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19013

Distr.
LIMITED

ID/WG.505/4(SPEC.)
31 May 1991

ORIGINAL: ENGLISH

United Nations Industrial Development Organization

Workshop on Technological Co-operation among
Developing Countries for the Development of
Pharmaceutical-related Ancillary Industries

Amman, Jordan, 4-6 November 1991

A STRATEGIC PLAN FOR THE PACKAGING OF PHARMACEUTICALS IN PLASTIC*

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* The views expressed in this paper are the author's and do not necessarily reflect the views of the Secretariat of UNIDO. This document has not been edited.

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SUMMARY

Plastics can be used to pack most pharmaceutical products. The approval of a plastic pack requires more intensive and more extensive testing than a conventional glass pack. However, in depth knowledge of the product, the plastic and the pack, can optimise the time scale and overall costs. To effectively achieve this requires a strategic policy, with guidelines to be discussed in order that a cost effective plan can be produced.

This paper provides background requirements so that such a plan can be produced.

INTRODUCTION

The attached papers entitled

- (a) "The Packaging of Pharmaceuticals using plastics"
(an Appendix to this paper) and
- (b) "Use of plastics in the Pharmaceutical Industry"

indicate the feasibility of using plastics for the packaging of pharmaceutical and allied products. A strategic plan is recommended so that products and packs are developed in the most effective way to minimise time, work-load and costs. Certain priorities which are critical to this proposal are outlined below.

POLICY GUIDELINES

It is necessary to identify policy guidelines so that a strategic plan can be produced. These must consider:-

- (i) Aspects leading to product production, the identification of the products, and the development of suitable plastic materials with supporting plastic conversion industries together with the roles of various pharmaceutical factories in terms of what they produce as part of a multinational approach.
- (ii) Techno-economical factors so that all resources (human and material) can be optimised in a common pursuit.

The total guidelines and priorities cannot be quantified until points (i) and (ii) above have been discussed in full detail and initial propositions identified against capital, revenue costs and time scales.

Such discussions in expanding points (i) and (ii) should include:-

(i) ASPECTS LEADING TO PRODUCTION

- a) Clear indication of products, product ranges, size of markets, etc.
- b) Defining where and how the products and production ranges are to be developed in geographical locations.
- c) Identification of factories where products and product ranges are to be produced.
- d) Identification of types of pack that may be employed.
- e) Identification of the types of plastic required and sources of supply.
- f) Identification of quantities of packs, packaging materials and components required.
- g) Identification of sources of supply for all raw materials (drugs, excipients, packaging materials, equipment).

In the case of packaging materials, consideration is required to cover both conversion and printing equipment.

Progress on the above therefore relates to QUANTITY PREDICTIONS AND QUALITY STANDARDS from INITIAL INVESTIGATIONS through to likely MARKETING over the first 5, 10, 15 years. If world-wide exports are to be envisaged QUALITY STANDARDS will assume particular importance.

(ii) TECHNO-ECONOMICAL FACTORS

- a) COSTS and BUDGET predictions associated with (i) Aspects leading to production are an essential part of any plan.

- b) An INFORMATION BASE, NATIONAL COMMITTEES, supported by Regional Packaging Institutes, are necessary to discuss the technical aspects of proposals in detail and to provide expert advice.
- c) Since any proposals require the development of HUMAN RESOURCES associated with a wide range of disciplines (package development, package engineering, production and manufacture, quality assurance and quality control, stability and shelf life testing, managerial administration, etc.) how these people are obtained and trained must have a high priority.
- d) QUALITY STANDARDS as related to both products and packs must be investigated as this will reflect on the areas of manufacture required, the equipment to be employed, the quality of the polymers chosen and the conversion processes/production facilities for packaging materials to be used.
- e) Input from Medical and Marketing must also be constantly available to assist in the creation of technical guidelines.
- f) A watching brief on environmental issues. This is now an important world-wide priority with consideration to utilisation of the earth's natural resources, conservation of energy, recycling, reuse and possible pollution.

It is recognised that a broad review will be necessary by a team of experts before the above can proceed. Such a review could be carried out through UNIDO. It is important that any weaknesses related to the above proposals [(i) and (ii)] be identified at an early stage so that areas where information is lacking or incomplete can be strengthened. For instance, deciding what products are required must be backed by information on illness and disease in the areas where a product is to become the likely mode of treatment.

