Fermentation Technology : Prospects in India

Shri B. V. Patel Education Trust
"Kaka-Ba" 13, Sanjiv Baug,
New Sharda Mandir Road,
Ahmedabad-380 007.

Guidelines for the Entrepreneurs Seeking Government Approval for Antibiotic Production by Fermentation

P. K. Ghosh, Hindustan Antibiotics Limited

1 Introduction :

The sector of the drug industry that specialises in the production of microbial metabolites which in dilute concentrations inhibit and even destroy other microorganisms including bacterial cells but have sufficient separation between their toxicity to mammalian hosts compared to microbial cells, belong to antibiotic industry and the metabolites thus produced are known as antibiotics. Except a few, all antibiotics are produced by aerobic fermentation of chosen nutrient media by use of selected microorganisms under preset conditions of temperature, aeration and agitation. Antibiotic production is highly energy intensive. The industry is distinct from the synthetic drug producing counterpart in many respects and requires much more perfection in equipment selection and installation, layout design and skill of operating personnel. However, such distinctive features have not given any special status to this sector of the drug industry in the eyes of law; all the laws applicable to drug industry are also applicable to this sector.

Antibiotics production through fermentation is highly science based. It is also capital intensive. A minimum size economic unit for undertaking basic production through fermentation cannot be set up in the small scale since the investment limits in plant and machinery (Viz Rs. 20 lakhs) for the small scale sector are too small for setting up such a unit.

The number of antibiotics consumed in the country are about 50 of which only 17 are indigenously produced. The indigenousiy produced antibiotics are always expensive than the imported stuff, and is about 2 to 3 times more costly. Small size plants, second grade technology, higher cost of input

materials, lower level of technical skill as well as inferior R&D base are some of the important reasons for such state of affairs in our country. The problems have now been largely identified and there has, of late, been more emphasis on the setting up of cost effective plants. However, it would take several years before our country could think to catch up the developed world.

In the process of setting up a basic antibiotic industry an entrepreneur has to have great support from the Government right from the conceptual stage. The major supports needed are sanctions for going ahead, sanctions for foreign collaboration (technical, financial or others) as also support in finance. The support in finance varies in the nature, extent and source depending upon whether the entrepreneur is a Centrally or State owned Public Secter Undertaking, a joint sector unit, a Private Indian entrepreneur or a Foreign Company and an elaborate write up is necessary to explain its details. In this article, the scope has been limited to the considerations that go in for clearing an antibiotic project under Industrial (Development & Regulation) Act 1951.

2. Proposal :

Antibiotic production is covered under serial No. 22 of the First Schedule to the I (D & R) Act 1951. The provisions of the Act are applicable to such production in industrial units set up by any person or authority including the Government. For new undertakings to be set up, the approval in the first instance is issued in the name of the applicant and subsequently when the company has been floated, necessary endorsement to that effect is made in the approval.

In the conceptual stage before preparing an application for industrial approval, the entrepreneur must have a knowledge about the demand for the product, estimated investment on the project, approximate idea about the technology to be procured in terms of main contents to be received and payments required to be made, approximate cost of the product, main material inputs per unit weight of the finished product in quantities as

well as costs. Besides, a knowledge about the CIF cost of imported materials together with the CIF cost of imported antibiotic is useful. It is in fact, advantageous to have a detailed project report made in advance, but is not necessarily a pre-requirement, this could be undertaken later on. It may be emphasised here that decision for the setting up of a basic antibiotic industry has tc be arrived at with great care. Assuming that the entrepreneur is otherwise capable, great emphasis must be laid on the selection of an appropriate technology. It is almost a stupidity to start such an industry with a half proven technology. An entrepreneur must, therefore, go ahead only when the technology selected has adequately been tested by all financial and economic tools and also full information about the exploitation of the technology in running plants has been gathered.

A proposal is made out by the entrepreneur by accurately filling prescribed I.L. forms. Eleven copies of such application along with prescribed fees (in the form of a Bank Draft), are submitted to the Secretariat for Industrial Approvals (SIA), Department of Industrial Development, Udyog Bhavan, New Delhi.

A short cut method for getting an approval of the project through D.G.T.D. Registration for certain entrepreneurs under certain conditions, is also available. However, such approval must precede foreign collaboration (FC) approvals as well as Capital Goods (CG) clearance, for which procedures described a little later are to be followed. Since the proposal for antibiotic production is likely to require clearance of one or both of FC & CG, the registration procedure has not been further elaborated.

