

IPJ

The Official Journal of FIP



Chronopharmaceutics

A future strategy for drug delivery

Imagine for a moment it's the year 2050

Excerpts from the speech by J. Lyle Bootman, Ph.D., Sc.D., at his acceptance of the 2008 Remington Award

Historical non-involvement and future opportunities

Pharmacy and TB

The Future of Medicines Use

Where it's going, who is steering it and how we're trying to keep up.



advancing pharmacy and science to the benefit of the patient



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Dear Reader

What if, in the future, there were no medicines? Or even better (would it be?), there was no *need* for medicines? What if we were now disease-free, pain-free, worry-free because we were also now fit enough, preventative enough, beautiful enough... *healthy* enough. Would we be satisfied? Would we finally say "*Finally*, we've done it!?" Or would our brains, hard wired through evolution to want ever *more*, finally be able to turn full attention to faster, stronger, *better*? Will the future of medicines lie not in enough health, but in pushing ourselves beyond our limits?

And... where does that leave us, a profession that is now still just beginning to take our place in the improvement of health?

The "yes, but..." responses to this scenario are already resonating, with many immediately brandishing the thought with a label of "*never!*". But our current reality is based on this very scenario: the ultimate fulfillment of our work as pharmacists and pharmaceutical scientists, along with our colleagues in healthcare, is to render ourselves redundant. This is a sentiment expressed on more than one occasion; and one that proves difficult to dispute.

This issue of the IPJ does not necessarily address that [contemplated] endpoint, but rather the journey. We have chosen as the theme "The Future of Medicines Use" so that we may explore how new technologies are changing medicines and their use and

more importantly how these advancements will affect our role as pharmacists and scientists.

We are confident that the articles in this issue fully take on that challenge. They offer us both visionary and proven advancements in medicine; we hear of countries challenged by current needs and future expectations; and together with J. Lyle Bootman, the 2008 APhA Remington Award Winner, we are taken on a theoretical journey into the future, meant to guide us now along the right paths. Not to mention some very interesting thoughts from some possible future leaders in healthcare!

As always, we hope this issue imparts knowledge and insight, but we also hope it inspires to you envision the future and your place in what is to come.

Myriah Lesko Editor

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Industrial Manufacturing in 2020

Linda Hakes

Predicting the future is a dangerous occupation, even as a hobby. By definition one is almost certain to be wrong, and at best one can only hope to be partially correct. On that basis, it needs to be made clear that the following article is not intended to be a prediction of the future but simply an overview of technologies, philosophies, science and other factors that may influence or even significantly change the way the pharmaceutical industry develops, manufactures and distributes medicines in the future.

In recent years we have all heard a lot about genomics and personalised medicine. We have been told that they will revolutionise the way we develop and use medicines and that the blockbusters of the past will be no more as the world, and the pharmaceutical industry, adjusts to the idea that every individual is unique and that medicines must be selected, or even tailored, to the specific individual, taking into consideration his genetic make-up and his ability to respond, or react to, a particular medicine. There is no doubt that such medicines are being developed (Herceptin was one of the first) but it is unlikely that we will see the demise of blockbusters in the immediate future. 25 years ago the predictions were that protein drugs would replace small molecules as the main-stay of medical treatment, but we still have major R&D efforts in the small molecule domain.

So what are the real changes occurring in the industry that might affect the medicines of the future? One major consideration relates to the understanding and control of the manufacturing process. We no longer rely on testing the final product to ensure the quality of the medicines we produce. Instead, we use a range of techniques and technologies to identify critical steps in the manufacturing process and to monitor the performance of equipment and the process throughout the entire manufacturing chain of activities. This concept begins during the development of the product (Quality by Design) and aims to ensure that all steps in the manufacturing process are well understood and are robust enough to give the same quality product, even under the stresses of routine manufacture and the vagaries of individual worker performance. If the product has

been well developed, we will know exactly which parameters to monitor during production, to ensure that all is proceeding according to plan. Such parameters may be equipment related (temperature, pressure, mixing speed, mixing time, etc) or may be material related (particle size, viscosity, crystal form, assay etc). By making such measurements throughout the manufacturing process, we gain a much better insight into the consistency and quality of the entire batch and eliminate the problems associated with sampling and testing. After all, who really believes that a sample of 100 tablets from a batch of several million gives an accurate indication of the true variability within the batch?

Another focus, also quality related, is the integrity of the supply chain. In spite of all our best efforts, counterfeit or defective products still manage to infiltrate the legitimate supply chain, even in developed countries. The industry is therefore employing increasingly sophisticated techniques to ensure that all the materials used in the manufacturing process are of high quality and that once manufactured, the finished products reach the patient without the risk of tampering, substitution or damage. The specific actions taken range from using sophisticated analytical methods to check the quality of incoming materials, preferable in a non-destructive way (NIR monitoring for example) through to use of electronic tagging to track the location and history of a product package all the way from factory to patient. For further security, some companies are considering direct to patient distribution in order to reduce the risks associated with intermediaries such as wholesalers (or even pharmacies?). ▶

What could all this mean for the manufacture and distribution of medicines in the future? Perhaps we will see the development of 'made to order' medicines that are compounded to suit the specific combination of diseases or symptoms suffered by the patient, taking into consideration their ability to metabolise the drugs and their sensitivity to particular molecular entities. The on-line technologies both available and in development, would ensure that such products could be manufactured quickly and with a high level of confidence in their quality, without the need to do end-product testing on each one. It could be considered as extemporaneous dispensing with modern in-process control.

