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REGULATORY DEVELOPMENTS

CMOs Find Valuable New Tool in Risk-MaPP

Earlier this year, the International Society for Pharmaceutical Engineering (ISPE) published its document entitled *Baseline Guide: Risk-MaPP–Risk-Based Manufacture of Pharmaceutical Products* in an effort to provide a scientific risk-based approach to manage the risk associated with cross contamination while manufacturing multiple products in the same facility. The document is designed to help manufacturers deal with the increased volume of highly potent compounds, including hormones, cytotoxic compounds, genotoxic compounds and live vaccines.

Risk-MaPP is based on the ICH Q9 Quality Risk Management document, and incorporates elements of the ICH Q8 Pharmaceutical Development and the ICH Q10 Pharmaceutical Quality System documents. It is intended to guide manufacturers through the risk assessment process and adoption of control strategies on a case-by-case basis in order to meet acceptable limits for cross contamination at a multi-product facility.

Oso Biopharmaceutical Manufacturing (Albuquerque, N.M., USA) was one of the early adopters of Risk-MaPP. In fact, the company was highlighted as a case study for implementation of quality risk management procedures at the ISPE conference last year. Four years ago, Oso first became involved with the program after hiring Julian Wilkins, VP, PharmaConsult US, and the head of the ISPE containment committee, as an independent consultant to evaluate its manufacturing processes.

"We first got started with Risk-MaPP when Julian came out and assessed our facility on its ability to manufacture highly hazardous compounds," explained Kimberly Ray, senior manager, Lean Sigma Six Black Belt – Project Management & Customer Service, at Oso. After this initial visit, the company compiled an action item list and formed teams to address the items on the list.

"Once we got our hands around what it was going to take, we brought Julian back out and we looked at our worse-case scenario product for the facility. At the time, it was a highly potent API that was a lyophilized powder," continued Ray. "We walked through every step of the production process, from bringing in the raw materials through shipping the product. For each step in the process, we looked at the potential for any one of the four types of cross contamination – mix-up, retention, airborne sedimentation, and mechanical transfer – to occur. Then we used the failure mode and effects analysis (FMEA) risk-based assessment tool to give each step a priority number."

This was a very robust process that took almost nine months to complete. Oso scored the entire model, ranking each event by severity, occurrence and detection. These rankings were then used to calculate risk priority numbers. "Any score from 0 to 100 was considered acceptable. A score from 101-200 required investigation, and anything above 200 required immediate attention," explained Ray.

Oso's initial site-wide assessment of its capability to handle a highly hazardous compound at its facility is now used as the basis for analysis when the company considers bringing in any new hazardous products. "If there are any outliers [after comparing the assessment results for a new potential product with those from our original assessment], then we evaluate those from a gap assessment perspective" continued Ray. "In other words, we use the Risk-MaPP approach when we assess whether we can bring a new product into the facility, and to identify any minor modifications that need to be made to how we routinely practice."

Advantages Become Clear

Oso has seen great value in the adoption of Risk-MaPP from both a manufacturing and business perspective. "From a business standpoint, Risk-MaPP provides a science-based tool that allows us to evaluate how we bring a product into our multi-purpose facility," commented Milton Boyer, VP, Business Development, at Oso.

"Risk-MaPP gives manufacturers more flexibility in how they operate and design their facilities. It provides the scientific rationale and control mechanisms to manage risk without the use of dedicated or segregated facilities," explained Stephanie Wilkins, President, PharmaConsult US, and leader of the document's worldwide task team.

"Dedicated facilities and dedicated systems are not always available, or are not always prudent financially or otherwise for every product, especially products in development," continued Boyer. "Risk-MaPP is a science-based mechanism that companies can use to determine if they can put a product into a particular facility. On one end, the company may have thought that a product could not be produced in its multipurpose facility and realize that it could. Or, on the other end, the company may end up saying no to a product that they originally thought could fit. Not only does Risk-MaPP give a science-based approach to evaluate this, it also allows companies to generate data for clients and regulatory agencies that support their decisions."

