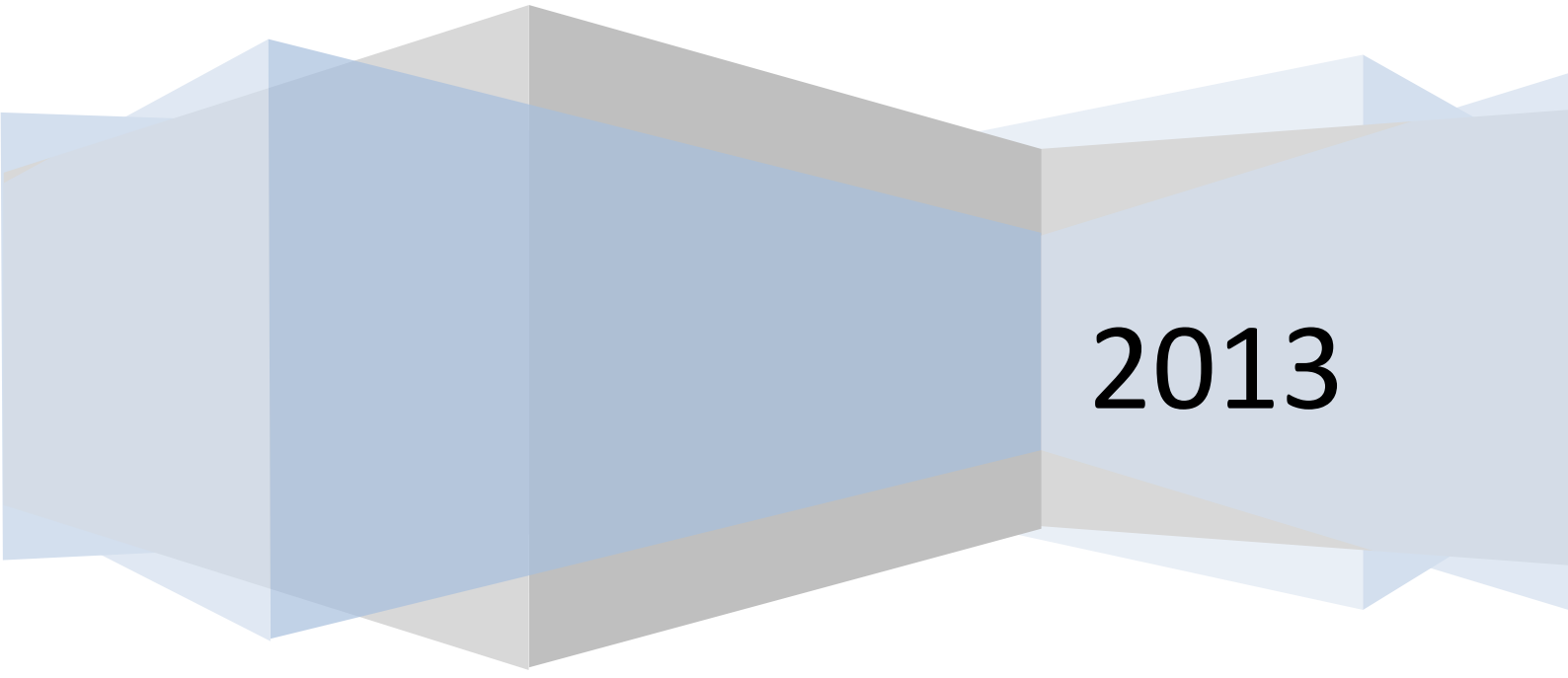
RA Consultants (SMC-Pvt) Ltd

CONTRACT MANUFACTURING

Nadeem Hussain Alamgir



2013

RA CONSULTANTS (SMC-PVT)LTD

CONTRACT MANUFACTURING

Background and Draft Policy

Nadeem Hussain Alamgir

October 14, 2013

This document reviews the current trends in Contract Manufacturing across the globe and its impact on economies of the countries. A draft Contract Manufacturing policy is also provided in the document.

CONTRACT MANUFACTURING

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EXECUTIVE SUMMARY

Contract Manufacturing is a global phenomena and is a business model practiced in many industries including, Aerospace, Defense, Semiconductors, Energy, Medical Device, Personal care products, Biotechnology and Pharmaceutical Industry. Where all the industries including medical device and pharmaceutical Industry is using the services of contract manufacturers for manufacturing of parts/some steps of manufacture and even complete manufacturing that may or may not include quality control. This practice is also referred to as outsourcing.

CRAMS (Contract Research and Manufacturing Services) have emerged in the biopharma industry in the 1980s and over the years took on a significant role in research and development, expanding from drug discovery, preclinical research to clinical trials, and pharmaceutical drug manufacturing.