The competence of the entrepreneur is judged greatly by the preparatory work done by him as will be evidenced by the information submitted by him in the application. For an individual, the technical qualifications he possesses and also the experience he has are also greatly counted.

3. Appraisal Prior to Approval :

A proposal submitted to the Government is examined on first come first served basis. If, however, several applications are received simultaneously within a short period, all such applications are examined together. Such instances are not frequent. The merits of an application are judged by examining several factors, the most relevant and important among them are given below.

(i) The location of the factory should be at a permissible site in accordance with the current location policy of the Government.

(ii) It is to be ascertained if the antibiotic is allowed for marketting in India. Office ot the Drug Controller of India (DCI) in the Directorate General of Health Services, Nirman Bhavan, New Delhi, is the competent authority who grants such permissions only after the antibiotic is clinically evaluated in certain Hospitals under the authority of DCI. Once an antibiotic is cleared for marketting in favour of a company, others willing to undertake manufacture need not take fresh approvals.

(iii) The title of the applicant must authorise him to take up the manufacture of the proposed antibiotic. As per New Drug Policy, 1978, certain antibiotics are reserved for production in the Public Sector Units, while some are jointly reserved for Indian Private Sector as well as Public Sector Units. Antibiotics not reserved for production in any sector can be taken up by any entrepreneur from the basic stage.

(iv) There has to be sufficient demand for the antibiotic. In case past approvals had been accorded or if already producing plants existed, the gap will have to be intelligently anticipated. Creation of newer capacities is regulated so that there is no overcrowding of units for the same manufacture beyond a certain limit.

(v) The capacity proposed to be set up must be economically viable. It should not however, be so large as to capture

the entire market to become a monopoly company, except when the applicant is a Public Sector Company.

(vi) The proposal must be so made as to ultimately commit to undertake manufacture from the basic stage. Initial production during the earlier phases could be undertaken from the intermediate stages, for which each proposal has to be viewed on individual merits.

(vii) The technology should be such that the production should be cost effective. Details for enabling to appreciate the cost of the drug are appreciated. In their absence, based on the details of materials cost, a rough guess is made to have a feeling of the ex-factory price by utilising the concept of value added. In antibiotic industry, generally the material cost, in the event of basic production, would represent about 50 to 60% of the ex-factory price.

(viii) The productivity of the strain is an important indicator of the technology. Knowledge of the titre, turnaround time and overall recovery efficiency enables a deep insight into the nature of the technology. Similarly, such information as the power input and aeration per unit volume of the fermented liquor are indicators of energy requirements for the production. Other information such as the temperature of fermentation as also knowledge of heat load to be handled during production enables an evaluator to guess about the cooling energy required. These information greatly helps in enabling to compare with similar information from other technology sources. Besides, with these information it is possible to roughly guess about the peak load of electrcity, steam, compressed air, refrigeration as well as the chilled water unit and thus enables an evaluator to meaningfully estimate the investment on services. Similarly, the knowledge of the titre and also some details about the process enables one to guess about the number and the size of fermentors and other key equipment and these data could be converted into costs by standard approximate methods. If a list of major equipment proposed to be installed by the applicant,

as also their cost are made available, these two sets could be compared for useful conclusions.

(ix) Once it is possible to intelligently guess the cost of major equipments including the service equipments, it is possible to estimate the project cost with the other information available in the application and also by estimating the working capital margin money and interest during construction (after assuming a reasonable gestation period). The project cost, which is the sum total of the cost of land, building, installed machinery, know-how (if applicable), interest charges (during construction of factory) and working capital margin money, as also the annual turnover at full capacity are compared. The project is rated fair if the annual turnover is not less than the total cost of the project.

(x) In case the production is proposed to be taken up from intermediates which are to be imported, the CIF cost of all the imported materials per kg of the antibiotic must be less than the CIF price of the antibiotic itself. For rating a proposal fair, such costs should be atleast 20% less.

(xi) The foreign exchange balance in five years, after the commencement of production should be very favourable. In making such calculations, the foreign exchange outgo by way of import of raw materials and components, capital goods, know-how and royalty fees, profit sharing through dividend remittance if any and all other form of foreign exchange outgo linked with the project are taken into consideration. The inflow is calculated on five years production, limited to internal demand plus committed exports, if any.