Several other CMOs have begun adopting these practices in their facilities as the benefits of this approach become clear. The advantages of incorporating the Risk-MaPP guidelines include a better understanding of a facility's processes and capabilities, in addition to the products being manufactured at the site. This approach also enables a thorough understanding of the point at which products and processes pose the least amount of risk. This allows CMOs to make decisions based on this understanding and eliminates over-engineering of both facilities and processes, which saves money and time.

However, adoption of this approach is not something that can be achieved overnight. "There is a lot of work and potential capital that needs to be expended to meet all the intentions of ICH Q9," commented Terry Novak, president, **Norwich Pharmaceuticals** (Norwich, N.Y., USA), which has begun implementing some of the measures outlined in the Risk-MaPP guidelines.

For CMOs interested in adopting these practices, Oso offers advice based on the lessons it learned during the implementation process. "My advice to any company adopting Risk-MaPP is: Don't try to eat the elephant all at once. Companies must understand that it is going to take an extensive amount of time and that senior management has to absolutely buy into this process 100%," advised Ray. "From an execution perspective, my advice is to start small and work big. Walk though the Risk-MaPP guide step-by-step and remember that communication is key."

Boyer continued, "Some education internally about Risk-MaPP is crucial for any company adopting these practices. It is very important to define what the system is and what each step involves, and then communicate each step while you are doing it."

Regulators and Clients Get On Board

From the beginning, Oso recognized the importance of selling this approach to the regulatory agencies before its clients. The company commented that Risk-MaPP has been well-received by both the FDA and EMA. It has had product-specific requests for audits from the EMA and has undergone a general inspection by the FDA since implementation. "Before seeking client input, we sought acceptance from the regulatory agencies," explained Boyer. "The acceptance by regulators has been validated by [positive] inspections and by the renewal of certificates for manufacture. [Both agencies] were very pleased with what we provided to them, and there were no major issues with our risk-based approach to bringing in difficult-to-handle compounds to our facility." Additionally, representatives from both agencies have presented at the *Dedicated Facilities, Cross Contamination and the Risk-MaPP Approach* conferences in Brussels, Belgium, and Washington, D.C., USA, where Risk-MaPP was discussed as a reference document.

However, a large part of the puzzle for CMOs adopting Risk-MaPP is getting clients to embrace the new changes at their facilities. Mike Ruff, VP, Pharmaceutical Development, **Metrics** (Greenville, N.C., USA) explained, "Risk-MaPP … reinforces the need for CMOs to not only be compliant with ICH Q9 but also more proactive in advising their clients how to comply." Metrics began adopting a risk-based approach at its facility after ICH Q9 was issued in June 2006. "The potential for cross contamination is always a concern for our clients. We must satisfy each potential client's [concerns, and explain] that our facility, equipment, procedures and personnel work together to minimize any cross-over" continued Ruff, who added that Metric's clients have been generally accepting of its implementation of the Risk-MaPP guidelines.

Novak commented that Norwich Pharmaceutical's clients have been very supportive of the adoption of these guidelines, but explained that clients want assurance that cleaning validation is robust and that air handling is not being re-circulated from adjacent areas.

To provide this level of assurance, Oso has set up a special review process for current and potential clients during which the company outlines the quality risk management plan for its facility, for a client's product and for any new product entering the facility that might affect that of the client. "The feedback has been mixed and across-the-board. I think a lot of it has to do with the risk profile of each individual client's product, as well as their background, approach, and knowledge of what is going on within the industry," explained Boyer. "We have not had any client that has chosen not to manufacture here because of [our risk-based approach]. While most clients have accepted it, some have been more hesitant than others and have asked for more details. So, it hasn't been an overnight acceptance by any means."