Companies involved in giving contracts and those who accept those contracts do have many reasons to justify the outsourcing of their production to other companies or work as producers of products of other companies, these include Cost Savings, Mutual Benefit to Contract Site, Advanced Skills, Quality, Focus, Economies of Scale

Whereas the opponent of outsourcing does attach some risks with contract manufacturing that can include Lack of Control, Relationships, Quality concerns, Intellectual Property Loss, Outsourcing Risks, Capacity Constraints, Loss of Flexibility and Responsiveness.

However both the opponents and those favor the contract manufacturing does not deny the economic benefit of contract manufacturing. Keeping in view all the pros and cons the health authorities of developed countries and WHO favor contract manufacturing of pharmaceutical drugs and provided guidelines for contract manufacturing requirements.

Contract manufacturing or outsourcing is now a global phenomenon and is providing economic benefits not only to manufacturers but also to the countries encouraging the practices that include India, Bangladesh, China, Malaysia and South Korea. The global pharmaceutical contract manufacturing/outsourcing market is likely to swell to a whopping 150 billion by 2015. The contribution of emerging markets is expected to double by 2016, as compared to 2006. The growth in emerging markets is expected to be led by China and India in the near future (China with a CAGR of 15 per cent–18 per cent during 2012–2016 and India with a CAGR 14 per cent–17 per cent during 2012–2016).

Pakistan has a big pharmaceutical industry, manufacturing large number of common products. Compared to the market the number of manufacturing units is too large and the number of registered products is also huge. The Pakistan pharmaceutical market's worth is US & 2 Billion and according to "Pakistan Bureau of Statistics" Pharmaceutical industry of Pakistan is the 4th largest growing industry in the country after Textile/ Food, Beverages & Tobacco/ Petroleum Product.

During the nineties the (now defunct) Ministry of Health started allowing contract manufacturing for the reasons like force majors, breakdowns or for revamping of factories. Due to which a large pharmaceutical industry was established in previous years resulted in increased economic activity and provided jobs to hundreds of Pharmacists for production and quality control purposes in the manufacturing units and sales people in the franchising companies. Thousands of patients living in far flung areas where availability of drugs is

scarce and who cannot afford expensive medicines also benefited from this franchising business.

The contract manufacturing also helped in sustained availability of products use to be manufactured by Multinational Companies (MNC's) that now have lost the financial viability for the manufacturers due to increase in manufacturing cost and ever increasing burden for return against investment (ROI) to the share holders of parent organizations due to a fast depreciating Pak Rupee. This issue of reducing ROI from subsidiaries in Pakistan of MNC's in light of global deterioration of economies is resulting in decreasing financial interest for continuing businesses in Pakistan Thus in recent years we have seen disinvestment in Pakistan by some large MNC's including Merck Sharp & Dohme of Pakistan Ltd, (Merck & Co of USA) Roche Pakistan Ltd (F. Hoffman La-Roche Basal Switzerland), Bristol Mayer Squib and now Johnson & Johnson Pakistan (Subsidiary of Johnson & Johnson USA) is pulling out its investment from Pakistan.

However the uncontrolled development of this sector has also created number of problems that include availability of substandard, counterfeit and spurious medicines in the country. This has also increased tremendous burden on the meager resources of the regulatory authority (Defunct MOH & Now DRAP) and compounded with weakly trained entrepreneurs this has created a big mess.

The Contract Manufacturing Policy that was developed by DRAP is not helpful in saving the huge investment put in by the entrepreneurs in establishing the manufacturing units and also not in line with international trends and lacking in support for commercial aspect of business. Further to that the current policy is ultra vires to Article 18 of the constitution of Pakistan regarding "Freedom of trade, business or profession".

It is therefore imperative that the current policy be revised by taking into account the international practices, global guideline, local situation of the pharmaceutical industry and more importantly the freedom of trade and business enshrined in the constitution. The Business of Pharmaceutical production is also related to Article 38 of the constitution that directs the government for providing basic necessity of life including medical relief.

Under the above narrated facts it is important that the policy should focus on improving the health of industry and to protect the fundamental right of Freedom of Business & Trade. The policy should also focus on improving chances of earning forgiven exchange by the contract manufacturing Industry. For this purpose the Drug Regulatory Authority is required to make rules that may include strict adherence to cGMP requirements by both the contract giver and acceptor. However this policy shall be free of restrictions on type of drugs to be produced by contract manufacturing barring "psychotropic, narcotic products". The policy shall ensure development of the industry to meet international standards. The policy shall focus on attracting outsourcing companies from global market, like it is being done in case of India, China, Singapore, South Korea and Malaysia etc.

A well formed policy that results in gains for the industry in general & country in particular is imperative for Pakistan today more than ever because of dwindling economy of the country. Such policy will be a great service to the country by DRAP.

