FEATURES OF GRINDEKS FACILITIES AND SAFETY MEASURES

The Public Joint Stock Company "Grindeks" is the largest drug manufacturer in the Baltic countries.

This enterprise has two business structures applying diverse technology.
At drug dosage form facilities hazardous chemicals (active pharmaceutical) are applied in ingredients small amounts and in the state of multiply dilution either with water (e.g., for injectable preparations) or inert excipients (e.g., for tablet and capsule manufacture).
At the facilities of pharmaceutical actives, multistage syntheses are performed with the application of different hazardous chemicals including solvents.

In their entrepreneurship, PJSC "Grindeks" strive for producing efficient and safe medicines of quality. Attention is regularly paid to measures of enhancing employees' safety and health.
Since middle 90-ies, systematic work for risk evaluation and elimination started and was developed on basis of EU Directives (then not yet available in translation) and seminars arranged by EU institutions, State Labour Inspection, Latvian association of testing laboratories, Baltic environmental forum, Latvian association of chemical and pharmaceutical employers and other organizations, *viz.*:

- In 1997, **the identification and evaluation of Company's hazard risks** were made by Quality System Institute.
- In 1997/98**, risks in structural units** were evaluated, and the **most essential and critical risk factors** were discovered. Facilities were appraised and prioritised as to their hazard risk. Starting from this phase, the medium technological staff and qualified workers were widely engaged in risk evaluation. Application of chemicals was the reason why 9 of the 10 production sites of the highest risk happened to belong to the structural unit of active pharmaceutical ingredients manufacture. Schedules of working place improvement were formulated.
- In 1998/2002, **complex occupation health and safety audits** took place at the Company to detect disparities, imperfections and their causes entailing the most serious risks. Corresponding measures and the control of their performance were implemented to correct discrepancies and deficiencies. An appraisal coefficient was introduced to compare structural units as to risk importance and trends of selected corrections.
- In 2002 concurrently with the publication of the new Occupation Health and Safety Law, another phase began in the internal supervision of working environment. Regular control of working places and **systematic evaluation of labour environmental risks** are performed by Occupation Health and Safety Group together with site managers and specialists, attaching fiduciaries and employees. See a risk evaluation document in Annex No.1.
- In 2002, Company joined the International Programme of Chemical Industry, *viz.* **Responsible Care**, promising to function with the provision of high level in environment protection, safety and health for employees, consumers and public which is regarded as a relevant and integral part of company entrepreneurship.

At the Company, there exists a documented procedure of evaluating working environment risks which includes all phases of risk appraisal and recording results as well as planning labour protection measures and control of their implementation.

To compare facilities and particular risk factors, a risk index has been introduced at the Company. This index shows the total risk level at the particular working place (see Annex No.1 and No.2). If the total risk index is about 20 or more, preventive measures are usually necessary; if it exceeds 60, urgent labour protection measures must be performed to improve working environment. A comparison shows that the group of chemical risk factors commonly have the highest risk indices, and preventive measures must be regularly performed.
In Annex No.3, a risk evaluation summary for particular facilities of Active Pharmaceutical Ingredient production unit is presented using risk index. Discrepancies, risk sources and reasons causing a major or elevated risk as well as already implemented preventive measures intended to reduce the risk down to acceptable level are recorded. Basing on risk evaluation a schedule of labour protection measures is compiled where measures necessary for working environment improvement, their implementation terms and responsible are entered.

Solutions for risk elimination or reduction are prioritised, too:

- First, an option of the substitution of a less hazardous chemical for a more hazardous one is considered;
- To decrease the impact of the hazardous chemical on the employees, it is isolated as far as possible – the corresponding equipment is improved;
- Engineering techniques and other means of collective protection, e.g. improved ventilation are applied;
- Other means being excluded, individual protecting equipment is used, and extraordinary examination of employees' health is carried out.

Almost always concurrent organizational undertakings and training are expedient which bring real effect.

For competitive appraisal appropriate examples of each of the above measures resulting in essential improvement of Company's working environment are submitted:

I. Hazardous chemicals are replaced with less hazardous ones.

II. Equipment is installed (for loading chemicals into a dryer and drying) which prevents a direct contact of employees (workers) with the chemical (product).

III. The quality and efficiency of ventilation is improved which result in air flow direction from the clean area of the room towards the contamination source.

IV. Employee's (worker's) direct protection from the impact of working environment with the application of individual protective equipment and non-standard measures, e.g. special extraordinary health examination.