Wilkins concluded that, although gaining client acceptance may be difficult in the beginning, the adoption of Risk-MaPP will eventually serve as a good marketing strategy for CMOs. "It allows CMOs to say, 'We will take care of your product and make sure it is not compromised,' " she said.

For more information on the business and capabilities of Oso Biopharmaceutical Manufacturing, LLC, click on this box or go to www.pharmsource.com and search by company name. If you need your access codes, just call 1-703-383-4903 (ET).

For more information on the business and capabilities of Norwich Pharmaceuticals, Inc., click on this box or go to www.pharmsource.com and search by company name.

For more information on the business and capabilities of Metrics, Inc., click on this box or go to www.pharmsource.com and search by company name.

COMMERCIAL DOSE MANUFACTURING

Aenova Takes Over SkyePharma Site

Aenova Holding (Kirchberg, Switzerland) has leased SkyePharma's tablet manufacturing facility in Lyon, France. As part of the agreement, Aenova will continue to manufacture products at the site that incorporate SkyePharma's drug delivery technologies. Solid dose products on the market that are manufactured at the Lyon site include Sular (Sciele Pharma), Triglide (Sciele Pharma), Lodotra (Horizon Pharma), Coruno (Therabel), and Zyflo (Cornerstone Therapeutics).

The Lyon facility will be Aenova's first solid dose facility authorized to manufacture products for the U.S. market. Aenova has a softgel facility in Miami, Fla., USA.

Aenova was formed through the combination of two European-based CMOs, **SwissCaps** and **Dragenopharm**; it had revenues of EUR 250 million (USD 350 million) in 2010 and 1500 employees.

For more information on the business and capabilities of Aenova Group, click on this box or go to www.pharmsource.com and search by company name.

Cenexi Takes Over Osny Pharma

Cenexi (Paris, France) apparently has taken over **Osny Pharma** (Osny, France). The development has been reported by the French pharma blog Actulabo, but Cenexi has not yet officially announced the takeover. However, visitors to the Osny Pharma website are redirected to the Cenexi website. According to Actulabo, Osny Pharma had applied to the French courts for bankruptcy protection in March of this year.

Osny Pharma specialized in the manufacture of high potency solid dose products, especially hormone products. Catalent sold it in 2009 to the German private equity firm Bavaria Industriekapital. Osny Pharma's revenues were about EUR 20 million at the time of the sale, but had fallen to EUR 11 million last year after the loss of key clients, including Takeda and Grunenthal, according to Actulabo.

For more information on the business and capabilities of Cenexi, click on this box or go to www.pharmsource.com and search by company name.

For more information on the business and capabilities of Osny Pharma SAS, click on this box or go to www.pharmsource.com and search by company name.

Commercial Dose Manufacturing in Brief

Catalent Pharma Solutions (Somerset, N.J., USA) announced the expansion of its 2 to 8 degrees Celsius and -80 degrees Celsius storage capabilities at its facilities in Bolton, UK and Schorndorf, Germany. The expansion projects are to be completed by the end of 2011.

Famar (Athens, Greece) completed the integration of the solid dose and sterile manufacturing site in Madrid, Spain that it recently acquired from sanofi-aventis. The two companies entered a supply agreement under which Famar will provide sanofi-aventis with products manufactured at the site. Famar intends to expand the plant's sterile non-injectable product capabilities with the addition of a new 1000-square-meter sterile core that includes two compounding rooms and three filling and packaging lines. The additional capacity will be dedicated to the production of sterile ophthalmic and nasal spray products, with an annual capacity of 30-35 million units. The expanded area will be operational by Q4 2011.

Haupt Pharma (Berlin, Germany) announced the addition of a third line for inspecting 1 ml ampoules at its Gronau, Germany site. The line will have an optoelectronic inspection system for detecting sub-visible particles and an automatic leak detection system. Haupt also has inspection lines for 3-50 ml ampoules and 5-20 ml ampoules.

