Blood Dyscrasia	Restricted Use
Aspirin	1986	Raynaud's Syndrome (Children)	Restricted Use
Spironolactone	1988	Carcinoma in Animals	Restricted Use
Methipranone	1990	Anterior Uveitis	Forbidden
Terolidine	1991	Cardiac Arrhythmias	Forbidden

Pharmacovigilance (from *pharmakon* - Greek for *drug* and *vigilare* - Latin for *to keep watch*), also known as **Drug Safety**, is the pharmacological science relating to the *collection*, *detection*, *assessment*, *monitoring*, and *prevention* of adverse effects with pharmaceutical products.
It heavily focuses on **Adverse Drug Reactions** (ADRs).

By **12.07.2010 г**. Pharmacovigilance Department of Ukraine had registered **14,478** cases of **Side Effects** of **medicines**, including
1,777 cases of **Serious SEs**:
12% - Serious Expected ADRs
0.04% - Serious Unexpected ADRs
37 cases of Death due to **ADRs** during medicine administration

Legislative Bases of Pharmacovigilance System Functioning in Ukraine

1996 – Subdivision of the **Pharmacological Committee** of MH of Ukraine – **the Centre of Side Effects of Drugs**

1999 – Department of Pharmacological Supervision of the **State Pharmacological Centre** of MH of Ukraine (legal successor of the Pharmacological Committee)

The Law of Ukraine «About Medicinal Agents»(1996)

«The Order of the State Registration of Medicinal Agents», approved by the Resolution of Cabinet Council of Ukraine from 13.09.2000. №1422

Orders of MH of Ukraine :

«Instruction about Supervision over Adverse Reactions/Effects of Medicinal Agents»,approved by the order of MH of Ukraine from 19.12.2000 №347

«About the organization of reporting about Side Effects of Drugs» from 8.02.01. №51

«About Refinement of Organization of Reporting about Adverse Reactions of Drugs» from 16.07.01. №51