CONTRACT MANUFACTURING

Background

Contract Manufacturing is a global phenomena and is a business model practiced in many industries including, Aerospace, Defense, Semiconductors, Energy, Medical Device, Personal care products, Biotechnology and Pharmaceutical Industry. Where all the industries including medical device and pharmaceutical Industry is using the services of contract manufacturers for manufacturing of parts/some steps of manufacture and even complete manufacturing that may or may not include quality control. This practice is also referred to as outsourcing.

CRAMS (Contract Research and Manufacturing Services) have emerged in the biopharma industry in the 1980s and over the years took on a significant role in research and development, expanding from drug discovery, preclinical research to clinical trials, and pharmaceutical drug manufacturing.

Companies involved in giving contracts and those who accept those contracts do have many reasons to justify the outsourcing of their production to other companies or work as producers of products of other companies, these include;

- **Cost Savings** – Companies save on their cost of capital because they do not have to pay for a facility and the equipment needed for production. They can also save on labor costs such as wages, training and benefits. Some companies may look to contract manufacture in low-cost countries, such as China, to benefit from the low cost of labor.

- **Mutual Benefit to Contract Site** – A contract between the manufacturer and the company it's producing for may last several years. The manufacturer will know that it will have a steady flow of business until then.

- **Advanced Skills** – Companies can take advantage of skills that they may not possess, but the contract manufacturer does. The contract manufacturer is likely to have relationships formed with raw material suppliers or methods of efficiency within their production.

- **Quality** – Contract Manufacturers are likely to have their own methods of quality control in place that helps them to detect counterfeit or damaged materials early.

- **Focus**– Companies can focus on their core competencies better if they can hand off base production to an outside company.

- **Economies of Scale** – Contract Manufacturers have multiple customers that they produce for, therefore they can offer reduced costs in acquiring raw materials by benefiting from economies of scale. The more units there are in one shipment, the less expensive the price per unit will be.

However, the opponent of outsourcing does attach some risks with contract manufacturing that can include;

- **Lack of Control** – When a company signs the contract allowing another company to produce their product, they lose a significant amount of control over that product. They can only suggest strategies to the contract manufacturer; they cannot force them to implement them.

- **Relationships** - It is imperative that the company forms a good relationship with its contract manufacturer. The company must keep in mind that the manufacturer has other customers. They cannot force them to produce their product before a competitor's. (It is important to note that in this case most companies mitigate this risk by working cohesively with the manufacturer and awarding good performance with additional business.)

- **Quality concerns** – When entering into a contract, companies must make sure that the manufacturer's standards are congruent with their own. They should evaluate the methods in which they test products to make sure they are of good quality. The company has to rely on the contract manufacturer for having good suppliers that also meet these standards.

- **Intellectual Property Loss** – When entering into a contract, a company is divulging their formulas or technologies. This is why it is important that a company not give out any of its core competencies to contract manufacturers. It is very easy for an employee to download such information from a computer and steal it. The recent increase in intellectual property loss has corporate and government officials struggling to improve security. Usually, it comes down to the integrity of the employees.

- **Outsourcing Risks** – Although outsourcing to low-cost countries has become very popular, it does bring along risks such as language barriers, cultural differences and long lead times. This could make the management of contract manufacturers more difficult, expensive and time-consuming.

- **Capacity Constraints** – If a company does not make up a large portion of the contract manufacturer's business, they may find that they are de-prioritized over other companies during high production periods. Thus, they may not obtain the product they need when they need it.

- **Loss of Flexibility and Responsiveness** - Without direct control over the manufacturing facility, the company will lose some of its ability to respond to disruptions in the supply chain. It may also hurt their ability to respond to demand fluctuations, risking their customer service levels.

International Guidelines/Regulations.

As discussed earlier Contract Manufacturing (Outsourcing) is a commercial activity undertaken by the pharmaceutical and other industries around the world. The Regulatory Authorities in the world including WHO and EMA have formulated and implemented guidelines in order to minimize the risk associated with the outsourcing. These guidelines are followed across the globe by the industry. On the other hand the Industry is also taking

protective measures to minimize the risk associated with outsourcing specially related to intellectual property loss and quality control as any failure can hurt the global image of the company.

WHO Guidelines

A compendium of guidelines and related materials Volume 2, 2nd updated edition on "Good manufacturing practices and inspection" published in 2007 provided guidelines for contract manufacturing that are reproduced below

7. Contract production and analysis

7.1 *Principle*. Contract production and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.

General

7.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

7.3 The contract should permit the contract giver to audit the facilities of the contract accepter.

7.4 In the case of contract analysis, the final approval for release must be given by the authorized person.

The contract giver

7.5 The contract giver is responsible for assessing the competence of the contract accepter in successfully carrying out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

7.6 The contract giver should provide the contract accepter with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract accepter is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

7.7 The contract giver should ensure that all processed products and materials delivered by the contract accepter comply with their specifications or that the product has been released by the authorized person.