Pharmalucence (Bedford, Mass., USA) announced the addition of a Bosch isolated pharmaceutical filling line to its new production facility being constructed in Billerica, Mass., USA. The company expects that the line will be available for commercial production by early 2013.

SIDE EFFECTS

Side Effects identifies CMOs and CROs that might be impacted by key events affecting their clients, including company acquisitions, product acquisitions and licenses, product approvals, late clinical product terminations and FDA rejections.

Contractor	Pharma Company	Event	Product	Relationship
Potentially Positive				
Patheon	Gentium S.p.A.	Gentium submits an NDA for defibrotide	Defibrotide	Injectables manufacturing
Lonza Group	Human Genome Sciences	Human Genome Sciences receives European marketing authorization for BENLYSTA.	BENLYSTA	Process development, cell culture
Therapex	Apricus Biosciences	Apricus Biosciences files for Swiss marketing approval of Vitaros	Vitaros	Semi-solid & liquid manufacturing
Patheon	QRxPharma	QRxPharma files an NDA with the FDA for MoxDuoIR	MoxDuoIR (Q8003IR)	Solid dose manufacturing
PPD	Takeda Pharmaceutical	Takeda resubmits an NDA for alogliptin	NESINA (alogliptin)	Analytical chemistry and stability
Patheon	Janssen Biotech	Janssen receives approval from Health Canada for ZYTIGA	ZYTIGA (abiraterone acetate)	Solid dose manufacturing
E-Z-EM Canada	Apricus Biosciences	Apricus Biosciences files for marketing authorization to sell Vitaros in Latin America	Vitaros	Semi-solid & liquid manufacturing
WuXi PharmaTech	Vertex	Vertex receives FDA approval for Incivek	Incivek (telaprevir)	Solid dose manufacturing

Source: PharmSource Lead Sheet

CLINICAL DOSE MANUFACTURING AND PACKAGING

Parent Plans to Grow PharmaForm but Resources Tight

After shutting down its one remaining proprietary product development program, **AKELA Pharma** (Austin, Texas, USA) has announced plans to focus on its contract services business, **PharmaForm** (also in Austin). However, AKELA will have to navigate some difficult financial waters to make that happen.

AKELA recently announced that it has ended its development program for Fentanyl TAIFUN after its Japanese partner Teikoku served notice that it was terminating the development and licensing agreement. AKELA said it is negotiating with its other licensing partner, Janssen Pharmaceutica, for return of product development rights, and will seek buyers for the Fentanyl TAIFUN assets.

With the termination of the Fentanyl TAIFUN program, AKELA no longer has need for its development operations in Finland, and the Finnish subsidiary has filed for bankruptcy protection. The subsidiary owes USD 6.2 million to a Finnish government agency for loans and subsidies that were provided in support of the development activities at the facility.

Focus on PharmaForm

In its announcement, AKELA said its strategic focus is now on PharmaForm business, which provides formulation development and clinical scale manufacturing for solid dose products. The business is built on PharmaForm's capabilities in drug development, especially bioavailability enhancement technologies including hot melt extrusion (HME) and spray drying. PharmaForm had revenues of USD 3.5 million in Q1 2011, up 80% from USD 1.95 million in Q1 2010, and had an operating profit of USD 1 million.

AKELA says it will grow via expanded business development, commercial manufacturing, capacity expansion and targeted acquisitions. PharmaForm is expanding its small-scale HME capacity with the purchase of 16mm and 18mm extruders, and plans to add a 27mm extruder for Phase III and pilot scale manufacture later this year. It has been named by Corcept Therapeutics as the commercial manufacturer on its NDA for Corlux, a product for treating Cushing Syndrome.

What it means

Financial realities could interfere with AKELA's plans for PharmaForm. As of March 30, 2011, the company had just USD 140,000 in the bank and USD 1.6 million in accounts receivable against USD 16.5 million in debt and accounts payable (the bankruptcy of the Finnish subsidiary could reduce the debt by USD 6.2 million if fully forgiven). AKELA also has several judgments outstanding that could increase what it owes.