(xii) The project should generate sufficient new employment.

(xiii) It is useful if raw materials and components needed for the production are tied up through sub-contracts to small scale and ancillary units.

(xiv)In general it is to be understood if adequate attention had been paid while preparing the proposal to :

(a) the availability of raw materials

(b) maximum utilisation of indigenous materials

(c) utilisation of byproducts,

(d) availability of water, power, fuel and transport, and

(e) arrangements to ensure proper treatment and disposol of effluents.

Besides, the past records of the entrepreneur in implementing other approvals, if accorded, are also taken into consideration.

(xv) Applicants attracting MRTP Act 1969 are required to get a clearance from the Department of Company Affairs. Without a clearance from the latter no further processing is possible.

In the light of the above examination carried out by the various departments of the Government including the Department of Chemicals & Fertilizers (Administrative Ministry), the Directorate General of Technical Development (DGTD), the Office of the Development Commissioner, Small Scale Industries, Directorate General of Health Services, Department of Science and Technology, the Council of Scientific & Industrial Research, National Research Development Corporation, the Planning Commission, the Finance Ministry as well as the Dept. of Company Affairs, the comments are consolidated and discussed in a Licensing Committee (LC) Meeting, Chaired by the Secretary, Ministry of Industrial Development. A decision arrived at in the L.C. requires to be ratified by various other authorities and may need the clearance from the Cabinet Committee for Economic Affairs.

An approval is accorded to the applicant, if the proposal stands on merits. If the proposal does not need further clearance such as foreign collaboration and imports of capital goods an Industrial Licence is issued straightaway. In other cases,

approval is given in the form of a Letter of Intent (LI) with certain conditions. The L.I. is valid initially for 12 months but is renewable if there is a proper justification. The applicant has within the validity period, to take further steps to submit his application for foreign collaboration as well as clearance for Capital Goods which could be done simultaneously also.

4. Foreign Collaboration :

An L.I. in hand is considered to be advantageous for an entrepreneur to meaningfully negotiate with a foreign collaborator since the latter usually demands the LI to start negotiation. Once a deal is struck, a proposal is made out and sent again to the SIA in the prescribed forms. The application may or may not accompany a draft agreement at this stage. The proposal is received by the Department of Chemicals & Fertilizers from the SIA. The concerned joint Secretary of the Department in consultation with the departmental experts can give a judgement on the case if the foreign exchange out go on know-how fees including lumpsum and royalty together are less than Rs. 50 lakhs and if further the proposal does not involve any foreign equity participation and the applicant is not a company with foreign equity.

In case the foreign exchange outgo on lumpsum and royalty fees together exceeds Rs. 50 lakhs and also if the applicant does not satisfy other conditions as mentioned above the proposal is examined by the Foreign Investment Board (FIB) Chaired by the Secretary or Additional Secretary of the Ministry of Finance where comments from all the Departments as in the case of Industrial Approvals are received.

Examination of foreign collaboration proposals is also made in the same lines as discussed earlier; in addition this time special emphasis is on the following :

(i) Content of Technology :

the content of the technology must be well understood; it must be possible to know whether or not the technology package covers supply of strain and full information on

know-how, demonstration of guarantee in the proposed plant, technical assistance in terms of training of the personnel of the recipient party as well as assistance in the construction and certification of the plant (for understanding its readiness for commercial production) of the recipient party.

(ii) Reputation of the Technology Supplier:

The reputation of the technology supplier in terms of its activities, annual turnover, past experience in collaboration, etc., is very important. Moreover, it is to be seen if the supplier has a running plant or not. If it does not have a running plant, it must have tie ups with other reputed producing firms where the technology is being exploited and where guarantees could be demonstrated. Besides, it should also be possible for the recipient to get its personnel trained in such plants. If more than one supplier of technology is known, it should be possible to ascertain why the recipient party preferred the particular source.

(iii) Cost of the technology :

The cost of the technology depends upon its content, reputation of the supplier and the importance of the product. There is no set method for ascertaining it. Usually however an acceptable percentage of the annual turnover or the project cost is taken as a rough guide for the total payments including lumpsum as well as recurring royalties. Five to eight percent are considered as the upper limits for such purposes. In certain cases the outgo on all accounts within a period of five years is calculated and is tied up with first five years production so that this does not exceed an acceptable percentage; lumpsum payments as well as recurring royalties are then apportioned from the total outgo.