The contract accepter

7.8 The contract accepter must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily

the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

7.9 The contract accepter should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract accepter and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract accepter.

7.10 The contract accepter should refrain from any activity that may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

The contract

7.11 There must be a written contract between the contract giver and the contract accepter which clearly establishes the responsibilities of each party.

7.12 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

7.13 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP.

7.14 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.15 The contract should describe clearly who is responsible for purchasing, testing and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract accepter should take samples at the premises of the manufacturer.

7.16 Manufacturing, analytical, distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

7.17 The contract should describe the handling of starting materials, intermediate and bulk products and finished products if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

EUROPEAN COMMISSION

Pursuant to The Rules Governing Medicinal Products in the European Union as mentioned in Chapter 7 on "Outsourced Activities" and to fulfill the legal requirements of Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products, the "EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use" being implemented from January 31, 2013 are reproduced below;

Principle

Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality Management System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility.

General

7.1 There should be a written Contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorization for the product concerned, where applicable.

7.3 Where the marketing authorization holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.

The Contract Giver

7.4 The pharmaceutical quality system of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include:

7.5 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the Contract that the principles and guidelines of GMP as interpreted in this Guide are followed.

7.6 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in

accordance with regulations in force, and the Marketing Authorization for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

7.7 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.

7.8 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He should also ensure, either by himself, or based on the confirmation of the Contract Acceptor's Qualified Person, that all products and materials delivered to him by the Contract Acceptor have been processed in accordance with GMP and the marketing authorisation.

The Contract Acceptor

7.9 The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.

7.10 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him are suitable for their intended purpose.

7.11 The Contract Acceptor should not subcontract to a third party any of the work entrusted to him under the Contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.

7.12 The Contract Acceptor should not make unauthorized changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.
7.13 The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

The Contract

7.14 A Contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the Contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorization for the product concerned and agreed by both parties.

7.15 The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials,

undertaking production and quality controls (including in-process controls, sampling and analysis).

7.16 All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.

7.17 The Contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or his mutually agreed subcontractors.

HEALTH CANADA

Health Canada's Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2 GUI-0001 issued on March 4, 2011 to be implemented from the same date provides following guidelines for contract manufacturing as produced below;

3. To ensure compliance of contractors performing fabrication and packaging/labeling:

3.1 All arrangements for contract fabrication or packaging/labeling are in accordance with the marketing authorization for the drug product concerned.

3.2 There is a written agreement covering the fabrication or packaging/labeling arranged among the parties involved. The agreement specifies their respective responsibilities relating to the fabrication or packaging/labeling and control of the product.

3.2.1 Technical aspects of the agreement are drawn up by qualified personnel suitably knowledgeable in pharmaceutical technology, and GMP.

3.2.2 The agreement permits the distributor or importer to audit the facilities of the contractor.

3.2.3 The agreement clearly describes as a minimum who is responsible for: purchasing, sampling, testing, and releasing materials;

3.2.3.2 undertaking production, quality, and in-process controls; and

3.2.3.3 process validation.

3.2.4 No subcontracting of any work should occur without written authorization.

3.2.5 The agreement specifies the way in which the quality control department of the distributor or importer releasing the lot or batch for sale, ensures that each lot or batch has been fabricated and packaged/labeled in compliance with the requirements of the marketing authorization.

3.2.6 The agreement describes the handling of raw materials, packaging materials, in-process drug, bulk drug and finished products if they are rejected.

3.3 The contractor's complaint/recall procedures specify that any records relevant to assessing the quality of a drug product in the event of complaints or a suspected defect are accessible to the distributor or importer.

3.4 The fabricator, packager/labeler, distributor, or importer provides the contractor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The fabricator, packager/labeler, distributor, or importer ensures that the contractor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

3.5 The fabricator, packager/labeler, distributor, or importer is responsible for assessing the contractor's continuing competence to carry out the work or tests required in accordance with the principles of GMP described in these guidelines.

3.5.1 Distributors of drugs fabricated, packaged/labeled and tested at Canadian sites are required only to have a copy of the relevant valid Canadian establishment license held by the Canadian fabricator or packager/labeler or tester. Health Canada / Health Products and Food Branch Inspectorate Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2 (GUI-0001) / March 4, 2011 Page 37 of 100

3.5.2 Importers of drugs fabricated, packaged/labeled, or tested at a foreign site must meet the requirements described in Health Canada's document entitled Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites.