GOOD PRACTICE EXAMPLE No. 1	
FIELD (THEME)	*Technology revision*
MEASURE CONTENT	*Replacement of a hazardous chemical with a less hazardous one*
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SECTION	73.10 – performance of research and experiments in natural and technical sciences 24.42 – manufacture of pharmaceuticals 24.14 – manufacture of chemicals

TASK

To exclude the impact of hazardous chemicals on employees.

In the technological process, chloroform was used as a solvent; its concentration somewhere in the air of working area exceeded the occupational exposure limit. As result, the employees were compelled to lasting use of a face mask (respirator); nevertheless, a high risk of chloroform impact persisted.

PROBLEM (hazard/risk/result)

At the area of production Ftorafur active, the contamination of working air environment with chloroform vapours was observed when chloroform was used as solvent. In working places at synthesis reactors, during filtration at the centrifuge and during drying as well as even on a neutral zone (more than 2 meters from the direct working zone), the employees had to use personal protective equipment (respirators) in moments of equipment unit opening. See Figure No.1-1.

Taking into account the wish of a Japanese firm, the consumer of the active, to diminish chloroform content in the product from 0,2 % to 0.006 %, our Company suggested to replace chloroform with ethanol in the technology. The volatility of chloroform and that of ethanol are nearly equal while occupational exposure limit (OEL) for ethanol is 1000 mg/m^3 and its hazard is 100 times less than that of chloroform (OEL being 10 mg/m^3). Besides, chloroform impact is associated with risk phrases R40 – partly proved cancerogenity.

SOLUTION (risk prevention)

Solvent substitution in the technological process caused several problems.

One of them is the following: while using chloroform, a readily friable crystalline product like sugar was obtained, and no difficulties appeared in drug dosage form production. The new technology gave a flaky product which actually could not be used for drug dosage form (tablet, capsule) production.

A series of experiments were made in the laboratory to find out the conditions on which suitable product may be obtained. A reactor was built which permitted special cooling conditions and had a control system providing for the obtaining of an appropriate product. In Annex, see photograph No. 1-2.

Before implementation in manufacture, the modified technology was carefully developed in laboratory and afterwards proved in the production equipment.

Two impurities (not observed before) formed in small amounts in the modified process. With the application of very expensive analytical procedures they had to be identified. For the control of crystalline structure (polymorphism), contract laboratories abroad were also engaged.

These changes, their argument and a substantial report had to be agreed with all the countries where this product of our Company was used.

RESULT EFFICIENCY

As result of solvent substitution, working conditions in Ftorafur production process improved:

- Chloroform impact on employees working in the corresponding room was excluded;
- In this process, employees can work without respirators;
- Chloroform is noxious to environment as contributes to ozone destruction before the change implementation, chloroform emission made 1.7 tons yearly;
- The problem of eliminating waste containing chloroform was solved;
- Customer's claims were satisfied. As no more chloroform is used in technology, competitiveness in market enhanced.

COST/BENEFIT (personnel, social, economic)	Costs: • Due to peculiar requirements of medicine legislation, the seemingly simple issue aroused a series of problems; their investigation and solution costed about LVL 120,000 including LVL 32,000 for equipment construction. Benefit: • In the economic aspect, there is no testable benefit. Ethanol price is lower, but products yield after change implementation is lower, too. • Chloroform was purchased in Germany, ethanol is produced in Latvia. Transportation cost decreased. • Chloroform impact on employees is completely excluded. • The satisfaction of customers' wishes allowed to maintain market in Japan, Eastern Europe, Central Europe what markets LVL958,000 annually.

GOOD PRACTICE EXAMPLE No. 2	
FIELD (THEME)	*Equipment improvement*
MEASURE CONTENT	*Employees' screening of from contact with chemicals*
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TASK *To prevent contact of employees with hazardous chemicals because many active pharmaceutical ingredients and their intermediates are very potent. Small amounts getting into human body can cause a violent impact on it. Moreover, drying and related processes is the release of large solvent vapour amount into air.*	
PROBLEM (hazard/risk/result) During outloading from a centrifuge and drying, a strong impact of pharmaceutical actives, intermediates and solvents is exerted on employees (workers). After centrifuging, the product is outloaded onto trays and brought to a drying cabinet of shelves type where it is regularly mixed and analysed throughout drying period. When specified quality criteria are achieved, the product is packed into packing material. For risk reduction, personal protective equipment including respirators is used; however, there exists an elevated risk of chemical hazards in the working room which can lead to health detriment.	
SOLUTION (risk prevention) While visiting an exhibition in Germany, Company's specialists were acquainted with the equipment of novel technology including closed dryers where filling and drying processes precede in completely sealed equipment. Facility improvement was carried out. It consisted in the formation and installation of closed dryers with the cooperation of the Latvian firm *Peruza,* according to the requirements of Company's specialists. As result, the product is mechanically loaded into the centrifuge where it is dried completely isolated from environmental air; it is outloaded into packs which have a sealed joint to the outload orifice of the dryer. It fully prevents employees' direct contact with the pharmaceutical active and excludes solvent vapour diffusion into the air of working environment.	