Another potential consequence of direct to patient delivery could be the use of medicines with much shorter stability shelf-lives. If we start to manufacture medicines to order, without the long distribution chain that we currently use, the need for a 2 or 3 year shelf-life will no longer be valid. If the patient can receive the product within a few days of manufacture, we can develop compounds and formulations that would not be viable in today's world. This would expand the range of potential products and thereby increase the treatment options for patients. This is not to imply that we would accept lower quality standards, but a product with 6 months shelf-life is commercially viable if it doesn't need to spend 2 years on a shelf in a warehouse!

Pharmacists will need to consider how they would respond to such potential changes in the manufacture and distribution of medicines. Some companies may see this as an opportunity to cut out all the middle-men including pharmacists, but others will see the role of the pharmacist as even more important in order to ensure that these special medicines are used correctly and appropriately. Pharmacists will need to be able to offer advice covering all aspects of the product's use, ranging from the pharmaceutical considerations such as storage and stability through to maximising the clinical benefit by monitoring the patient's response. In some cases, pharmacists may again become involved in compounding medicines, as they did in the past, but this time using modern technologies to assure the quality and traceability that is necessary in the modern world.

It may seem that in a future world we will in fact return to the past, harnessing the "old fashioned" skills of the pharmacist in order to make best use of high technology medicines. As technology moves forward and high-tech instruments and equipment become smaller and cheaper, it will be possible to manufacture to high standards on a small scale. As new types of medical treatments become available (gene therapy, cell-based therapies, antisense etc) it may be essential to have manufacturing facilities close to the patient, in a hospital or community pharmacy. Many types of medicine may continue to be manufactured in the "traditional" way by large companies but the pharmacy of the future is likely to have to embrace a much wider range of products and sources of products, than it does at present. The question is whether we are all ready to embrace the new challenges or whether the security of "tried and trusted" approaches

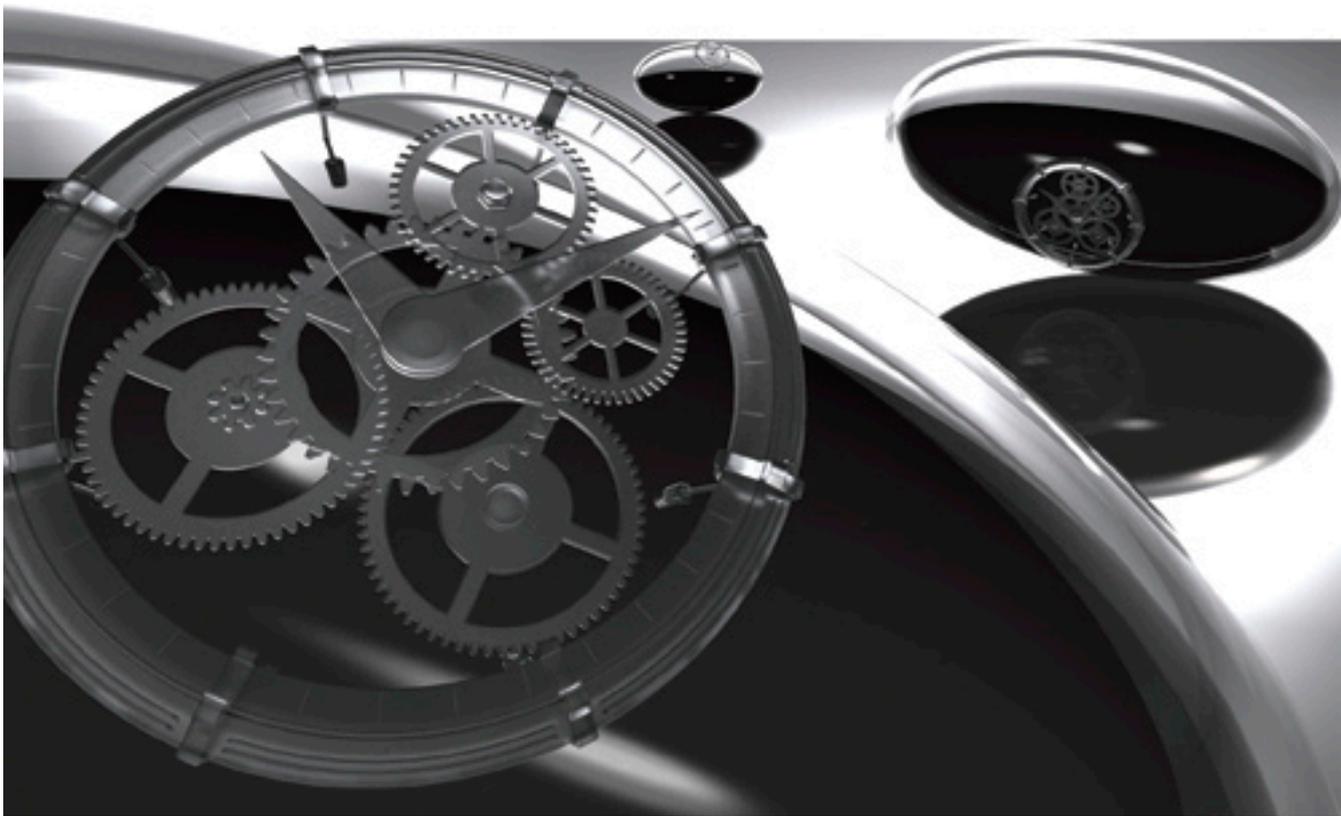
will prevent us from providing the best possible service to patients. ■

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Chronopharmaceutics: A future strategy for drug delivery



Pedro Barata, Rita Oliveira, Delfim Santos

Nowadays pharmaceutical companies face substantial challenges in discovering new drugs that represent significant advances in the treatment of disease. Due to the constant urge for innovation the idea of developing new intelligent systems that optimize the performance of known drugs and that will significantly improve the treatment of common medical conditions and diseases is therefore very interesting for all players in the pharmaceutical market. ►



Chronopharmaceutics has been described (Youan, 2004) as a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy.