(iv) Equity participation :

Policy towards permitting foreign equity participation is rather selective and it is usually discouraged to have foreign

equity above 40%. Even if foreign equity is less than 40%, the special consideration justifying the factors favourable to such participation will have to be highlighted. In case foreign equity is permitted, this has to be by way of cash and must be linked to imports of equipment or payments for know-how or others.

A proposal is cleared on merits based on the above considerations. An approval letter is made out to the company incorporating the quantum and the mode of payments, the duration of the agreement, the services to be rendered and also certain other standard conditions such as mentioned below :

(i) The Indian party should be free to sub-licence the technical know-how under the agreement to other Indian parties on terms to be mutually agreed upon by all the parties concerned including the foreign collaborator and subject to the approval of the Government.

(ii) There should be no requirement for the payment of minimum guaranteed royalty regardless of the quantum and value of production. The royalties wherever allowed will be calculated on the basis of net ex-factory sale price on the product exclusive of excise duties, minus the cost of standard bought out components and the landed cost of imported components, irrespective of the source of procurement including ocean freight, insurance, custom duties, etc. The payment of royalty at the rate mentioned above will be restricted to annual approved capacity plus 25% in excess thereof. In case of production in excess of this quantum, prior approval of Government would have to be obtained regarding the terms of royalty in respect of such excess production.

(iii) All payments shall be subject to Indian Taxes unless otherwise specified.

(iv) There should be no restrictive clause in the agreement specially in regard to exports, purchase of machinery or raw materials, sale of finished goods, etc. In certain cases

restrictive clauses for exports to certain countries are agreed upon where the collaborating firm has already a producing plant in such cases the names of the countries are to be specially mentioned in the agreement. In a few cases where initial imports of bulk drugs followed by imports of intermediates during the initial phase of production become unavoidable from the foreign collaborator due to limited source of supply, such a situation is permitted subject to the conditions that such purchases are made by open tender and that the rates from the supply sources are internationally competitive.

(v) There should be no provision for the use of foreign brand names for internal sales.

(vi) The agreement must specify the effective date and the duration of the contract. Govt do not normally favour requests for extension of the duration.

(vii) Suitable provision should be made in the agreement for the training of Indian Technical personnel in the plants of the collaborator. There should also be arrangements for R & D and other measures for the absorption, adaptation and development of the imported technology. Such measures could be undertaken through the in-house R&D facilities or similar facilities established in the National Laboratories.

(viii) If the process of the proposed item of manufacture is covered by a patent in India, it should be ensured that the payment of royalty/lumpsum for the duration of the agreement would also constitute compensation for the use of patent rights till the expiry of the life of the patent and that the Indian party would have the freedom to produce the item even after the expiry of the collaboration agreement without any additional payment.

(ix) Collaboration agreement will be subject to Indian laws.

(x) Consultancy services required to execute the project should be obtained from Indian consultancy firm.

The approval letter for foreign collaboration is valid for a period of six months,

The entrepreneur has to execute the agreement with the collaborator and the agreement must be strictly in accordance with the approval letter. Such signed agreements in 10 copies are then to be submitted by the entrepreneur to the Department of Chemicals & Fertilizers, who if after scrutiny finds them to be in order take them on record and send an intimation to the party. A copy of the agreement is also sent to the Reserve Bank of India (RBI) through the Department of Economic Affairs on the basis of which remittance to the foreign collaborator is authorised by the RBI.

5. Capital Goods :

The policy for the imports of Capital Goods is laid down in the current Import Policy Book (Green Book) published by the Office of the Chief Controller of Imports & Exports. The policy is updated every year and is valid for one year. An entrepreneur must look into the procedures to be followed in preparing his C.G. application. In general the broad procedures to be followed by an entrepreneur for importing C.G. above Rs. 10 lakhs (which is likely to be the case for setting up a basic antibiotic Industry) are as under :

(i) There is an advertisement procedure which is to be followed (for details please consult the current Hand Book of Import-Export procedures). In the advertisement the applicant must state positively quoting the relevant portion of the current Import Policy that the C.G. proposed for purchase is allowed for imports. After waiting for 45 days from the date of advertisement so as to enable the interested indigenous suppliers to contact him with their offers, the intending importer will execute an affidavit in a form given in the current Hand Book of Import-Export procedures, and swear before an appropriate judicial authority to the effect that he had advertised according to procedure. The affidavit in original and a photocopy of the advertisement should accompany the application to be made to the Chief

Controller of Imports and Exports, Udyog Bhavan, New Delhi for the grant of an import licence. There is a prescribed application form for C.G.