INFORMATION COLLECTION - DATA BANKS

It has been emphasised that the gathering of INFORMATION is a prime factor before guidelines can be produced. Information needs input from

Medical Services
Marketing
Development and Packaging Development
Production engineering and production
Quality Assurance and Quality Control

Medical Services, for example, (in conjunction with marketing) should identify diseases and methods of treatment and establish what clinical evaluations will be necessary to confirm efficacy.

INFORMATION AND TRAINING

In order to obtain an effective and efficient back up to PACKAGING, NATIONAL AND/OR REGIONAL PACKAGING INSTITUTES would be advised. Although a proportion of the packaging expertise would relate to PHARMACEUTICAL PRODUCTS, this would need to share common knowledge with many other PRODUCT CATEGORIES (e.g. FOOD, DRINKS, HARDWARE/HOUSEHOLD GOODS, TOILETRIES and COSMETICS, etc.) PACKAGING INSTITUTES are therefore essential to service many types of industry as virtually all CONSUMER and most industrial materials have to be effectively packed.

Effectively packed infers that the goods/products are adequately protected against mechanical, climatic, biological and chemical (interaction - compatibility) hazards, well presented to optimise sales, in an economically viable form until such time as the goods/products are used (shelf life) or removed from the pack for ultimate use.

INFORMATION is therefore essential to establish the NEEDS of the MARKET, leading to clearly defined progress plans which can be coupled to techno-economical requirements.

Of particular importance in this latter area is the DEVELOPMENT OF HUMAN RESOURCES. If one looks at the development of pharmaceutical industries and the use of plastics in the U.S.A., Europe, Japan, etc. progress was largely made through experience and was as a result relatively slow. For example, following the introduction of thermoplastics around 1953, much time was spent finding out the weaknesses of plastics and identifying how these problems could be overcome. Liaison between scientists in the pharmaceutical industry and polymer chemists in the plastics industry was, in the early days, particularly poor. As indicated in the attached paper, the knowledge of how to use plastics, learnt from slow experience is now widely available, hence if correctly used by TRAINED STAFF enables companies to do in five years what others took 20 - 25 years to learn and apply. Thus, whilst there still is no total replacement for experience, detailed training can increase alertness and awareness to a point where faster and more effective progress can be made. In this context some employment of experienced polymer chemists may prove particularly useful.

INFORMATION AND THE ENVIRONMENTAL ISSUES

Today world-wide concern is being expressed on many environmentally based issues. These include reference to attacks on the ozone layer, wastage of energy, depletion of natural non-renewable resources, general pollution of land, water and air, possibilities of recycling, reuse and how to improve resource management, etc. As part of this general concern, packaging receives more than its fair share of criticism with plastics generally causing the greatest emotion. Thus whilst 95% of fossil fuels are used as energy for creating heat, electricity, transportation, etc. the 2 - 3% which are converted to plastics, of which about half finish up as packaging materials, receive out of proportion attention. In this context the pharmaceutical industry, compared with foods, drinks, household goods, is a minority user. However as the pharmaceutical industry has the

reputation of being a 'caring' industry, those involved in devising its packaging must have a clear awareness of the environmental issues. The pharmaceutical industry therefore cannot afford to operate in isolation from those other industries which have a majority interest in plastics.

INFORMATION ON QUALITY ASSURANCE and QUALITY CONTROL
and GOOD MANUFACTURING PRACTICES

It is inevitable that standards for Pharmaceutical Products fall into two categories, i.e.

- i) those for the sophisticated world
- ii) those for the third world

since this at present makes economical sense. (High standards equate with high costs which cannot be afforded by poorer nations).

There is therefore a situation where the gap between i) and ii) above is not significantly reducing as the sophisticated world demands higher standards of quality and safety. This is particularly true with sterile products where the risks to the user or patient are obviously greatest. 'Sterility' therefore puts higher demands on the production environment, the procedures (standard operating procedures), the equipment, the packaging materials, the process operators and QA/QC.