Even though the roots of clinical chronobiology date back to the 5th century with the description of the nocturnal occurrence of asthma by Caelius Aurelianus, the concept of Chronotherapeutics is not new. In 1814 Joseph Virey empirically recommended that opium should be dosed late in the evening, rather than in the morning; in the last few years recognition of the importance of the circadian rhythm to the health sciences has increased significantly.

Sustained Release systems have been consistently developed by academics and the pharmaceutical industry during the last decades. The principal advantages to be gained from controlling the variables of drug release in sustained release formulations are as follows: (i) a more uniform plasma drug profile with fewer occasions when super- or subtherapeutic concentrations

of the drug, or its active metabolite(s), occur; and (ii) a smoother therapeutic response over the dosage interval (provided the time-course of drug effects reflects the plasma concentration-time profile).

One of the goals of these systems is to provide zero-order, constant rate, delivery of bioactive agents, however it is now well known that living organisms do not require constant rate delivery or provide “zero order” response to drugs.

In fact the human circadian time structure presents peaks of actions directly related to the daily routine of most human beings. Peaks for basal gastric acid secretion and white blood cell count occurs late at night or early in sleep, while plasma cortisol, renin, angiotensin and aldosterone peak in the morning and insulin and hemoglobin peak at noon and in the afternoon.

As human physiology and biochemistry predictably vary during a 24 hour period it is easy to understand that some medical conditions present prevalence at certain periods of the day. It has been well established that peptic ulcer attacks and gout are most

frequent a night. Also, episodes of asthma and acute pulmonary edema are known to worsen during the night period. On the other hand episodes of acute myocardial infarction, sudden cardiac death and hypertensive crises are most frequent during the morning.

The circadian rhythm also affects the organism-drugs interactions. Consequently the fact that kinetics and dynamics of drugs are directly affected by biologic rhythms and the time of drug administration is very important to the pharmacological effect. As an example, one can quote the decrease of ranitidine therapeutic effect during overnight hours, probably related to partial blockade of the H₂ receptor.

For some diseases enough scientific evidence has been collected in order to recommend the use of chronotherapeutics instead of a conventional drug administration.

The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant during the day, tending to be higher in the early morning and lower in the evening. This seems to be related to the arousal pro-

pensity in the morning and the sleep requirement after an awake period. Wake propensity is mediated through factors as increases in body temperature, respiration, cortisol and adrenaline levels, which has obvious effects on heart rate and blood pressure. This documented rise in blood pressure (Prisant, 2004) near the time of awakening is responsible in significant part for the increase of cardiovascular risk in the morning.

The circadian period of blood pressure is a challenge for sustained delivery systems, as blood pressure may be lowered excessively during certain times due to the zero order drug delivery provided by the system. Chronopharmaceutics address this limitation by delivering drugs in concentration that vary according to the body's circadian rhythms. In this way it is possible to reduce blood pressure at the times where patients are at highest risk for cardiovascular events without excessive reduction during low periods.

Circadian changes can also be observed in lung function and affect diseases like asthma. It has been demonstrated (Martin, 1998) that airway resistance increases progressively at night in asthmatic patients. Since bronchoconstriction and exacerbation of symptoms vary during the day, asthma is well suited for chronotherapy, namely with b2-agonists and oral corticosteroids.

Also glucose and insulin levels' circadian variation have been studied and their clinical importance acknowledged (Rigas, 1968). Since the goal of insulin therapy is to mimic the normal physiologic patten of endogenous insulin in healthy individuals, chronotherapeutics seems an obvious path for insulin substitution therapies.

Chemotherapy has also been reported (Haus, 1972) as being more effective and less toxic when drugs are administered at selected times that take advantage of tumour cell cycles. The blood flow to tumours and tumour growth rate are much higher during day activity phase than during the daily rest phase. Clinical studies that

determine the times at which effects are higher with lower undesirable side effects are of great importance to establish new drug regimens.

Chronopharmaceutics also plays a major role at pain control therapies. Many scientists are convinced that pain intensity is rarely constant over a 24 hours period. The daily pain profile must be used to determine the best time to administer an analgesic drug to a patient. The time dependant rhythms in pain intensity depend on the medical conditions present. Morning pain is found in patients with angina pectoris, myocardial infarction, migraine, toothache and arthritis rheumatoid whereas nighttime's pain is more common in arthritic pain, gastro-oesophageal reflux and renal colic (Bruguerolle, 2007).

In many other situations as hypercholesterolemia, in some neurological diseases (mainly those related to noradrenalin levels), in duodenal ulcers and gastrointestinal tract diseases, chronotherapy can be used as a great tool to optimize the drug regimen, thus increasing the efficiency of the treatment.

Various systems have been developed taking Chronopharmaceutics in consideration. Systems like CONTIN®, OROS®, CODAS®, CEFORM®, DIFFUCAPS®, TIMERx® have been proposed. The use of hydrophilic matrixes is also very promising as release can be tailored to achieve the desired release programs without the need of specific industrial machines, the GEOMATRIX® is a good example.

More complex strategies can include the use of microchips in controlled release systems in order to obtain a determined release program (Langer, 1999). Hydrogels, namely stimuli-sensitive hydrogels and temperature sensitive-hydrogels (Smolensky, 2007) have been reviewed as interesting drug delivery technology for chronopharmaceutics.