Global Scenario of Pharmaceutical Market:

Because of the above mentioned guidelines the contract manufacturing is flourishing across the globe. In recent years the concept of outsourcing has made considerable inroads into manufacturing, primarily because manufacturing accounts for roughly one- quarter of company costs. Manufacturing a drug places a large strain on a company's resources including time, money and manpower. Using contract manufacturing and outsourcing helps big pharmaceutical companies achieve corporate goals by saving tremendous resources that would otherwise be required for capital investment in facilities and equipment. With the development of new molecules the manufacturing processes become more complex and regulatory requirements become more burdensome, compounded with economic woes worldwide, several countries are seeking ways to minimize drug expenditures. Pharma and

biotech companies have been charged with the difficult task of minimizing drug costs, which in turn has lead them to evaluate opportunities for manufacturing outsourcing.

Various dynamics in the pharma arena are influencing companies' manufacturing and development strategies. Companies are increasingly positioning themselves to respond to needs and provide customers with efficient and simple solutions. Consumer demand is simple: they want less expensive, well-made drugs available when needed. Pharma contract research and manufacturing companies are scrambling to make this occur.

To fulfill this need the Pharmaceutical companies are increasingly relying on contract manufacturing, research, and packaging services to fulfill many basic needs and specialized competencies. The companies endeavor to save costs and product development time while simultaneously being efficient and productive.

This process often results in pharmaceutical companies dealing with other manufacturers, but these contract manufacturer need to be able to deliver a full-service offering to compete for business. For a pharmaceutical entity to strategically outsource, the company must reinvent this relationship via persistent discussions with its preferred partners on planning, common objectives, and the responsibility of operating more effectively versus key metrics. Because of this cumbersome process and to avoid complications the pharmaceutical companies are developing longer-term, more beneficial strategic deals.

Because of this trend the global pharma contract manufacturing market has generated robust growth in recent years and the future of this segment holds great opportunities for the industry. From big pharma to smaller specialty entities, contract manufacturing serves as a strategy for various industry players. Significant factors driving market growth include continued efforts to cut costs, outsourcing by pharma companies' of non-core businesses, and an increasing amount of specialty and biotech firms that do not have in-house manufacturing capabilities.

During recent years pricing pressures have driven manufacturing contractors to form operations in emerging markets. Off shoring has resulted in companies establishing facilities in India, China, Singapore, South Korea, and more recently Malaysia. Significant investment continues to flow into Asia with many western CMOs expanding operations there, especially in China. As the marketplace becomes more prices competitive, the option to outsource certain projects to lower-cost Asian regions – particularly for producing large-volume products – will become a valuable option. This trend should have a strong impact on the worldwide CMO arena.

Based on the current trends this can easily be concluded that the contract pharma market will continue to rise as companies cut costs to offset problems regarding pharmaceutical productivity trends. Non-core businesses being outsourced include manufacturing and product/process optimization.

According to study published in 2011 "the worldwide contract pharma market could generate up to $50 billion in annual revenue within the next five years. It was estimated that the worldwide contract manufacturing organization (CMO) market is growing at a rate of about 10% annually during the upcoming years. Thus between 2011 and the early part of the next decade, this market could more than double in value".

However it is believed that even though outsourcing to low-cost countries may offer considerable savings and growth possibilities, the companies accepting contracts may not have the technical or regulatory capabilities that some businesses need. For example Aseptic/sterile production and injectable manufacturing processes, require a significant investment in terms of expertise, equipment, process, technology and quality control. Thus outsourcing of high tech products to Asian countries will remain a question mark, however outsourcing of common products like Paracetamol, Diclofenac, Amlodipen etc will be a more viable choice.

GBI Intelligence report published on may 16, 2012 declares that India and China represent the fastest-growing countries in the CMO services sector having witnessed drastic changes in their government and regulatory policies that encourage pharmaceutical outsourcing in order to increase business and attract foreign clients. For example, in 2005, the Indian Biotechnology Policy issued simplified procedures for regulatory clearance and exemptions from import duties and service taxes, encouraging foreign investments within the country.

In China, the State Food and Drug Administration (SFDA) has clearly stated contract manufacturing as a long-term goal for the country's economic growth. In early 2001, Article 13 of the new edition of the "Drug Administration Law" was issued, legalizing pharmaceutical contract manufacturing in China.

It was reported that India, with more than 175 US FDA-approved and more than 80 MHRA approved manufacturing facilities, is one of the most preferred locations for outsourcing manufacturing services in India by the multinationals and global pharmaceutical companies. The Indian CRAMS (Contract Research and Manufacturing Services) market was valued at US$2.5 billion in 2009 and is expected to reach US$7.6 billion by 2012, growing at a CAGR of 47.2% (2007-2012). Out of the total CRAMS market, contract research stood at US$0.9 billion in 2009 and is expected to touch US$3.4 billion, reflecting a CAGR of 62.51% (2007–2012). The contract manufacturing segment of CRAMS market was at US$1.6 billion in 2009 accounting for the major share (approximately 64%) of the total Indian CRAMS market.