While PharmaForm is apparently growing and profitable, AKELA will no doubt need additional investment to achieve its potential and put the company on stable footing. The company was rumored to be looking for investors or an outright sale for PharmaForm earlier this year, but no transaction has been announced as yet.

We are aware that there are a number of potential buyers looking for CDMO acquisitions currently. The PharmaForm business would appear to be attractive on an operating basis, but the financial structure could be a deterrent.

For more information on the business and capabilities of PharmaForm, LLC, click on this box or go to www.pharmsource.com and search by company name.

Clinical Dose Manufacturing and Packaging in Brief

JHP Pharmaceuticals (Parsippany, N.J., USA) entered into a contract manufacturing agreement with an undisclosed company to produce clinical trial batches of a heart failure treatment. The drug will be manufactured at the company's sterile injectables facility in Rochester, Mich., USA.

Pharmaceutics International, Inc. (Pii – Hunt Valley, Md., USA) announced the expansion of its services portfolio with the addition of hot melt extrusion to its formulation and process development capabilities. Pii added 16mm and 18mm extruders. The addition will allow the company to conduct feasibility studies using a minimal amount of API, and to offer pilot scale cGMP production for Phase I and II clinical trials.

Scil Technology opened a new service unit, **Formycon** (Martinsried, Germany), which will offer liquid, freeze-dried, liposomal and specialty formulation development services, as well as drug product manufacturing, process development, quality control and analytics. Formycon will provide protein characterization, preformulation, formulation development, product manufacture and analytics under GMP and non-GMP conditions.

Sherpa Clinical Packaging (San Diego, Calif., USA) opened its new cGMP production facility in San Diego, Calif., USA, next to the site of **Althea Technologies** (San Diego, Calif., USA). In March 2011, the two companies entered a partnership whereby Sherpa will provide labeling, packaging, storage and distribution services to clients of Althea Technologies. The new facility houses five controlled access and monitored packaging suites, along with 2 to 8 degrees Celsius and -20 degrees Celsius storage areas. Sherpa plans to hire additional employees to staff the site.

API – BIOMANUFACTURING

Angel Biotechnology (Northumberland, UK) announced the appointment of an engineering firm to design the expansion of its cell therapy manufacturing capabilities at its newly acquired facility in Cramlington, UK. The company will increase its cell therapy manufacturing capacity five-fold at the facility, which is expected to be operational by early 2012.

Angel Biotechnology also hired **BioProcess Technology Consultants** (Acton, Mass., USA) to provide business development and marketing services in North America for its cGMP cell therapy manufacturing capabilities.

CEVEC (Cologne, Germany) raised EUR 6 million (USD 8.52 million) in a financing round. The funds will be used to advance the company's protein and vaccine commercialization business, and its proprietary CAP Technology platform. The platform is used for the manufacture of complex biologics and therapeutic antibodies with human-like glycosylation and sialylation patterns. CEVEC intends to offer vaccine development services to partnering companies using the platform.

Laureate BioPharmaceutical Services (Princeton, N.J., USA) announced that it has entered into a multi-year development and manufacturing agreement with an undisclosed generic pharmaceutical company to produce a biosimilar product. Laureate intends to complete the first batch of clinical product during H1 2012. Financial details were not disclosed.

Lonza (Basel, Switzerland) entered into a contract manufacturing agreement with IMMUNE Pharmaceuticals to produce clinical supplies of Bertilimumab (iCo-008) at its mammalian development facility in Slough, UK. Bertilimumab, a human immunoglobulin monoclonal antibody intended for the treatment of several inflammatory disorders, will be evaluated in a Phase II trial.

Lonza also entered into a process development and scale-up agreement with Genesis Biopharma to produce CONTEGO, Genesis Biopharma's autologous cell therapy designed for the treatment of Stage IV metastatic melanoma.