(ii) To enable post facto monitoring of imports, the applicant shall simultaneously send to the D.G.T.D. a statement showing full details of offers, if any, received from any of the Indian party, as well as the C.G. item proposed to be imported.

A decision is arrived at on the basis of the C.G. application in an Inter ministerial meeting headed by the C.C,I. & E. The important considerations that go in are :

(i) the C. Gs are essential and not indigenously manufactured.

(ii) the sizing of the C.G. is in accordance with the capacity sanctioned for the antibiotic manufacture.

The applicant can also call global tenders for implementing his "full project" and in such an event he need not bother for the items which are manufactured indigenously. This facility is available for certain industries and production of antibiotics from basic stage is also covered. The selection of suppliers on the basis of such global tenders, foreign or Indian will be subject to scrutiny by a Committee (Empowered Committee) set up by the Department of Heavy Industry, Udyog Bhavan, New Delhi. Comparison will be made between competitive Indian offers and foreign offers on the basis of landed cost of the latter. The recommendations of the Empowered Committee will be considered by the Department of Commerce for deciding the grant of import licence.

An import licence is issued to the applicant by the Office of the C.C.I. & E. based on which he proceeds further.

6. Industrial Licence :

Once the Foreign Collaboration and the C.G. licence are approved and other conditions of L.I. are fulfilled, the applicant can seek coversion of the L.I. into an Industrial Licence. The application is to be addressed to the S.I.A.

An Industrial Licence (I.L.) is issued to the Company (application by the Department of Industrial Development, Ministry of Industry. The I.L. is usually valid for 2 years within which period commercial production will have to be established. This period can be extended on valid grounds. The extension is accorded by the Department of Chemicals & Fertilizers. Progress of the I.L. is monitored through information received by the Government and supply of such information is mandatory on the part of the entrepreneur every six months in a prescribed form (Form G) till regular production is commenced.

Before production is taken up, it is mandatory to have approval under Drugs Act from the concerned State Drug Control Administration. This approval is different from permission under I (D & R) Act. This approval is accorded only after an I.L. is issued to the applicant and after the Drug Control Authorities are satisfied about the suitability of the production premises and other requirments of production under Drugs Act.