Bangladesh in its Drug Policy formulated and implemented since 2005 encouraged contract manufacturing even for foreign companies not having plants in Bangladesh for the purpose of technology transfer and also allows contract manufacturing for the foreign companies for the purpose of Export only. This policy has resulted in a number of FDA, MHRA Approved Plants in Bangladesh. This has also improved the quality of medicines produced by manufacturers.

Pakistan Scenario of Pharmaceutical Market

Pakistan has a big pharmaceutical industry manufacturing large number of common products. Compared to the market the number of manufacturing units is too large and the number of registered products is also huge.

During the nineties the defunct Ministry of Health started allowing contract manufacturing for the reasons like force majore, breakdowns or for revamping of factories. To give a legal protection to the process of "Contract Manufacturing" a Rule (20-A) was added in the Drugs (Licensing Registration & Advertising) Rules 1976 vide SRO 470 (I) 98 dated 15 May 1998. For giving effect to the rule and for operational purpose a schedule "H" (formerly "G") Was

also inserted in the above mentioned rules vide the same SRO. Due to this flexibility the industry started approaching the defunct Ministry for getting contract manufacturing permission for all sort of products. This policy also resulted in growth of pharmaceutical units across the country for the purpose of contract manufacturing and another type of business named as "Franchising" in which the manufacturing units produce the products for individuals who sell the products through marketing to their set of customers.

This development on one hand increased economic activity and on the other provided jobs to hundreds of Pharmacists for production and quality control purposes in the manufacturing units and sales people in the franchising companies. Thousands of patients living in far flung areas where availability of drugs is scarce and who cannot afford expensive medicines also benefited from this franchising business.

The contract manufacturing also helped in sustained availability of products use to be manufactured by Multinational Companies (MNC's) that now have lost the financial viability for the manufacturers due to increase in manufacturing cost and ever increasing burden for return against investment (ROI) to the share holders of parent organizations due to a fast depreciating Pak Rupee. This issue of reducing ROI from subsidiaries in Pakistan of MNC's in light of global deterioration of economies is resulting in decreasing financial interest for continuing businesses in Pakistan Thus in recent years we have seen disinvestment in Pakistan by some large MNC's including Merck Sharp & Dohme of Pakistan Ltd, (Merck & Co of USA) Roche Pakistan Ltd (F. Hoffman La-Roche Basal Switzerland), Bristol Mayer Squib and now Johnson & Johnson Pakistan (Subsidiary of Johnson & Johnson USA) is pulling out its investment from Pakistan.

Unfortunately the huge pharmaceutical industry is not in a position to sustain by itself after the disinvestment of MNC's from Pakistan as almost all the local manufacturers are producing only the generic (me-too) brands of MNC's and non of the manufacturers have invested in research & development (R&D) for new molecules. Further to that the cGMP practices are very weak compared to the minimum practice adhered to by the MNC's.

The uncontrolled development of this sector has also created number of problems that include availability of substandard, counterfeit and spurious medicines in the country. This has also increased tremendous burden on the meager resources of the regulatory authority (Defunct MOH & Now DRAP) and compounded with weakly trained entrepreneurs this has created a big mess. Thus it is imperative that the local pharmaceutical industry be developed in line with the international standards to be ready for attracting outsourcing (contract manufacturing) by international manufacturers already investing in India, China and Malaysia. This will not only help in improving standards of manufacturing but also help the government exchequer by increased inflow of foreign exchange.

The DRAP in order to improve the current situation is trying its level best to devise policies that can help improve controls and ensure provision of Quality medicines to the people of Pakistan. For the said purpose after consultation with the Industry the Authority developed a Contract Manufacturing Policy that was circulated to the stake holder in February for implementation. However this policy is not helpful in saving the huge investment put in by the entrepreneurs in establishing the manufacturing units and also not in line with international trends and lacking in support for commercial aspect of business. Further to that the current policy is ultra vires to Article 18 of the constitution of Pakistan regarding

“Freedom of trade, business or profession”. The Article clearly states that “Subject to such qualifications, if any, as may be prescribed by law, every citizen shall have the right to enter upon any lawful profession or occupation, and to conduct any lawful trade or business:

It is therefore imperative that the current policy be revised by taking into account the international practices, global guideline, local situation of the pharmaceutical industry and more importantly the freedom of trade and business enshrined in the constitution. The Business of Pharmaceutical production is also related to Article 38 of the constitution that directs the government for providing basic necessity of life including medical relief.

Under the above narrated facts it is imperative that the policy should focus on improving the health of industry and to protect the fundamental right of Freedom of Business & Trade. The policy should also focus on improving chances of earning forgiven exchange by the contract manufacturing Industry.

For this purpose the Drug Regulatory Authority is required to make rules that may include strict adherence to cGMP requirements by both the contract giver and acceptor. However this policy shall be free of restrictions on type of drugs to be produced by contract manufacturing barring “psychotropic, narcotic products”. The policy shall ensure development of the industry to meet international standards. The policy shall focus on attracting outsourcing companies from global market, like it is being done in case of India, China, Singapore, South Korea and Malaysia etc.