Chronopharmaceutics certainly seems to hold the potential to improve patient outcomes and optimize disease management in the future. The selection of

the appropriate technology will have to take in consideration factors as the application range, ease of manufacture, cost-effectiveness and flexibility of the desired pharmacokinetic profile.

In time where pharmaceutical companies strive to offer better solutions to the market the use of these intelligent systems could not only offer better therapeutic results but also increase patient compliance. ■

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Down the hatch

The oral route of proteins: How far we are?

Bruno Sarmento

Therapeutic proteins currently represent a significant part of the new pharmaceuticals coming on the market every year (1, 2). The progresses in biotechnology have accelerated the economical, large-scale production of therapeutically active peptides and proteins, monoclonal antibodies, hormones and vaccines, making them readily on hand for therapeutic applications. At the present, they show a strong position in the novel area of nanomedicine, using nanotechnology for medical applications for both institutional and industrial fields (3). Most of these proteins are used for life-threatening and seriously debilitating diseases such as diabetes, cancer, rheumatoid arthritis or hepatitis. The high activity and specificity of proteins compared to the more conventional, low molecular weight drugs often allows for a better treatment of these diseases. However, the production and the delivery of these proteins occur under unfavorable stress conditions (4).

Oral drug delivery is the preferable route for drug administration because it is non-invasive, avoids pain and discomfort associated with injections, decreases risk of contamination and fits their molecular weight or structure. It is also physiologically desirable, since the exogenous protein imitates the physiological pathway undergoing first hepatic bypass. Moreover, among the non-invasive routes of administration that have been evaluated for the delivery of proteins, the oral route remains the most convenient, although it is not the most efficient for peptides and proteins due to their low absorption rate. Nevertheless, low oral bioavailability of proteins has been pointed out as the main drawback for the accomplishment of their commercialization. It is thought that a prerequisite for the successful delivery of oral peptides and proteins is the maximization of the absorptive cellular intestinal uptake and stabilization of the biologicals at all stages before they reach their target (5). These difficulties are related to chemical and

conformational stabilities, cellular and luminal enzymatic degradation in the gastrointestinal tract, poor intrinsic penetration of the intestinal membrane (5-7) and clearance mechanisms such as first-time pass effect and excretion in the bile (8). However, there are polypeptide drugs, such as cyclosporine and desmopressin that are available in oral dosage forms, indicating that polypeptide size should not be an absolute limitation (9-11).

Advances on an effective oral delivery system for proteins requires a comprehensive perception of their physicochemical properties, such as molecular weight, hydrophobicity, ionization coefficient and pH stability, as well as of the biological barriers that limit protein absorption through the gastrointestinal tract (12). The important therapeutic proteins and peptides being explored for oral delivery include insulin, calcitonin, interferons, human growth hormone, glucagons, gonadotropin-releasing hormones, enkephalin, vaccines, enzymes, hor-

mone analogs, and enzyme inhibitors (13). These are outstanding model proteins used in the pharmaceutical development, mostly due to its well-established physical-chemical properties and social impact of their therapeutic applications.

Strategies to improve the oral bioavailability of proteins have ranged from changing their physicochemical properties by modification of their lipophilicity and enzyme susceptibility, to adding novel functionality using transport-carrier molecules that are recognized by endogenous transport-carrier systems in the gastrointestinal tract and/or to their inclusion in specially adapted drug carrier systems (5). Marketed polymeric-based systems have attracted considerable attention in the controlled release in targeting particular organs/tissues, as carriers of DNA in gene therapy and in their ability to deliver proteins, peptides, hormones, antibodies and genes (14). They can effectively deliver the proteins to a target site and thus increase the therapeutic benefit, while minimizing side effects (15). Protein association with polymer-based carriers, such as polymeric microparticles, nanoparticles, hydrogels or patches is one of most promising approaches proposed to improve oral protein bioavailability. Polymer-based carriers can protect proteins from the gastrointestinal environment and allow the modulation of physicochemical and protein release properties and consequently the biological behavior (16). Also, from the perspective of improving oral absorption, the major effect of carriers is to increase epithe-

lial membrane permeability, thereby leading to higher bioavailability (17).

The problems facing oral delivery of peptides and proteins have traditionally been approached from many different angles, namely formulation, encapsulation, macromolecular conjugation and chemical modification (9), but there are many other criteria that must be satisfied to bring an oral protein formulation to the market. For example, the low bioavailability implies a large variation in absorption and a high manufacturing cost, which is unacceptable for the development of most peptide and protein drugs. For proteins like insulin that has a relatively narrow therapeutic window, the effects on intestinal absorption of age, genomic factors, physiological conditions and other individual variations must be carefully investigated. Finally, most peptide and protein drugs require chronic administration and hence the effects of long-term oral administration of absorption carriers on both the intestinal and systemic physiology must also be carefully evaluated (9).

Insulin: a case study

A pragmatic example is the research around insulin. The development of efficient systems for administering insulin orally has met with limited positive results, despite the use of many strategies to overcome the barriers to absorption that are presented by the gastrointestinal tract. Enhancing the chemical stability of insulin, protecting against proteolytic enzymes, incorporating insulin into nanoparticulate systems and using surfactants

or emulsions to increase the permeability of the intestinal mucosa have achieved only limited and variable success in improving absorption. Clinical studies have been conducted by pharmaceutical companies regarding the introduction of oral human insulin on the market. Using proprietary eligen® technology, Emisphere Technologies has orally delivered insulin, safely and effectively, in humans (18, 19). The eligen® technology relies on the development of small organic molecules (200–400 Da), termed carriers, that interact non-covalently with macromolecules like insulin, enabling insulin to cross cell membranes by transcellular transport process (20). The eligen® delivery agent then dissociates from the insulin, which reestablishes its natural conformation and returns to its therapeutically active state without involving chemical modification of the protein or the integrity of the cell membrane and cytoskeletal structure. The safety of this approach has been confirmed in more than 100,000 human doses (18).