SynCo Bio Partners (Amsterdam, the Netherlands) announced the expansion of its Class A zone services in its aseptic filling facility in Amsterdam. SynCo's aseptic filling facility offers filling and lyophilization services for a range of biopharmaceuticals, including proteins, monoclonal antibodies, polysaccharides, nucleic acids, aluminum-containing vaccines, RNA and live biotherapeutics. The company supplies clinical and commercial scale quantities.

API – SMALL MOLECULE

Corden Pharma Adds Peptide Capability

The International Chemical Investors Group (ICIG), the parent company of **Corden Pharma** (Plankstadt, Germany), entered an agreement to acquire Roche's manufacturing facility in Boulder, Colo., USA. The site, which will be renamed Corden Pharma Colorado, specializes in the production of synthetic peptides, including Roche's Fuzeon for HIV, with capabilities up to the metric ton scale. The site includes three production plants, three small-scale production labs, and two pilot plants. It employs 265. Under the terms of the deal, Corden Pharma will produce several APIs for Roche at the Boulder facility.

This facility will be Corden Pharma's first operation in the U.S. It has six facilities in Europe, including three for manufacture of APIs and intermediates, and three for dosage forms.

ICIG has acquired 16 chemical and pharmaceutical facilities since 2004, and claims revenues of EUR 700 million (USD 980 million) and 300 employees.

CORDEN PHARMA FACILITIES

Facility	Location	API/Dose	Former Owner
Corden Pharma GmbH	Plankstadt, Germany	Dose	AstraZeneca (2007)
Corden Pharma Latina S.p.A.	Latina, Italy	Dose	Bristol Myers-Squibb (2011)
Corden Pharma S.p.A.	Caponago, Italy	Dose	AstraZeneca (2009)
Corden Pharma Switzerland LLC	Liestal, Switzerland	API	Genzyme (2011)
Corden PharmaChem Ltd.	Cork, Ireland	API	Cambrex (2006)
Synkem S.A.S.	Chenove, France	API	Solvay (2007)
Corden Pharma Colorado	Boulder, Colo., USA	API (peptides)	Roche (2011)

For more information on the business and capabilities of Corden Pharma, click on this box or go to www.pharmsource.com and search by company name.

API – Small Molecule in Brief

Novasep (Pompey, France) received FDA approval of its API small molecule manufacturing facilities in Freeport, Bahamas and Lyon, France. The FDA inspected the Freeport facility in March 2011 and the Lyon facility in May 2011.

ANALYTICAL SERVICES

Vela Laboratories (Vienna, Austria), a company that offers analytical services for proteins, including potency and release testing, entered a partnership with **Protagen** (Dortmund, Germany) to jointly provide analytical services for biopharmaceuticals and biosimilars.

EARLY DEVELOPMENT

Cetero Research (Cary, N.C., USA) received a warning letter from the FDA for several GLP violations at its bioanalytical laboratory facility in Houston, Texas, USA, following an inspection of the site in May 2010. The warning letter cited the company for falsifying laboratory records of sample extractions, manipulating equilibration samples to meet acceptance criteria and failing to document equilibration runs. The FDA indicated that it now doubts the validity of data generated by Cetero from April 2005 until June 2010.

PHASE II-IV CLINICAL RESEARCH

INC Research (Raleigh, N.C., USA) completed its acquisition of **Kendle International** (Cincinnati, Ohio, USA) for USD 232 million. Both companies will operate under the name INC Research, and James Ogle will continue to serve as its CEO.

INC also announced that it will manage a clinical study for an unnamed development candidate for Debiopharm Group and that the companies have established a framework within which INC will conduct further trials for Debiopharm, which may include risk and reward sharing provisions.