Acting System of Pharmacovigilance in Ukraine

Order of MH № 898 from 27.12.2006

Ministry of Health of Ukraine

State Expert Center

After Registration Pharmacovigilance Administration

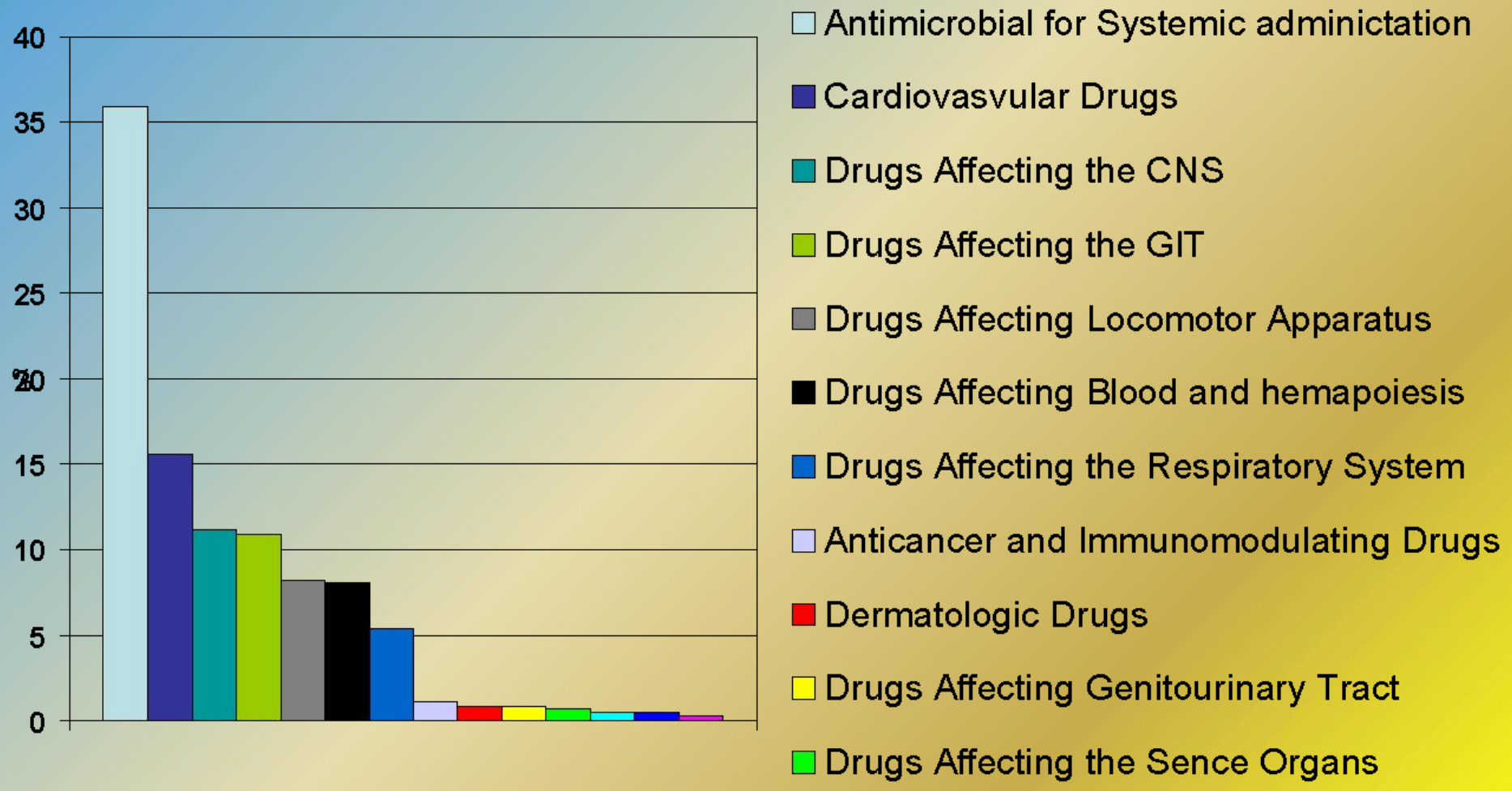
Regional Departments of After Registration Pharmacovigilance Administration

Spontaneous reports method

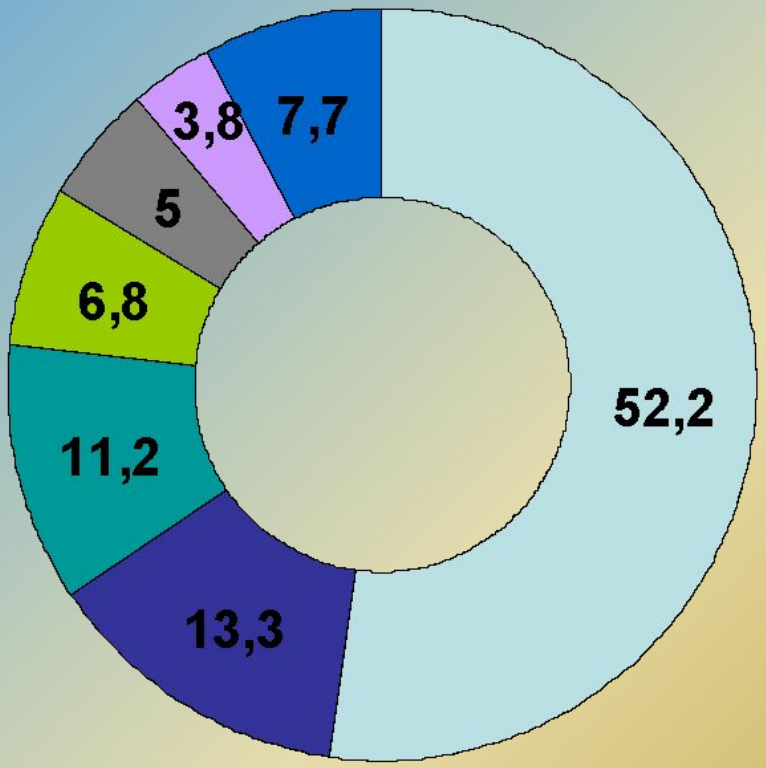
Examples of Approaches to Realization of Regulation of Turnover of Medicines in Different Countries of the World