Another example is the rapid-acting, orally administered recombinant human insulin formulation Oral-ly® (Generex Biotechnology), which has displayed improved absorption properties when compared with subcutaneous injection of human regular insulin, with an onset of action similar to that of rapid-acting insulin analogues, but earlier maximum effect and shorter duration of action (21). Regular insulin and Oral-lyn® had similar glucodynamic effects in subjects with type I diabetes receiving twice-daily insulin analogue as baseline therapy, ►

being presently approved for use in Ecuador.

NOBEX® oral drug delivery, from Nobex Corporation is another technology applied successfully to insulin creating an orally absorbed, bioactive conjugate, hexyl insulin, which is safe and rapidly absorbed and which demonstrates dose-dependent, glucose-lowering effects in animal models, healthy volunteers and type 1 diabetic patients (22). This technology is based on modification of peptides, proteins and small organic molecules by attachment of one or more amphiphilic oligomers (22). Attachment of these oligomers results in stability to enzymatic degradation, improved solubility to allow optimized formulation, and modification of pharmacology to prolong circulating half-life and activity. Bioavailability of 5% has been reached in ongoing phase I and II clinical trials.

Coremed Inc is currently in development of Intesulin®, an orally administered insulin and have recently announced positive findings on its oral insulin formulation from a study conducted in diabetic animals (23). The findings demonstrated an effective insulin action over a wide range of insulin doses. The study also showed significant reduction in blood glucose levels.

Apollo's oral delivery technology, Oradel®, provides a coating that protects insulin from the stomach and uses targeting agents to promote absorption of insulin from the intestine. Preclinical studies on the oral delivery technology using large proteins have been conducted in more than 120 animals, demonstrating effective delivery

of bioactive molecules. The oral insulin studies confirm these findings.

Despite this progress, it seems understandable that the success of insulin oral delivery may be based on its encapsulation into new nanomedicines. The massive amount of research presently on the encapsulation of insulin into these carriers regarding insulin oral delivery and absorption, is promising.

However, apparent unexpected barriers arise; the first commercially available product as alternative to regular subcutaneous insulin administration was the inhaled human insulin Exubera®, already approved in the European Union and the United States for preprandial use in adult patients with diabetes mellitus (24). This formulation of insulin has a more rapid onset, but similar duration, of glucose-lowering activity compared with subcutaneously administered regular human insulin. But despite the good results, Exubera® has failed to gain the acceptance of patients and physicians, being withdrawn for commercial reasons. Exubera® did not make any market impact since its launch; bring to light the discussion about the financial viability of such costly technology. The intensive, high volume manufacturing process for alternative protein delivery routes has resulted in drugs only being available at premium prices. This may limit their market penetration.

In summary, the oral route for peptide and protein delivery might be possible in the near future using innovative delivery systems. Pharmaceutical companies are evidently interested in the potential of oral proteins to reach

an enormous share of the market, and investment in research is substantial and continuing. The therapeutic protein market is forecast to achieve high sales in the new few years. Growth to date has been dominated by erythropoietin, calcitonin and insulin, while future growth will reflect the increasing significance of monoclonal antibodies and therapeutic vaccines. However, there are a number of critical issues that companies must overcome to be successful on oral administration. ■

Author's Information

Bruno Sarmiento is an Assistant Professor of Pharmaceutical Technology and Research Scientist associated to Institute Superior of Health Sciences in Gandra-Portugal and Faculty of Pharmacy of University of Porto, Portugal. He has been involved with the comprehension of insulin oral absorption mechanisms and its relation with the Diabetes diseases as well as islet transplantation. His actual interests of research are focused on oral delivery of insulin by means of colloidal targets, development of new drug delivery systems using polymeric nanoparticles and controlling delivery of drugs across biological barriers, namely gastrointestinal tract related with the studying of *in vivo/in vitro* correlation of intestinal absorption of proteins using animal models and Caco-2 based co-culture cell lines.

He is also an active member of several international associations (AAPS, CRS, EUFEPS, EFSD, FIP, BRG).

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Take it personally

Personalized Medicine: Past, Present and Future

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Looking at the history of medicine use, it is clear that personalized medicine has always been practiced. Physicians took patients' age, gender and the state of health and disease affecting major organs such as liver and kidneys into consideration when deciding to prescribe a medicine. In oncology, samples were taken from the tumor site and examined under microscope for pathological examination and then a therapeutic plan or surgery was decided based on the observations made on that sample obtained from the tumor of an individual. Therefore, personalized medicine is not a new field. It has been always here. Practitioners always took into account the mental, physical, spiritual and emotional aspects of their individual patients. Pharaohs and Kings had personal physicians so that they could receive the best possible medical care tailored to their individual needs according to standard of care of the time.