<table>
<tr><td colspan="2">RESULT EFFICIENCY
By arranging a closed type dryer and delivering the product to the dryer not manually we obtain the following:
• Direct contact of employees with the product is excluded;
• Solvent vapour impact on employees is reduced;
• Physical stress is reduced since product loading, product outloading, mixing and packing proceed mechanically;
• An improved product quality is warranted because drying conditions are observed more accurately, and possible product cross-contamination with other chemicals (intermediates) is excluded.
See Figures No.2-1, 2-2, 2-3 and photographs No.2-4, 2-5.</td></tr>
<tr><td>COSTS/BENEFIT
(personnel, social, economic)</td><td>Costs:
• Closed type dryers were made in Latvia, and their cost was LVL 12,000, what is 8 times less than that of those offered in the exhibition.
Benefits:
• The impact of the pharmaceutical active on employees is excluded, and solvent vapour concentration in air is reduced. The occupational exposure diminishes about twice.
• The need for personal protective equipment decreases.
• Working conditions have improved, physical/manual work has decreased.
• Productiveness has increased because drying period has diminished about 6 times, number of analyses has decreased, too.
• A homogeneous product of good quality is obtained.
• Local companies – equipment manufacturers are engaged.</td></tr>
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GOOD PRACTICE EXAMPLE No. 3	
FIELD (THEME)	*Ventilation rearrangement*
MEASURE CONTENT	*Improving room ventilation quality and efficiency*
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TASK

To prevent or diminish the emission of hazardous chemicals in production rooms and their impact on employees. Chemicals used as pharmaceutical actives and their intermediates have high biological activity. Various hazardous chemicals including volatile solvents are used in their manufacture.

PROBLEM (hazard/risk/result)

It was found that concentration of hazardous chemicals in the air of working environment in particular production rooms is high not only near the emission source but also farther – in the neutral zone. Testing results showed that it occurred while performing operations with open products: pouring solutions, opening reactors, outloading the centrifuge, drying, and similar cases. It was we concluded that room ventilation lacked sufficient quality and efficiency. Figures No.3-1, No.3-2.

To enable adequate reconstruction of income and exhaust ventilation, complete air flow research was performed in the production room with application of German measuring device "Testo" and smoke generator "Cumulus" according to a procedure developed at our Company. This procedure is based on measuring air movement velocity and direction in many places of the room and on different levels for the purpose of representation of air flow in the whole room.

For instance, while producing the pharmaceutical active Zopiclone, there are several operations where chemicals emission out of the reaction mixtures possible because the mass must be kept at solvent boiling temperature for several hours, hot liquids are poured, etc. The equipment was placed in the room so that insufficient air exhaust immediately at the contaminant source existed. Sometimes the contamination diffused on floor level round the room, rising risk even for employees on the other side of the room.

The total air exchange rate in the room was sufficient or even increased; at the same time there were vortex zones and air flows directed incorrectly. Therefore hazardous chemicals diffused throughout the room, and occupational exposure measurements showed a surplus contamination in the room. Therefore an instruction existed in the manufacture documentation that employees always had to apply personal protective equipment including respirators while performing corresponding operations.

Similar situation existed in several rooms of laboratory type where contaminated air diffused throughout the room and employees had to use respirators.

Anyway, in both the cases the risk was not sufficiently reduced. On account of the results of room ventilation quality tests, reconstruction of the ventilation systems in corresponding rooms has to be made.

SOLUTION (risk prevention)

Basing on the test results, room ventilation systems were reconstructed: exhaust of contaminated air being arranged or improved immediately at emission sources and air flow directed from pure air zone to contamination sources. The zone of pure air was arranged in the part of the room where operations not involving chemicals are performed.

Concurrently with an order of Zopiclone area re-design to a specialised organisation, Company's employees performed a gradual optimisation of all air flows. It was achieved through elimination of particular ventilation orifices, regulation (increase or decrease) of air flows, change of ventilation orifice geometry. As result, „vortex zones" were eliminated and air flow in the direction of pure air zones towards exhaust ventilation orifices at reactor holes, centrifuges e.a. contamination sources were established.

For room re-design and reconstruction at Zopiclone facility, out source designers planned the cost of ~LVL 15,000; the performance of these works with Company's forces reduced it to ~LVL 1,200.