Countries	Pharmacovigilance	Quality control
EC (European Commission)	European Medical Agency EMEA – Committee Health Medical Products CHMP –Pharmacovigilance working group PhVWP	European Directorate for the Quality of Medicines and Health Care EDQM
Sweden (MPA)	Evaluation and Regulatory Administration – Pharmacovidilance department	Supervision and Scientific Information – Drug Inspectorate
Great Britain (MHRA)	Vigilance and Risk Management of Medicines Division	Inspection, Enforcement and Standards Division
Germany (BfArM)	Pharmacovigilance Division	Strategy and Planning – Process Organization and Quality Assurance
Denmark (DMA)	Consumer safety Division	Medicine Control Division
Ukraine (MH)	State Expert Centre – After Registration Pharmacovigilance Administration	State service for medicines of MH of Ukraine

Pharmacotherapeutic Groups Inducing ADRs (2010)



Systemic Manifestations of ADRs (2010)



- Allergic Reactions
- GIT disturbances
- CNS disturbances
- Cardiovascular disturbances
- General Irregularities
- Respiration Disturbances
- Other Disturbances

Adverse Drug Reactions (ADRs) **are** defined as any response to a drug which is ***noxious*** and ***unintended***, including lack of efficacy.

ADR is a **side effect** occurring with a drug where a **positive** (*direct*) **causal relationship** between the **event** and the **drug** is **thought**, or has been **proven**, to **exist**.

The condition that this definition only applies with the doses **normally used** for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological disorder function **was excluded** with the latest amendment of the applicable legislation.

Adverse Event (AE) is a **side effect** occurring with a drug. By definition, the causal relationship between the **AE** and the drug is **unknown**.

Adverse Event Reporting involves the **receipt**, **triage**, **data entering**, **assessment**, **distribution**, **reporting**, and **archiving** of AE data and documentation.

ADVERSE DRUGS REACTIONS include:

1. Side Effects - are produced with therapeutical dose of the drug They may prove useful under some circumstances.
2. Untoward effects - develop with therapeutical dose of the drug, but are undesirable and, if severe, necessitate the cessation of treatment.

Tetracycline => Resistant Staphylococcal Diarrhea

Loop and thiazide diuretics => K^+ loss

Potassium sparing diuretics => ⇧ K^+

3. Toxic effects: are seen when a drug is administered repeatedly and /or in large doses. Drug toxicity is the primary attribute of a drug and is dose dependent,

Morphine => Depression of respiration

Streptomycin => Deafness, Renal failure, Paralyses.

4. Allergic effects: are linked to immunological reactions.
5. Idiosyncratic effects: are qualitative intolerance due to other than immune mechanisms.

Classification of ADRs (*according to the WHO*)

A. Dose-related **- 75%-** Augmented or Attenuated – Quantitative ADRs - may develop during administration of a drug at therapeutical doses: *Common, Predictable, Expected,* with *Low Mortality* and **related to a Pharmacological Action of the drug.**

1) a Hyper-Response: to the Main Action of a Drug:

Insulin ⇨ Hypoglycemia

2) Pharmacological **ADRs:** depends on **properties** of the drug:

β-adrenoblockers **=>** Bronchospasm

M-cholinoblockers **=>** ⇧ Intraocular Pressure

3) Toxic ADRs – typical for drugs with **narrow breadth** of **action**:

Aminoglycoside**,** Cardiac Glycosides**,** Cytostatics

4) Secondary ADRs - consequences of a drug action

Antibiotics **=> inhibit** Normal Microflora

Glucocorticoids **=>** secondary [consecutive] infection

B. Non-dose-related – 25%- - Bizarre - qualitative ADRs.

Uncommon, Unpredictable, Unexpected with High Mortality and **not related** to a **Pharmacological Action** of the **Drug**

The **mechanism** may be **known** (either **genetic** or **immunological**) but may often be **unknown**.