Over past century, physicians began to practice a more advanced form of individualized medicine using biochemical assays, pathological examination of tissues obtained from patients, radiological examination and imaging techniques to diagnose diseases, watch for drug side effects and/or assess the function of major vital organs such as liver, heart, or kidney. For instance, physicians started to use creatinine and BUN levels, and the presence of albumin in urine to investigate kidney function. Liver enzymes, serum albumin, bilirubin, and serum coagulation factors were used to investigate liver function. The laboratory information was used to assign a correct diagnosis, and tailor therapy to the individual needs of the patient who suffered from kidney or liver disease. CK-MB, troponins and myoglobin were used to investigate myocardial infarction and the patients were then treated based on these cardiac biomarkers. Hence, in comparison to ancient time, this was of course already a very futuristic form of individualized medicine practiced by clinicians.

In the investigation of albumin levels, hemoglobin levels or CBC clinicians look at a value which is then compared with a reference range established in an apparently healthy population. Hence by using biochemical tests the degree of the disease could be quantified and compared to a reference point or range for assessment of severity of disease. For example, in diabetes patients serum glucose levels and HBA1c are used in the diagnosis and assessment of the patients' compliance with the therapy or recommended life style changes. These are the examples of modern personalized medicine in every day practice of today. However, in this model all patients who have an elevation in blood glucose or lipids are placed in one category, which means that it is more likely we tailor therapy to an individual disease, and not to an individual patient.

We are now at the interface of traditional personalized medicine and personalized molecular medicine in which a molecular test can be used for diagnosis, prognosis, the selection and tailoring of a specific medication or therapeutic plan, follow up, outcome assessment, implementing preventive course or even discovering new therapy

based on novel molecular therapeutics according to individual needs. What makes personalized molecular medicine different is that we look at the molecular level to stage a disease instead of gross pathology or tissue staging under a microscope.

The good news is that we have made progress. From a technological perspective, we are able now to investigate variation in genes, gene expression, protein and metabolites levels as well as developing new treatments based on novel molecular targets to correlate the findings with disease stages, prognosis, drug response and outcome to individualize therapy according to the molecular characteristics in patients. These new features have been made possible because of the advancement in molecular biology, nucleic acid research, chemistry, biology, development of novel technology and the completion of the human genome project. We are now able to look at the characteristics of specimen individually and use the information to detect disease at an early stage, select optimal therapy with minimal toxicity, increase patient compliance, select new targets for development of novel drugs, and reduce the time and cost of developing new medication, and shift medicine from treatment to early detection and prevention when the cure rate is significantly higher.

Success stories of personalized molecular medicine today include use of HER2 profiling for breast cancer therapy in women, who respond well to Herceptin®, an antibody which was developed to block this receptor. Breast cancer tissues that over-express this growth factor receptor respond well to the drug. Therefore a combination of diagnostic tests and a specific drug such as HER2 and Herceptin® can be used to target the drug towards a specific population of cancer patients who benefit the most from this type of approach. Hence using diagnostic tools to investigate a disease at a molecular level can be a powerful tool in therapy something that was not possible in the past.

Another example involving breast cancer patients involves patients whose biopsied tissue samples were found to ►

be positive for estrogen (ER) and progesterone receptors (PR). These patients are found to respond better to hormonal therapy (drugs such as tamoxifen). Again in this example a diagnostic test was used to investigate a molecular target to decide on personalized therapy. Recently it was discovered that tamoxifen, although active, needs to be metabolized by CYP2D6 to an even more powerful metabolite called endoxifen. It appears that ER and PR positive patients who are slow metabolizers and have inactive forms of CYP2D6 enzymes do not respond well to tamoxifen therapy. Hence a combination of ER, PR and CYP2D6 tests may be used to assess the effectiveness of tamoxifen in these patients. For instance, endoxifen may benefit the breast cancer patients who are ER and PR positive but have low CYP2D6 activity whereas tamoxifen may be prescribed to ER and PR positive patients with normal CYP2D6 activity. The effectiveness of such approach should be investigated in a carefully designed clinical trial.

Another example for the use of molecular medicine in oncology is TPMT (thiopurine s-methyltransferase). TPMT genotyping is used to identify individuals that are susceptible to 6-mercaptopurine therapy. TPMT is a phase II drug metabolizing enzyme that inactivates 6-mercaptopurine, which is used for treatment of ALL (acute lymphoblastic leukemia). The drug can cause severe myelosuppression and even death in individuals who have inactivated forms of TPMT genes. Another example includes irinotecan which is used for treatment of colorectal cancer. Irinotecan is a prodrug which needs to be metabolized to its active form. The active metabolite is very potent and can cause severe diarrhea and other serious side effects. It was determined that individuals who have the inactive form of UGT1A, a phase II drug metabolizing enzyme, cannot detoxify irinotecan effectively. Hence if the genotype of the individual patient is known, the drug dose may be tailored to the personalized need of the patient who carries the ineffective form of the UGT1A1 gene.

CML (chronic myelogenous leukemia) is another example of a success story in personalized molecular medicine. CML patients who are positive for bcr-abl gene respond

favorably to Gleevec®, an antibody against the abnormal bcr-abl protein which can stimulate cell division in white blood cells. Another example in oncology includes patients with colon cancer with p53 gene mutations who respond better to doxorubicin than 5-fluorouracil. The list of using molecular medicines to tailor and implement a personalized therapeutic plan for patients is growing fast not only in clinical oncology but also in all area of medicine such as cardiovascular, psychiatry and infectious disease. Hence, the future is now.