According to a professional bid, the reconstruction of ventilation systems in a laboratory type room would cost ~LVL 10,000; Company's specialists performed it, expending ~LVL 1,000.

RESULT EFFICIENCY

As result of room ventilation system reconstruction, ventilation quality and efficiency of its ventilation improved why:

- Chemicals risks excluded or reduced, Figure No. 3-3.
- Necessity to use respirators is reduced;
- The impact of chemicals on employees at the time when they do not operate with chemicals is eliminated or essentially reduced;
- By performing improvements by own forces, substantial finance is spared:
  - in case of the production room ~ LVL13,800,
  - in case of laboratory room ~ LVL9,000.

The experience gained from improving ventilation quality and efficiency in the first case (at Zopiclone area) was applied to the rooms of other active pharmaceutical ingredients facilities. The measures of ventilation improvement are usually performed during the period of facility or room reconstruction as well as arrangement of any new production rooms and installation of equipment.

COST/BENEFIT (personnel, social, economic)	Costs: • in case of a production room ~LVL 1,200; • in case of a laboratory room ~LVL 1,000; Benefits: • working conditions have improved and chemical hazard has been prevented or essentially reduced; • the use of personal protective equipment is restricted; • a zone of pure air is formed • products of higher products of higher quality are obtained because cross-contamination is diminished or excluded.

GOOD PRACTICE EXAMPLE No. 4	
FIELD (THEME)	*Occupational safety*
MEASURE CONTENT	*Safety issues in production technology development for new chemicals*
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TASK *Prevention of chemical impact on employees in conditions of incomplete equipment qualification why better protection of staff is necessary.*	
PROBLEM (hazard/risk/result) Company faced the necessity to develop technology and test the process on an experimental equipment for Warfarin – an active pharmaceutical ingredient used to diminish blood coagulation. At the start of employing any chemical, safety data sheets are required from the supplier; for chemicals produced in-house, the information for compiling safety data sheets is collected from databases and printed literature. (At present, safety data sheets for 270 chemicals have been prepared at the Company). It was found in databases that besides potent therapeutic activity, Warfarin may have mutagenic and allergic properties. The experimental status of the plant restricted possibilities to apply protective measures of the highest level; the main attention was paid to collective and individual protective measures and to specific undertakings.	

SOLUTION (risk prevention)

To provide harmless working conditions for employees as well as reduce risk in case of technological deviations or emergency, the evaluation of chemicals risk, prioritisation, consideration of technical and economic possibilities were made.

For the production room, an air lock with a shower were made where operators put isolates suits on. To facilitate working conditions, pure air for breathing was supplied through an independent air supply system. Particular material and waste air locks were arranged. To minimise contact with dust, even production records were not passed outside the production room but were copied. Air flows were regulated, sealed equipment and protective devices were provided for.

For the control of working environment, a selective analysis procedure for Warfarin and two its intermediates was developed. A particular laboratory of intensified ventilation was arranged for analytical work, and operations were performed in full masks supplied with pure air. See Figures No.4-1, 4-2.

For operating the plant, employees were selected: in addition to the mandatory examination of operators' health, supplementary analyses were made concerning blood coagulation. A specialised laboratory weekly making visiting rides performed 4 haemostatic analyses for about 17 employees of the Company (including mechanics, analysts, e.a. contacting Warfarin). In the meantime, Company's occupational doctor performed express tests of blood coagulation.

Antidotes were prepared for cases if employees' haemogram approached the critical limit. There was no need of using them since the contamination caused by the plant attained just 5% of the permissible limit (0,1 mg/m^3) even while cleaning the room. (see Figure No.4-3).

Nevertheless, operators worked for safety reasons in protective clothing throughout the shift.

RESULT EFFICIENCY

An experimental multiproduct plant has been arranged having:

- Double safety (sealed equipment + protective means);
- Double control (regular testing of working environment+special biologic tests);
- The plant was assessed as to room contamination with the dust of the hazardous chemical and its intermediates.

As result, no health detriment was detected for any employees engaged in Warfarin production and control.

COSTS/BENEFIT (personnel, social, economic)	Costs: • That of equipment formation: LVL 2,000. • Purchase of protective clothing: LVL 4,500. • The rides of the visiting laboratory performing blood tests cost LVL 1,300. Benefits: • The following have been excluded or essentially reduced: - risks caused by chemicals; - the impact of a potent active pharmaceutical ingredient on employees. • Methods have been developed for determining very low concentrations of working environment contamination. • Technology has been developed for a perspective product of intended annual turnover LVL 38,000, including the selection of relatively no hazardous solvents.