They include:

1) Idiosyncrasy (*non-immunological*) - qualitative intolerance of a drug due to other than immune mechanism

The mechanism may be known: genetically determined absence or reduced activity of some enzymes:

Primaquine, **Salicylates** and **Sulfonamides** => haemolysis in persons whose erythrocytes lack the enzyme glucose-6-phosphate dehydrogenase.

The mechanism may be unknown: Chloramphenicol => *Anaemia*

2) Allergy (*immunological*): e.g., *Penicillin* hypersensitivity (Types I - IV)

3) Pseudoallergy: e.g., *Ampicillin* rash

Classification of ADRs (*according to the WHO*)

C. Dose-related and time-related - Chronic : *Uncommon,*

Related to the the *Cumulative Dose*:

Corticosteroids => Hypothalamic-pituitary-adrenal axis suppression

Management: Reduce dose or Withhold

D. Time-related – Delayed: *Uncommon, Usually Dose-related,*

Occur some time after the use of the drug:

1) Carcinogenesis:

Diethylstilbestrol => Vaginal Adenocarcinoma, Uterus Cancer

2) Teratogenesis (birth defects): drugs such as Alcohol, some illegal drugs like Cocaine, and some prescription and over-the-counter medications including ACE inhibitors, Angiotensin II antagonists, Lithium, Male Hormones, Thalidomide, Isotretinoin, Vitamin A, Warfarin, some antibiotics (Aminoglycosides, Tetracyclines) anticancer drugs, antiepileptic drugs (Difenin, Valproic acid, Carbamazepine) are known to cause birth defects if taken during pregnancy.

3) Tardive dyskinesia – after administration of typical neuroleptics.

E. Withdrawal - End of use: *Uncommon, occurs soon after withdrawal of the drug* :

Withdrawal Abstinence Syndrome –

typical for drugs producing dependence:

Opiate withdrawal syndrome

Withdrawal Rebound Syndrome:

β-blocker withdrawal => Myocardial ischaemia

Management: Reintroduce and withdraw slowly

F. Unexpected failure of therapy – Failure of therapy:

Common, Dose-related, often caused by drug interactions :

inadequate dosage of an oral contraceptive,

particularly when used with Specific Enzyme Inducers

Management: Increase dosage,

Consider effects of concomitant therapy

Complications of Drug Therapy

1. Disturbances of Functions of Organs and Systems:
Neurotoxic, Hepatotoxic, Nephrotoxic, Hematotoxic, Ulcerogenic Effects.
2. Depression of Immunoprotective Properties:
Immunosuppressive Effect.
3. Effect on Foetus:

Embryotoxic (3 weeks of gestation) - manifests by failure of pregnancy. It may be produced by:
Hormones (oestrogens, progestins, somatotropic hormone, deoxycorticosterone acetate),
Antimetabolites (e.g., mercaptopurine) *et al.*

Teratogenic (4-10 weeks - *organogenesis* period). It is the most vulnerable period, and deformities may be produced.

Fetotoxic (period of growth and development) – developmental and functional abnormalities:
ACEIs => hypoplasia of organs, esp. lungs and kidneys.

Types of **Hypersensitivity Reactions:**

A. Humoral type:

Type I - Anaphylactic reactions – Immediate **IgE** mediated:
urticaria, itching, subepidermal necrolysis – Lyell's syndrome, angioedema, asthma, rhinitis, anaphylactic shock.

Type II - Cytolytic reactions are mediated by **IgG** or **IgM**:
blood transfusion reactions, haemolytic disease of newborns, autoimmune haemolytic anaemia, thrombocytopenia, agranulocytosis, aplastic anaemia, systemic lupus erythematosus, haemolysis

Type III - Retarded reactions are mediated by circulating antibodies (predominantly mopping antibody, IgG):

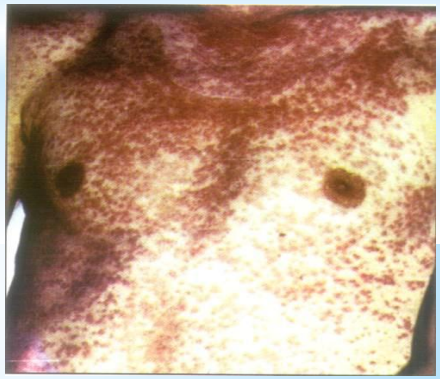
Serum sickness - symptoms develop within 7-10 days and include urticaria, lymphadenopathy, myalgia, arthralgia, fever, polyarthritis nodosa, *Stevens-Johnson syndrome*

Systemic lupus erythematosus is an autoimmune disorder that may be induced by *hydralazine*, *novocainamide, isoniazid* and other drugs.