The important role which QA and QC has to perform must therefore be clearly recognised as the lack of control on the supply of PACKAGING MATERIALS AND COMPONENTS can put the ultimate QUALITY at risk.

Creating adequate SPECIFICATIONS for PACKAGING MATERIALS and COMPONENTS, the choosing and AUDITING of SUPPLIES is therefore a fundamental part of GOOD MANUFACTURING PRACTICES.

The above is of considerable importance if products are to be EXPORTED to the SOPHISTICATED WORLD as these may insist that their standards are met and require inspections by their own

Regulatory Staff before products are accepted. Exporting to the third world countries is therefore likely to be less demanding.

To obtain packaging materials and components to high standards is likely to involve 'cleaner' production conditions where attention is paid to both BIOBURDEN and PARTICULATES. Ultimately such conditions may be shared with other industries, i.e. FOOD, DRINK, TOILETRIES and COSMETICS, etc.

Finally it must be stressed that QUALITY ASSURANCE (QA) which builds quality into all processes is now taking on a much more prominent role. QUALITY CONTROL (QC), which is part of any QA system, is now seen as measuring the quality produced thereby enabling information to be accumulated and assessed, so that long term quality can be either improved or guaranteed. As part of this QA approach, VALIDATION of equipment, processes, operators, is receiving increasing attention.

Before effective specifications can be established for polymers, packs and components, INFORMATION is necessary on the basic plastics - see below.

DATA BASE ON PLASTICS

A comprehensive data base on plastics is an essential feature of the project. Although obtaining initial information may be relatively simple, it must be recorded that polymer suppliers, compounders and converters, normally only provide the type of in depth information required by the pharmaceutical industry according to sales or forecast sales potential. In this context pharmaceutical requirements are significantly smaller than the quantities used by the food - drink industries, hence some opposition to give such detailed information might be anticipated.

The data required on plastics will also vary according to the end use of the polymer. More in depth detail will be required on materials used for sterile products than, for example, solid oral dose products. The former will require,

for example, data on residues, processing aids, additives and any added constituents associated with master batching. When specific plastics are adopted for a range of packs, components, etc. it would be advised that detail is recorded under a MASTER FILE system, which can be cross referenced as applications for the polymer extend.

It should be noted that it is unlikely that one grade of plastic will be suitable for all conversion processes (injection, injection blow, extrusion, extrusion blow, thermoforming, etc.) hence knowledge of a particular plastic cannot be used in isolation from packs and pack components which may be employed.

A polymer data base must therefore be used in conjunction with packaging development activities. The importance of this interface between materials and packs cannot be over emphasised as it is fundamental to successful progress.

INFORMATION TO ASSIST PRODUCT SHELF LIFE ESTIMATIONS -
PRODUCT - PACK STABILITY

In order to obtain realistic shelf life estimations some study of CLIMATIC CONDITIONS, as found during DISTRIBUTION and STORAGE (warehousing and point of sale/use), is advised. Although textbooks tend to divide the world under certain climatic conditions, i.e.

arctic/antarctic
temperate
sub-tropical
tropical

these fluctuate both locally (where the product is made and packed) and internationally (where the product is distributed and sold).

Since the cost of STABILITY TESTING tends to be high (equipment, trained analysts, etc.) a policy on test conditions and interpretation of results is essential to contain overall costs to an acceptable level. The level of testing will also be influenced by where the product will be registered for sale. Marketing policies must therefore be considered before stability testing units can be set up.

Use of 'accelerated testing' with certain plastic packs needs to be viewed with caution.

INFORMATION ON GENERAL TRENDS WORLD-WIDE

As mentioned earlier the pharmaceutical market can be divided between countries of low and high incomes and standards. Trends associated with both of these markets must be watched both in terms of the products required and the types of pack to be used. Long term both may become influenced by the environmental issues, hence the materials used for packs could reduce - at this moment in time there is a proliferation of the types of pack and materials employed. Maintaining a watching brief on what the rest of the world is doing is essential to long term success.