This development thus undertaken by DRAP will help economic growth of country in shape of attracting foreign companies for contract manufacturing, thus earning of foreign exchange and duties and taxes collected by the government. The proof of this is evident from development of a Contract Manufacturing Industry for foreign companies and earning of foreign exchange by both India & Bangladesh. This development also resulted in 175 FDA approved plants in India and about a dozen plants approved by FDA & MHRA in Bangladesh.

A well formed policy that always results in gains for the industry in general & country in particular is imperative for Pakistan today more than ever because of dwindling economy of the country. Such policy will be a great service to the country by DRAP.

PROPOSED CONTRACT MANUFACTURING POLICY

Principal

The contract manufacturing policy shall focus on adherence to constitution and the Drugs Act 1976. It shall result in improvement of general health of the industry and increase in business activity viable for economic growth of the country.

The policy shall be free of discrimination and shall treat the national and multinational industry at par with each other. The policy while improving economic activity shall ensure Quality, Efficacy & safety of the products produced in Pakistan and shall facilitate collaboration with foreign companies not having manufacturing facilities in Pakistan for production of their products and marketing of the same in the country. The facility shall also ensure toll/contract manufacturing for foreign companies not having plants in Pakistan for the purpose of marketing of the products in the countries of origin of the respective countries.

1. **Types of Contracts**

   In pursuance of Rule 20(A) of Drugs (Licensing Registration and Advertisement) Rules 1976, following types of Contract/Toll Manufacturing is allowed on the basis of human to human and veterinary to veterinary manufacturers of registered drugs;

   a. Contract/Toll Manufacturing is allowed between two licensed manufactures having licensed units in Pakistan on Short term bases for the reasons like breakdown / renovation / improvements / up gradation etc. in licensed manufacturing units for a reasonable time agreed by DRAP to complete the work done to move back to own manufacturing facility. This permission once accorded will not be extended for any reason whatsoever. Firm will be bound to submit progress report of eradicating reasons like breakdown / renovation / improvements or up gradation on which this concession was granted, after every 6 months for consideration of Registration Board.

   b. Contract/Toll Manufacturing is also allowed on long term bases between two licensed manufactures for a renewable period of a five years term each, for the products become non viable for production at the plant of registration holder due to financial viability, expansion constraints, line extensions or introduction of new molecules to be manufactured at the existing site rendering increased capacity constraint.

   c. Contract/Toll manufacturing can also be done for foreign companies not having plants in Pakistan for the purpose of marketing in Pakistan or for export to the country of origin for marketing purpose.

      "Provided that the permission given to foreign companies who wish to market their products in Pakistan the permission will be accorded only on the bases of assurance for setting up their own plant in Pakistan within a maximum period of 10 years."

d. To encourage local production of imported registered drugs, importers will be allowed for contract manufacturing of their registered drugs from local manufacturer having facilities to manufacture these drugs.

e. To encourage exports contract manufacturing permission will also be granted for export from any local manufacturers capable of manufacturing those drugs. However such drugs will be registered for Export only and sale of these drugs will not be permitted in the local market, and in case of violation contract manufacturing permission and registration of product will be withdrawn in addition to other legal proceedings. Moreover exporter will be required to furnish confirmation about receiving of stock in importing country after export.

f. Contract/Toll Manufacturing will not be allowed for Psychotropic & Narcotic Drugs in finished form.

g. In any case the total number of contract manufactured products must not exceed twenty (20) for a contract giver and fifty (50) for contract manufacturer provide contract acceptor has a surplus capacity duly verified by DRAP.

2. Procedure for application

2.1 The Contract giver submit an application explaining reason of contract manufacturing requirement and a written contract between the contract giver and acceptor and consent of the acceptor with a prescribed fee for each product to be manufactured on the bases of Contract/Toll manufacturing.

2.2 After getting itself satisfied the DRAP will cause the facility of contract manufacturer be inspected by an expert panel consisting of an independent expert of international repute. The scope of inspection will be evaluation of cGMP compliance for manufacturing, quality control, validation, stability and storage facilities etc of the contract manufacturers. The purpose of inspection would be to encourage and promote the cGMP compliance on part of contract giver and contract manufacturer.

2.3 DRAP will also encourage the manufacture of those drugs which either remain short or produced in insufficient quantity to meet the public demand. For this purpose DRAP may incorporate few drugs in the contract manufacturing list of any pharmaceutical unit, if it is required in public interest.

2.4 If the DRAP is satisfied, that all conditions of Contract manufacturing policy are fulfilled, than it will allow the requisite permission for a period as specified in this policy.