OUTSOURCING EVENTS

Contract Pharma 10th Annual Conference and Tabletop Exhibition
September 22-23, 2011,
New Brunswick, N.J., USA
http://conference.contractpharma.com/2011conference

Partnerships in Clinical Trials Asia
October 12-14, 2011, Shanghai, China
www.clinicalpartnershipsasia.com

AAPS 2011 Annual Meeting & Exposition
October 23-27, 2011, Washington, D.C., USA
www.aaps.org

ICSE 2011 – The International Contract Services Expo
October 25-27, 2011, Frankfurt, Germany
www.icsexpo.com

CPhI Worldwide 2011
October 25-27, 2011, Frankfurt, Germany
www.cphi.com

Partnerships in Clinical Trials
March 5-7, 2012, Orlando, Fla., USA
www.clinicaltrialpartnerships.com

DCAT Week 2012
March 12-15, 2012, New York, N.Y., USA
www.dcat.org

BUSINESS CONDITIONS

Turkey Overhauls GMP Requirements, Creates Bright Spot for Domestic CMOs

The Turkish Ministry of Health (MoH) recently released a detailed GMP/GDP audit guide and checklist to accompany its updated GMP requirements published in early 2010. The country's new GMP guidelines and auditing procedures now mirror those of Western regulatory agencies and cover topics such as manufacture of clinical trial drugs, supply chain management, as well as purchasing and testing of raw materials and components.

This is an important step for Turkey, which is recognized as one of the most promising pharmaceutical markets in Central and Eastern Europe. The current version of the Turkish GMP/GDP guidelines are more in line with international inspection criteria and, as of March 2010, require Turkish GMP certificates for all market authorization applications, including for imported products. "If a GMP certificate [from the MoH] is absent, the relevant product will not be licensed in Turkey," explained Omer Can Buharali, managing partner, Istanbul Ekonomi Consultancy.

Turkey's hope is that the new guidelines will increase the likelihood of reciprocity between its MoH and other regulatory agencies. "The new guidelines stipulate that the Turkish authorities will no longer accept any other authority's GMP certificates unless there is a bilateral agreement in place," explained Turgut Tokgoz, secretary general of the Pharmaceutical Manufacturers Association of Turkey (IEIS). If no agreement is in place, the Turkish authorities will inspect foreign manufacturing facilities before products made at these locations can enter the Turkish market. Currently, no bilateral agreements have been signed, but Tokgoz indicated that there was a bilateral meeting with EU officials last month during which the difficulties EU firms face with the new GMP requirements were discussed.

Backlog Criticized

Turkey's new requirement for GMP certification has been sharply criticized by U.S. and EU authorities for imposing a "de facto" ban on the importation of new pharmaceutical products into the country and giving an unfair advantage to generic firms in the domestic market. The EU-Turkey Customs Union Agreement stipulates that there should be no non-tariff barriers for EU products.

Without sufficient resources to review the applications, including multilingual inspectors, a backlog quickly developed after enforcement of the new policy began. "Turkey's own inspection team is relatively small and thus, unable to check all sites rapidly. As a result, the process became a lengthy one," explained Buharali. The average waiting time for an NCE quickly rose to an estimated two-year timeframe.

"This was a fair criticism in the beginning, but I don't think that manufacturers can rapidly gain access to the EMA or the FDA for inspections either – it takes time," argued Tokgoz. "Both the U.S. and EU authorities have criticized the new policy on the basis that it would take a long time, but [the MoH] has sped up the process after only a year and a half. The [MoH] has concluded quite a number of inspections." In fact, during the past year, Turkish authorities completed 110 inspections with regards to the approval of over 400 products.

The new audit guide released last month is an attempt by the MoH to provide consistency and streamline the inspection process for domestic and foreign facilities. "The [checklist] provides special guidelines as to how to implement the GMP requirements and to help prioritize which products to

inspect," explained Tokgoz. "To handle the bottleneck, Turkish authorities have put special emphasis on the most important drugs for the market." According to Tokgoz, Turkish authorities use a non-public priority list to categorize incoming applications before deciding which to process.