INFORMATION ON PACKAGING SUPPORT ACTIVITIES

Selecting and clearing the suitability of a plastic for a pharmaceutical product is only part of the total operation of launching a product into a market. Support activities which include placing information/identification on the pack (by labelling or printing), choosing design graphics, deciding whether the pack will contain an insert, be placed in a carton, etc. and how these will be finally protected for storage, transportation, display and use, etc. all need investigation. As with the establishment of the primary pack (the pack in immediate contact with the product), tests have to be carried

out, suppliers assessed, specifications written and standard operating procedures (instructions on how product and pack is filled, closed, assembled, etc.) produced.

These activities need close co-operation between development, production, engineering, warehousing, QA/QC, etc. so that all appreciate the objectives to be achieved. Warehousing and distribution which occurs last in this chain of events is frequently the one which is most neglected or least understood.

Tests, either actual or simulated, will be required to establish that the transit pack will reach its destination in good condition.

Special mention should be made to CLOSURES and PACKAGE TESTING.

CLOSURES

Closures are sometimes the weakest part of a pack irrespective of whether a single or multiple use system is involved, i.e. a weld, heat seal, screw cap, push on or push over closure, etc. Sophisticated countries are demanding attention to tamper evidence, tamper resistance, child resistance, as well as more specialised systems which assist both product administration and compliance. However as closures become more complex and medication becomes increasingly available to prolong the length of life, more attention has to be paid to special closures which are easily opened by the frail, arthritic, poor of sight and infirm elderly population. Expertise in closures and closure systems, identified above as a possible weakness in pack development, therefore requires a high level of technical knowledge in terms of closure efficiency and effectiveness of application.

PACKAGE TESTING

Package testing involves investigations into and the testing of materials, packaging components and packs both in a development and an ongoing production situation. Gaining adequate information in the product and package development stages is particularly important as poorly defined (specifications) can render any initial product-pack tests valueless. There is therefore a need for all materials used for investigative purposes to be checked and tested in greater depth than they ultimately would be when a full scale production situation is reached. These initial investigations should, for example, challenge the product and clearly establish how it may deteriorate (from light, moisture, oxygen, etc.). Armed with this information it is then possible to check whether the pack options to be considered perform an effective role of preventing degradation from the hazards previously identified. Only once adequate investigation tests have been completed should the preferred product-pack be entered into a formal stability programme.

Efficient package testing at the initial development stage should mean that the pack should never fail when put onto a formal (expensive) stability programme.

Package testing therefore requires well equipped laboratories with well trained operators, together with established and proven test procedures.

The level of package testing required will vary according to the 'risk' associated with the product, i.e. as mentioned previously, sterile products, and large and small volume parenterals in particular, will require the highest in depth studies. In all package testing work records of the tests and test procedures must be compiled as part of GLP (Good

Laboratory Practice) as this information may be required by Regulatory Authorities (either in a Standard Document form and/or available for inspection). Transit type tests are also part of package testing.

All of the above will require the support of good SPECIFICATIONS, adequate validation of equipment, staff and methodology, plus well documented Standard Operating Procedures when the product-pack reaches an ongoing production stage.

CONCLUSIONS

The above outline has endeavoured to cover the major contributions required to market a range of pharmaceuticals for either over the counter or ethical outlets. Discussion on these points should reveal any serious omissions.

The finally chosen order of activities will need to be quantified in terms of resources required, time scale, costs, etc. and entered on to some form of activity chart supported by a budgetary control system.

The attached paper "Use of plastics in the Pharmaceutical Industry" provides additional information which will need further consideration once initial detail has been quantified. It may also be useful as a discussion point for other industrial applications for plastics. In this context foods, drinks, toiletries, cosmetics, veterinary products, share much in common with pharmaceuticals - except that the level of package testing may be less intensive.

APPENDIX I

THE PACKAGING OF PHARMACEUTICALS USING PLASTICS

If the properties of plastic are studied in isolation it might be assumed that certain products cannot be packed in plastic or that there will be limitations on shelf life. There is some truth in this statement if only conventional packaging methods are considered with plastic. However with the use of modern packaging technology it is now possible to improve certain previously critical factors, such as lack of compatibility, inadequacy of barrier properties, problems of adsorption, absorption, etc. to a point where most pharmaceutical products can now be packed in plastic materials. This situation can be achieved in a number of ways, i.e. using plastic of increased thickness; use of composite constructions by lamination or coextrusion; additionally overwrapping the primary pack with a specific barrier material, or adding special coatings to the inside or outside of a container, etc. In following one or more of the above options, an adequate shelf life for the likely storage and use period should be achievable.