B. Cell mediated

Type IV - Delayed hypersensitivity reactions:

several hours or days after exposure to the antigen- are cell-mediated through production of sensitized **T-lymphocytes** carrying receptors for the antigen. On contact with antigen these T cells produce *limphokines* which attract granulocytes and generate an inflammatory response, e.g., contact **dermatitis, some rashes, fever, photosensitization**.



Causality assessment of suspected ADRs

1. Certain ADRs - a clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals:

Tetracyclines and other wide spectrum antibiotics =>
=> **candidiasis** and other mycosis

2. Probable / Likely ADRs – a clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal:

Glucocorticoids after long-term administration =>
=>**hypertension**

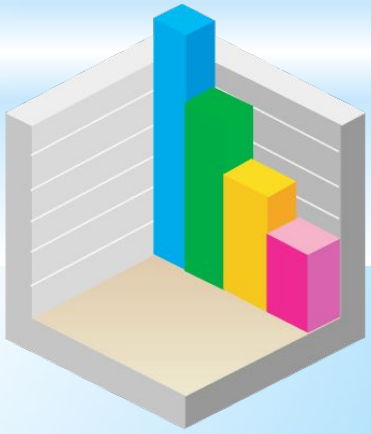
3. Possible ADRs – a clinical event, including a *laboratory test abnormality*, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.

Penicilins, Local anaesthetics – allergic reactions

4. Unlikely ADRs – a clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

5. Conditional / Unclassified - a clinical event, including a *laboratory test abnormality*, reported as an AR, about which more data are essential for a **proper assessment** or the additional data are being examined.

6. Unassessable / Unclassifiable – a report suggesting an AR that cannot be judged, because information is **insufficient** or **contradictory** and cannot be supplemented or verified.



Seriousness Determination

An adverse event is considered serious if it meets one or more of the following criteria:

- results in death, or is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- results in a congenital anomaly (birth defect); or is otherwise

"medically significant" - i.e., that it does not meet preceding criteria, but is considered serious because treatment / intervention would be required to prevent one of the preceding criteria.

From deadly cancer to fatal heart attacks,

some prescription drugs have been known to cause either slow or immediate death

Moderate ADRs

- Hormonal contraceptives: Venous Thrombosis
- NSAIDs: Hypertension and Edema

Common Serious Side Effects - any SE, which does not meet the criteria, defined as serious SE:

GI issues, including nausea, constipation and diarrhea; drowsiness, dizziness, pain and skin reactions.

Testosterone propionate => Seborrhea with akne-like skin rash after cancellation of the drug without consequences.

Counterfeit Medicines

The WHO estimates that **10%** of the **global market** is **counterfeit** and gives the **following definition**:
"A **Counterfeit Medicine** is one which is **deliberately** and **fraudulently mislabelled** with **respect** to **identity** and/or **source**. **Counterfeiting** can apply to both **branded** and **generic** products and **counterfeit products may include products** with the **Correct Ingredients** or with **the Wrong Ingredients**, **without Active Ingredients**, **with Insufficient Active Ingredient** or sold with a **False Brand Name**."

Otherwise, legitimate drugs that have passed their **date of expiry** are sometimes **remarked** with **false dates**. Low-quality counterfeit medication may cause any of several dangerous health consequences, including side effects or allergic reactions, in addition to their obvious lack of efficacy due to having less or none of their active ingredients.