Turkish CMOs Set to Benefit

The new GMP requirements in Turkey are set to improve the market for the country's CMO industry as companies turn to domestic manufacturers for production of their products. "Turkey has become an important market for the industry. Companies that do not want to lose the Turkish market may well consider contract manufacturing in Turkey … [in order] to avoid delays in their product's market entry," commented Buharali.

"The new standards have definitely helped local manufacturers get more business," continued Tokgoz. "We've seen a beef up in the number of [contract manufacturing] requests since, if an applicant moves towards a local manufacturer for imported products, it's a much speedier process. In fact, many current foreign applicants are actually working on transferring know-how and engaging a Turkish contract manufacturer."

CONTRACT MANUFACTURERS IN TURKEY

Company	Model	API	Solid	Semi/Liq	Inject
BirgiMefar	CMO				X
IDOL Pharmaceutical Filling Industry	CMO				X
PharmaVision	CMO		X	X	X
Atabay	Generics+CMO	X	X	X	
BERKO	Generics+CMO		X	X	
Mustafa Nevzat Pharmaceuticals	Generics+CMO	X	X		X
ABDi iBRAHim	Proprietary+CMO		X	X	
Biofarma	Proprietary+CMO		X	X	
Santa Farma	Proprietary+CMO		X	X	
Ali Raif	Generics		X		
Bilim Pharmaceuticals	Generics		X		X
Dincsa Pharmaceuticals	Generics	X	X		
Drogsan Pharmaceuticals	Generics	X	X	X	
Sandoz Turkey	Generics	X	X	X	
Toprak Pharmaceuticals	Generics	X			
Zentiva	Generics				
NOBEL ILAC	Generics+ proprietary		X	X	
Yeni Recordati	Proprietary		X	X	

LOCAL MARKET DEVELOPMENTS

India

Shilpa Medicare (Raichur, India) purchased a controlling stake in formulations development company, **Nu Therapeutics** (Hyderabad, India), for an undisclosed amount. Nu Therapeutics specializes in the development of fast-dissolving oral thin strips.

India

Dr. Reddy's Laboratories (Hyderabad, India) signed an agreement with Fujifilm to establish a joint venture for the production of generic drugs to be marketed in Japan. Fujifilm will hold a 51% stake in the agreement, while Dr. Reddy's retains a 49% stake. The joint venture will develop, manufacture and promote generic drugs utilizing both Fugifilm's quality control systems and Dr. Reddy's production technologies for APIs and formulations. The first products are expected to be released in the next three to four years.

Russia

Dr. Reddy's Laboratories (Hydrabad, India) entered into an agreement with JB Chemicals & Pharmaceuticals to acquire its pharmaceutical prescription portfolio in Russia and in other CIS regions for USD 34.85 million. The deal also includes a supply agreement for the manufacture of products associated with the acquired brands.

COMMERCIAL DOSE MANUFACTURING

Poland

Jelfa Pharmaceutical (Jelenia Góra, Poland) received a warning letter from the FDA for several cGMP violations at its commercial dose manufacturing facility in Jelenia Góra, Poland, following an inspection in October 2010. The warning letter stated that the company did not properly investigate batch failures, did not establish appropriate procedures to prevent microbiological contamination and did not institute adequate quality control measures.

API – SMALL MOLECULE

India

Granules India (Hyderabad, India) entered a joint venture agreement with fine chemicals producer **Ajinomoto Omnichem** (Louvain-la-Neuve, Belgium) to offer custom manufacture of APIs and intermediates for pharmaceutical companies. The joint venture, **Granules-OmniChem**, will operate out of a new facility now under construction in Andhra Pradesh, India. Construction is expected to be completed by the end of 2012 and production to begin by January 2013.

PHASE II-IV CLINICAL RESEARCH

Israel

Chiltern International (Berkshire, UK) established operations in Israel and will begin conducting clinical trials in the country.

BIO/PHARMACEUTICAL **Outsourcing Report**

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