What will personalized molecular medicine look like in 2025? This is a question we often ask ourselves. By then, we believe that the medical community and clinical laboratory would be routinely able to use and screen arrays of 3,000 genes and 140,000 SNPs on a single chip. We would be able routinely to screen for the expression of 3,000 genes at mRNA level. Proteomics techniques make it possible to screen and detect 100-1000 proteins in blood specimen and biopsied tissues simultaneously in one run. Reference ranges will be established for staging and sub staging all the diseases. New definitions will emerge for diseases based on molecular medicine and molecular profile rather than clinical presentations of the disease. Presence of a specific molecular profile will warrant a specific therapy for the diseases even though the clinical presentations may be different. We anticipate that future clinicians will increasingly move towards practicing personalized molecular medicine and that PhD scientists will be involved to a greater extent in patient care by providing highly complex diagnostics services and support in decision making and interpretation of the results.

In the future to be truly able to implement personalized molecular medicine we have to carry out significant amount of translational research. We will need PhD scientists with fellowship training in clinical diagnostic laboratory and pathology to be able to decipher the clinical aspects of developing novel diagnostic tools using molecular staging, biochemical, proteomic and genetic testing. We will need PhD scientists who work side by side clinicians to establish and validate new molecular profile and refer-

ence ranges for various stages of diseases. Physicians and pharmacists will be required to participate in research so that they can assist in addressing complex issues and problems associated with the development of new tests and the interpretation of the results for clinical staging and implementation of personalized therapeutic plan.

Considering the advances that we have made in technology, the only problems that we see that prevent us from achieving a fully integrated personalized molecular medicine in today medicine is an urgent need for education and the development of human resources. Arguably, the future of personalized molecular medicine depends solely on education.

Hence, to address the need for education in this area a new Special Interest Group was established on "Individualized Medicines" by International Pharmaceutical Federation in 2004. This is because scientists and medical communities are attempting to develop and tailor therapy for patients based on their individual needs, genetic makeup and uniqueness of the patient's disease to optimize therapy, reduce toxicity and minimize morbidity and mortality as a result of drug therapy or the disease itself. In this approach each patient is treated as an individual rather than just prescribing a drug or protocol or applying a procedure to all patients without considering the patient as a unique individual. Furthermore, individualized medicine will have a substantial influence on the design and development of new drugs in pharmaceutical companies, and on the medical care and pharmaceutical care provided by physicians, pharmacists and clinical scientists, respectively. The aims of establishing this focus group include: 1) Dissemination of the latest research and technology of individualized medicine to pharmacists and pharmaceutical scientists. As new knowledge emerges physicians, pharmacists and pharmaceutical scientists will need to learn about this new information which will shape how we will select a drug for specific therapy and monitor therapy in patients. And 2) To foster discussion about the regulatory, ethical and medico-legal issues related to use of individualized medicine.

In brief, personalized molecular medicine will provide us with a unique opportunity to redefine the practice of medicine by addressing important questions related to clinical problems that are unique and personal to patients. ■

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Honor Bound To Lead

Excerpts from the speech by J. Lyle Bootman, Ph.D., Sc.D., at his acceptance of the 2008 Remington Award.

Imagine with me for a moment that it is the year 2050.

In my home in Tucson, Arizona, I am awakened by the gentle sounds of waves lapping the shore. No, it's not that California has dropped into the ocean; climate change is under control now. It's the Soothing Snooze alarm function on my new i-PHARM – the Individual Personal Health And Records Manager that combines my phone, computer, and calendar with a digital hookup to the Global Health Medical Records Vault and my team of healthcare providers. My i-PHARM contains my own Personalized Good Health Regimen for the day, scheduling in not just the times to take my genetically determined medications but also the sleep, rest and exercise I need for optimal health. The i-PHARM tells me I have a morning tennis date (I am playing again after my third successful hip replacement), a short afternoon nap and dinner plans at a new restaurant with my wife.

In the bathroom, my body waste reclamation unit automatically takes and analyzes a urine sample, sends the results to my healthcare team at Health Central, to the Global Health Medical Records Vault and to my i-PHARM. The i-PHARM reminds me I need to take a low-dose aspirin, eat a banana, a bran muffin, an extra glass of water and an anti-inflammatory before any physical activity. Oh, and a good stretch wouldn't be such a bad idea either.

But I'm feeling a little achy and listless, for the second day in a row, so I use my i-PHARM to cancel my tennis date, to initiate a saliva analysis and vitals via my home diagnosis unit, and to make an appointment with my healthcare team.

The Internet is still impossibly slow; it takes 3.2 seconds to make the connection to Health Central. My doctor is at an international conference today, but is "seeing patients" from his hotel

room in Sydney. From his i-DOCTOR device, he sees all the information sent from my home diagnostic unit as well as my personal healthcare database from the Global Health Records Vault on his screen.

As the physician looks over my e-records and conducts a visual exam via hologram, he sees a note in my file from Health Central's theranostician, the new Pharm.D. on staff trained in pharmacogenomic therapy and diagnosis of drug-related issues. It seems that the medication I have been taking for the prevention of Parkinson's disease, formulated for me based on my proteome profile, may interact adversely with both chocolate and peanuts. Have I eaten either food in large amounts recently? Sheepishly, I confess to not checking my i-PHARM recently for interaction warnings and to having enjoyed the Super Scoop Tin Roof Sundaes twice this week at the new pharmacy chain in which I have invested. He applauds both my business acumen and my interest in restoring "old-fashioned" services to modern drugstores, but recommends I curb my enthusiasm for certain sundaes. He notes that he will bill my Medicare account in a week, based on whether his advice has solved my complaint. I promise to send in my follow-up health status report when the i-PHARM signals me, so my records are complete. We end our session with my recommending he visit a bistro I know near the Sydney Opera House.