3. Conditions for Contract Manufacturing.

3.1 All the provisions of SRO 470(1)98, dated 15th May, 1998 (Schedule-G) and

Rule 20(A) and Schedule "B" of Drugs (Licensing, Registering & Advertising) Rules, 1976 shall be applicable on contract manufacturing.

3.2 Both the contract giver and contract acceptor shall be liable for the contract manufactured drugs and both will submit a signed agreement containing the following clauses;

a. The written contract between the contract giver and the contract accepter shall clearly establish the responsibilities of each party.

b. The contract must clearly state the authorized person responsible for releasing of each batch of product for sale or issuing the certificate of analysis. Such person shall assume full responsibility of the product quality and ensures that each batch has been manufactured, and checked for compliance with the conditions of registration.

c. Technical aspects of the contract should be drawn up by competent persons having suitably knowledgeable in pharmaceutical technology, analysis and cGMP requirements.

d. All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

e. The contract should clearly describe, who is responsible for purchasing, testing and releasing the production materials (raw & packaging) and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. .

f. Manufacturing, analytical, distribution records and reference samples should be kept by contract acceptor and also be available to the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

g. The contract should describe the procedure to be followed if the contract analysis shows that the tested product must be rejected. It should also describe the handling of starting materials, intermediate and bulk products and finished products in case of rejection.

h. The Contract should have a detailed SOP for Recall of defective products from the market, clearly defining the responsibilities and procedure for such Recall including responsibility for communication with DRAP and the public if necessary or if instructed by the authorities.

3.3 Each contract manufacturing permissions already granted to various firms will be reviewed and approved by the Registration Board subject to fulfillment of these guidelines.

3.4 All pending applications and new applications shall be processed by the Registration Board, according to these contract manufacturing guidelines.

3.5 Both the contract giver and the contract acceptor shall retain 20 samples of each batch till the expiry of the product for reference.

3.6 Contract manufacturer shall submit the detail of production of each batch of the contract manufactured drug to the area FID including the copy of supply order and invoice / warranty issued to the contract giver.

3.7 Area FID shall maintain the record of each firm for the products manufactured on contract basis and monthly report shall be submitted to the Registration Sections, where record shall be maintained for each firm.

3.8 Contravention to any provision of this policy by the contract giver or contract acceptor shall lead to the cancellation of contracts by the Registration Board.

3.9 If any sample manufactured on contract basis is declared substandard / adulterated / spurious, case will be processed as per proceedings laid down in the law.

3.9 In case of change of source of raw material / machinery by the contract manufacturer, a change control instrument will be raised for such change by the contract acceptor or contract giver as the case may be, duly approved by the authorized persons of both.

3.9 The change as mentioned above will require stability studies & proper validation to be conducted that shall be duly approved by the authorized person of the contract giver. Report to this effect shall be submitted to the Registration Section and concerned official for record.

3.10 Change of contract manufacturer will not be allowed during contract period except once in five years and only on genuine reason. In case of change of contract manufacturer once, following conditions would apply and following steps will be observed:

- New contract manufacturer shall ensure that the trial batches be manufactured as per ICH guidelines for stability and validation of the product. The commercial batches cannot be manufactured before the results of stability study and validation are finalized. However a manufacturer already manufacturing same molecule and having the record of requisite studies will not be required conduct new validation testing.

- In case the previous contract manufacturer is still manufacturing the drug after change of its status, then it would be treated as Spurious Drug and legal action shall be taken accordingly.

4. Fee for contract manufacturing permission will be Rs.50000/- per product or as revised by DRAP from time to time.

5. Contract Manufacturing for Franchising Business

A new business that is flourishing and named as franchising is still not regulated but is important for the economy of Pakistan. This type of business helps in availability of medicines to people in areas where there are no distribution network established by the distribution companies. Thus this helps in sustaining life of patients requiring essential medicines.

However because the business is hitherto obscure from the application of law therefore it is required that contract policy shall also cover this aspect. The following clauses may be made part of the policy to regulate the franchising business.

5.1 The manufacturers doing business through franchisers shall register their franchisers with the local office of DRAP including the list of products to be marketed through franchisers and keep the record of all batches sold through franchisers till one year after the date of expiry of each batch.

5.2 There should be a written contract between the manufacturer and the franchiser that should be submitted along with the registration of franchiser to the local office of DRAP.

5.3 The franchiser should obtain DSL as prescribed by Drugs Act 1976 and shall have a qualified person for handling of the products sold through the franchise.

5.4 The franchiser should obtain a Drug Sale Warranty as per drugs act 1976 from the manufacturer for each batch purchased.

5.5 The franchiser shall maintain a physical office and shall keep record of all business transactions and are liable to produce the same when required by an inspector authorized under the Drugs Act 1976 or rules framed there under.

5.6 The franchiser shall ensure compliance to Schedule “G” of Drugs (licensing, Registration & Advertisement) Rules 1976 on Ethical promotion of drugs.