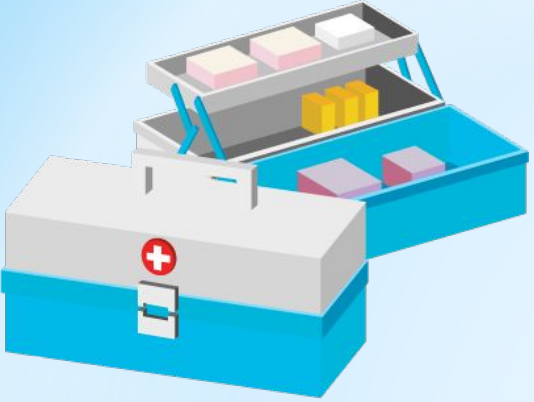
The number of confiscated fake medicines at European customs has **skyrocketed**, according to the current **customs report** of the **European Commission**.

In **2013**, authorities have seized about **3.7 mln** counterfeit drugs, **5 times** as much as the year before. Counterfeit drugs make up **~10%** of all confiscated fake products. It has been estimated by a **Pfizer** survey that **Western Europeans** spend **~10.5 billion** on illegal **drugs**, many of which are counterfeit and that **50-90%** of **medicines bought online are fake**.

Fake antimalarial medication has been threatening efforts to control malaria in **Africa**.

According to the **WHO**, in **2011**, **64%** of **Nigeria's** imported **Antimalarial Drugs** were **fake**.

Nigeria is **Africa's largest drugs market**, and **> 70%** of its **drugs** are **imported** from **India** and **China**, considered the "**Biggest Source of Fakes**."



Counterfeited Drugs Unmasked in Ukraine in 2006 – 2010 years:

1. **Cephasoline-KMP** , for injections - ВАТ «Київмедпрепарат» - 7 series
2. **Pentalgin-B**, tablets - ВХФТ «Біостимулятор» - 5 series
3. **Cocarboxilase** for injections - ВАТ «Дніпрофарма» - 21 series
4. **Biseptol-480**, tablets - В А Т «Фармак» - 5 series
5. **Trichopol**, tablets 250 mg- ВАТ «Polpharma» -22 series
6. 5-**NOK**, dragee 50 mg - «Lek» Slovenia- 2 series
7. **Viagra** , tablets 50 mg - «Pfizer» the USA-1 series
8. **Smecta**, powder- «Beaufour Ipsen», France - 3 series
9. **Decaris**, tablets 150 mg - АО «Gedeon Richter», Hungary - 3 series
0. **Valocordin**, drops 20 ml- «Krewel-MeuselbachGmbH» - 3 series

The State Quality Control Inspection of Medicinal Agents of MPH of Ukraine withdrew from circulation (marketing phase)

>30 drugs which were not registered in Ukraine and not permitted for medical uses

Marketing of Unregistered Drugs in Ukraine:

1. **Hemiton** («Аста Медика», Germany)
2. **Haemodes** N (OAO «Dnepropharm»)
3. **Dimedrol** (OAO «Белмедпрепараты», Belarus)
4. **Vaseline oil** (OAO «Lviv Pharmaceutical Factory», Ukraine)
5. **Metoclopramide** («Polpharma C.A.», Poland)
6. **Pantocalcin** (OAO «Shchelkovo vitamin plant», Russia)
7. **Pertussin** (Kirovograd region utility enterprise «Ліки Кіровоградщини», Ukraine)
8. **Pinosol** («Slovakopharma AT», Slovakia)

Criminal Liability for falsification of medicines:

Producing, Buying, Transporting, Sending, Storing, Possession with intent to sell of the counterfeit drugs or knowingly selling counterfeit medicines is punishable by imprisonment for a term of **3-5 years**, with confiscation of counterfeit medicines, raw materials and equipment for their manufacture.

The same actions committed repeatedly or by prior arrangement by a group of persons, or in large amounts, or resulted in prolonged injury to the health of a person - is punishable by imprisonment for a term of **5-8 years** with confiscation of counterfeit medicines, raw materials and equipment for their manufacturing and property.

If these actions resulted in human **death** or other **serious** consequences, or committed on a large scale, they are punishable by imprisonment for a term of **8-10 years** or life **imprisonment**.