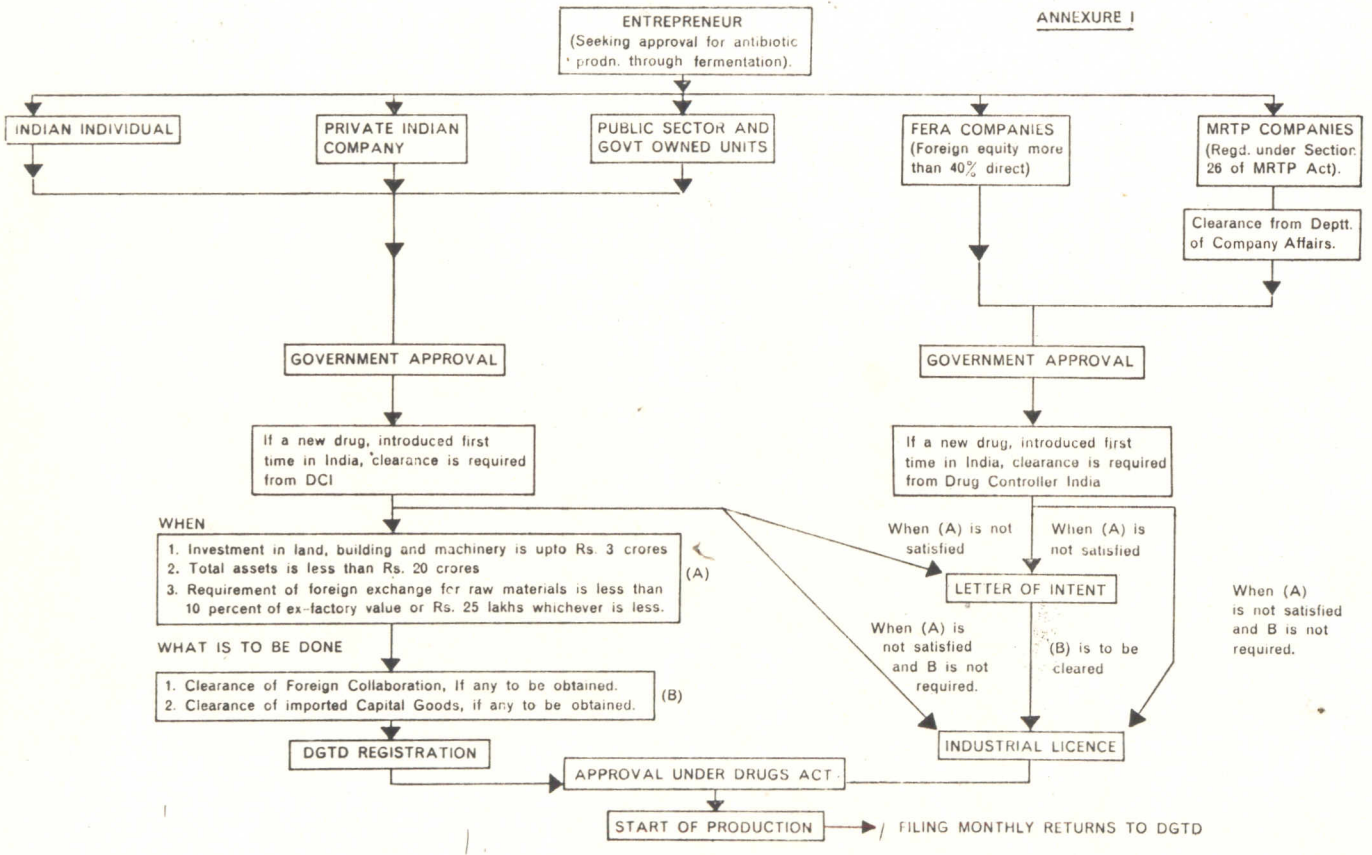
After undergoing all these formalities, the entrepreneur has to commence production. Once regular production is started, it is mandatory to send monthly production returns to the DGTD in prescribed forms.

7. Conclusion :

It will be seen from the above that several procedures are involved in obtaining an approval for the setting up of an antibiotic industry. A thorough knowledge of the Government procedures is very much necessary for the quick sanction of a project. The quality of information supplied plays a vital role in speeding up the work. Incomplete information as also superfluous documentation will only delay matters and may ultimataly cost the entrepreneur enormously.

For enabling an entrepreneur to have a quick understanding of the flow of proposals, and also procedures involved till the commencement of final production, a flow sheet is enclosed at Annexure I.

ANNEXURE I


ENTREPRENEUR
(Seeking approval for antibiotic prodn. through fermentation).
INDIAN INDIVIDUAL
PRIVATE INDIAN COMPANY
PUBLIC SECTOR AND GOVT OWNED UNITS
FERA COMPANIES (Foreign equity more than 40% direct)
MRTP COMPANIES (Regd. under Section 26 of MRTP Act).
Clearance from Deptt. of Company Affairs.
GOVERNMENT APPROVAL
GOVERNMENT APPROVAL
If a new drug, introduced first time in India, clearance is required from DCI
If a new drug, introduced first time in India, clearance is required from Drug Controller India
WHEN
1. Investment in land, building and machinery is upto Rs. 3 crores
2. Total assets is less than Rs. 20 crores
3. Requirement of foreign exchange for raw materials is less than 10 percent of ex-factory value or Rs. 25 lakhs whichever is less.
(A)
When (A) is not satisfied
When (A) is not satisfied
LETTER OF INTENT
When (A) is not satisfied and B is not required.
(B) is to be cleared
When (A) is not satisfied and B is not required.
WHAT IS TO BE DONE
1. Clearance of Foreign Collaboration, If any to be obtained.
2. Clearance of imported Capital Goods, if any to be obtained.
(B)
DGTD REGISTRATION
INDUSTRIAL LICENCE
APPROVAL UNDER DRUGS ACT
START OF PRODUCTION
FILING MONTHLY RETURNS TO DGTD