Under these circumstances plastics can also offer certain positive advantages such as lightness in weight, reduction in volume occupied, non-breakability, improved safety (no hazardous piercing or cutting features), possible savings in cost, etc. Other special features include collapsibility, squeezeable packs, and ready availability in a unit dose form which may offer additional benefits.

The disadvantages of plastics which may need special consideration include the need for special production line handling equipment, precautions to keep materials clean

(possibly due to electrostatic effects) in terms of bioburden and particulates and additional testing and investigation procedures to establish the best packaging system (see earlier suggested options) for a particular product. The latter will frequently mean that the time scale from initiation to launch may take longer than it would with the alternatives of using glass or metal materials. In reaching a decision on the plastic pack it would be normal to use glass as a comparative 'control'. However, one other factor that must be born in mind is the fact that plastic is currently viewed as being less environmentally friendly than glass or metal where both can be recovered and recycled. However extensive work is ongoing in Europe, U.S.A., Japan, etc. to make plastics environmentally or ecologically more acceptable.

In order that the economics of plastic can be fully exploited it is suggested most pharmaceutical applications should be restricted to the 'five' most economical plastics. For rigid containers these can be identified as the

polyethylenes (low, medium, high and linear
low densities)

polypropylenes (homopolymers and copolymers)

polystyrenes

polyvinylchlorides (unplasticized and
plasticized)

and polyesters (PETP and PETG)

This can also apply to composite materials where the minimum of the more expensive plastics as coatings, laminations, coextrusions, etc. should be employed. The use of high cost resins should only be considered and justified for exceptional circumstances.

If the above basic strategy is accepted then the supporting activities must be discussed and defined prior to the commencement of the (any) project.

ACTIVITIES ASSOCIATED WITH THE DEVELOPMENT OF A PLASTIC PACK

The activities which need consideration include:-

- i) Survey of plastic suppliers - identification and selection of suitable grades of economic plastics (International and local industry based on FORWARD PREDICTIONS - MATERIALS).
- ii) Establishment of suitable converters and supplies
based on FORWARD PREDICTIONS on types of PACK to be EMPLOYED.
- iii) Establishment of SPECIFICATIONS for material (polymer).
- iv) Establishment of SPECIFICATIONS for PACKAGING MATERIALS (Containers, closures, components, reel fed materials, etc.).
- v) Manufacture and clearance of chosen packs (prototypes, initial samples, production samples).
- vi) Investigational tests to confirm suitability of pack chosen.
- vii) Establishment of SPECIFICATIONS for products to be involved in investigational tests.
- viii) Production of product and packaging materials for STABILITY tests.

- ix) Assembly of product and pack for formal STABILITY tests.
- x) Clearance of stability data, compilation of documentation for registration purposes on a national and international basis.
- xi) Monitoring of production made product and packs (from launch onwards).
- xii) Ongoing STABILITY of regular production batches and monitoring of complaints.
- xiii) Updating stability, shelf life and any modification to product and pack.
- xiv) Maintaining an ongoing survey on environmental issues.
- xv) Ongoing review of any other special or changing requirements, e.g. related to good manufacturing practice, security, child safety, increases in elderly population, etc.

The above has to be considered against the product range to be investigated, particularly as the intensity of the testing will vary according to the product category, e.g. a plastic pack for an intravenous solution requires far more in depth testing than that of a solid oral dose product in a blister pack. In general sterile products fall into a similar category as intravenous solutions, i.e. safety standards must be maintained at a high level.

All work covered above must meet good quality standards with good attention to the principles of good manufacturing practices. This is particularly relevant if products are to be exported and the industry to be inspected by overseas inspectorates.

CONCLUSION

The packaging of pharmaceutical products in plastics is feasible for nearly all products, provided any initial limitations of the PRIMARY PACK (the pack in contact with the product) are overcome by additional precautions such as overwrapping, adding special coatings, etc. This means that packaging in plastic requires special knowledge and expertise and may take slightly longer to establish. Time and costs can be minimised by prestudy of the likely products to be involved and the establishment of a STRATEGIC plan as an initial PRIORITY.