Analysis of Fatal Cases:

A) According to Drug Groups:

1. Blood Substitutes - **22%**
   - **Rheopolyglucin** - 6
   - **Neohaemodes** - 1
2. Local Anaesthetics - **19.4%**
   - **Lidocaine hydrochloride** -7 cases
3. General Anaesthetics - **8.3%**
   - **Thiopental sodium** - 2 cases
4. Rentgenocontrast Substances - **8.3%**
   - **Triombrast** - 3 cases

B) By manufacturers:

I. Domestic:

1. "**Health**" - 6 cases (Lidocaine)
2. "**КЖР**" – 4 cases (2 - Thiopental sodium, 1 – Cyclophosphan, 1 - Doxorubicin)
3. "**Health - to people**" – 2 cases (1 – Fentanyl, 1 - Sibazon)

II. Foreign:

1. **Gedeon Richter - 3 (Turinal, Vincristine, Arduan),**
2. **Lechiva (Narcotan)**
3. **Nikomed (Actovegin), Smith Cline (Coldrex), LEK (Abactal), Berlin Chemi (Infesol)**

C) By the cause of death:

I - **Anaphylactic Shock** – 77.8%

(28 cases: 8 – infusion solutions)

II - **Lyell's Syndrome** – 5.56%

(2 cases – NSAID, on *Diclophenac*);

Circulatory Disturbance – 5.6% (2 cases on *Actovegin*);

Agranulocytosis – 5.6% (1 cases on *cytostatic*)

Electrolyte Disturbances – 2.8% (1 cases on *Turinal*)

The main method of gathering of information about SE of drugs in Ukraine is the Method of Spontaneous Notifications –

a Voluntary Presentation of Information about SE of drugs by the medical workers who have observed them.

Some Drugs withdrawn from the pharmaceutical market:

- Rofecoxib - was approved by the FDA in 1999 and withdrawn in 2004
- Valdecoxib: - was approved by the FDA in 2001 and withdrawn in 2005:

Both have been reported to be associated with increased incidence of myocardial infarction and stroke.

- Nimesulid - due to its high **hepatotoxicity**
- Fenfluramine - was withdrawn from the U.S. market in 1997 after reports of heart valve disease, pulmonary hypertension, cardiac fibrosis. After the US withdrawal of fenfluramine, it was also withdrawn from other markets around the world. It was banned in India in 1998.
- Dexfenfluramine (*Redux*) - was withdrawn from the U.S. market in 1997 due to its cardiovascular side-effects, and it was also pulled out in other global markets.

It was later superseded by Sibutramine, which, although initially considered a safer alternative to both Dexfenfluramine and Fenfluramine , was likewise

Measures to prevent and eliminate the effects of Adverse Reactions

a) reduce the dose;

b) cancel the drug and replace it by the other;

c) administration of antidotes ;

d) pathogenetic treatment;

e) symptomatic treatment.

Anaphylactic shock

Sympathomimetics:

Adrenaline h/ch **- 0.1% sol. 0.3-0,5-1** ml in 2-3 ml of 0.9% NCl solution SC in the region of injection and around it, SL or intratracheal instillation,
Mesaton 1% sol. 1-2 ml IV in 0.9% NaCl solution
Noradrenaline h/t **0.2%** in 0.9% NCl solution IV infusion

Glucocorticoids:

Prednisolone 3% solution 30-90 mg and more IV in 0.9% NCl solution

Broncholytics:

Euphylline 2.4% sol. 3-5-10 ml IV in 0.9% NaCl solution

Cardiac Glycosides:

Strophanthine
0.025% 1-2 ml IV in 0.9% NCl solution

Enzyme preparations:

Penicillinase 1000 000 UA in 2 ml of 0.9% NaCl solution in the region of injection

Oxygen inhalation for hypoxia control or prevention

World Medical Association

Declaration of Helsinki, 2008

The International Code of

Medical Ethics declares that,

" A physician shall act in the patient's best interest when providing medical care. "

Thank You for Attention!