In this utopian future, basic diagnostics, laboratory analysis and treatment protocols are home-based, instantly accessible and customized to contain an individual's health history, current medical regimes and lifestyle recommendations. This is a future where interprofessional teams of medical, pharmaceutical and patient-care specialists are accessible, no matter the locations of the healthcare

provider or the patient. In this future, health care is unfettered by economics, because outcome profiles and Bayesian modeling have solved most issues related to cost and effectiveness. It's a future where providers are rewarded financially for the results of their efforts, not just the intent. It's a setting that includes diagnostic specialists, robotic technologies for most surgeries, and the theranostician – the pharmacist who engages pharmacogenetics to develop therapies that result in having a less than one in 10 million adverse event rate and almost a perfect positive outcome. It's a future where devices like the fictional i-PHARM can identify interactions even before they occur and track the patient's ongoing health status. In this future, the patient is indeed at the center of his or her own health care.

So, how do we get to this almost-too-good-to-be-true future? And what is the role of the pharmacist in realizing the dream? The answer to both questions is the same: innovative leadership.

A Global Health Medical Records Vault is still a vision, and Apple hasn't yet developed a real i-PHARM, but the company's canny and creative Steve Jobs offers some wisdom that applies as much to our profession as to Silicon Valley. "Innovation has nothing to do with how many R&D dollars you have," he says. "It's about the people you have, how you're led, and how much you get it."

Tonight I call on the pharmacy profession to recognize that we have the talent and knowledge within our profession to take a leadership role in developing this future of patient-centered care achieved through new technologies and the therapeutic application of advanced genomics. We do "get it" and we are well-positioned to lead. We are already trusted

by patients, and accessible to them without appointments. We are often the health professional most aware of a patient's entire medication history and we are the professional best educated to understand all the possible adverse events and outcomes associated with those medications. We are in the best position to determine if the patient understands the purpose of the medication, and how to take it, and, often, whether he is taking it at all.

The pharmacy profession has already led the way in making many aspects of modern health care more patient-centered: because of our efforts, medication labeling is more clear, safety measures are in place to reduce dispensing errors and more patients, including the elderly and those people with language or mental challenges, receive face-to-face counseling.

The future I dream about, however, offers us the chance to become the pivotal healthcare professional, standing at the center of the healthcare team and contributing even more directly to the patient's quality of life. We can get there, if we think beyond today's model and if we are willing to take the steps that will forge a path to the future.

Before we go too much further, let's define the terms "Personalized Medicine" and "Patient-Centered Care" as I am using them tonight. They sound similar, but are actually two distinct concepts.

Personalized Medicine is simply 'meds for me.' Just me. My diabetes is different from your diabetes. Why should we be taking the exact same dosages of medications designed for the lowest common denominator? Why shouldn't my insulin regime reflect my body's needs right now, today? Yesterday and tomorrow

may be different and my Personalized Medicine program recognizes that and adjusts my dosage as required. Some of you here tonight are already unwrapping the promises of pharmacogenetics and pharmacogenomics. Within the next two or three decades, genetic research will identify bio-markers for nearly all our chronic diseases. The challenge will be not just to treat the disease as it manifests in the patient, but also to develop preventive protocols and inculcate appropriate personal lifestyle options that will ward off the onset of these diseases. This same research will allow us to design specific drugs perfectly crafted for the individual's specific physiology, with considerations for genetic makeup, medical history, family history, height, weight, gender, race and lifestyle. In the future, no two patients with the same disease will be treated in the exact same way.

That will be possible not just because of highly specialized drugs and individualized applications of those drugs, but because the patient is making more and more of the decisions about his own health. Patient-Centered Care does just what it says: it puts the patient at the center of care. The Institute of Medicine has identified several dimensions of quality Patient-Centered Care. First and foremost is the reason I got into this profession: to relieve pain, suffering and illness. And in that process, we identify and respect the differences in patients. We listen to their expressed needs. We coordinate continuous care. We educate and inform and communicate with them. We put them at the heart of the decision-making process. We advocate prevention, wellness and healthy lifestyle. We respect the involvement of their family and friends in their care. With the help of new systems and technologies, in the future, we will exchange information with them weekly or even daily.

Patients need reliable and understandable information about diseases and cures. Part of Patient-Centered Care is assisting them and directing them to modern, trustworthy sources in medical libraries, the Internet, associations and support groups formed around specific maladies. And in the future, the number one source for reliable information about their disease and their medication therapy can be their local pharmacist, their theranostician.

Pharmacy must stand on the front line to lead the entire healthcare system into an era of Personalized Medicine and Patient-Centered Care. I contend, perhaps with an understandable bias, that we are the only discipline that is taking a comprehensive approach and making strides in all areas of the Institute of Medicine's recommendations for achieving quality Patient-Centered Care. In our educational and research institutions, we are developing the curricula, refining the degree requirements, and publishing the findings of extensive research devoted to the IOM's mandate. If you were to plot our writings and our projects, we have been on the leading edge in quantifying, qualifying, proving and instituting these concepts from the bench to bedside and, moreover, from the bedside to the community, in a truly translational research practice for more than 40 years.

However, we can, and must, do more. We must not lose momentum and we must stretch our imaginations and our will.

Among the first things we must do is further refine our educational and training systems for pharmacists. Once a student enters upon a course of study in pharmacy, she can never go back to simply being a typical patient; being a practitioner or even scientist on the inside of the system automatically separates the profes-▶

sional from the patient. At our learning institutions we have to do everything in our power to help the student keep a mindful connection to the patient. If we teach our students to treat patients empathically while drawing on their superior knowledge, we will become the human interface between the complexities of health care and the patient.

If tomorrow's pharmacists are to usher in a new era of Patient-Centered Care, where the patient is the coach of a team consisting of doctors, nurses, genomicists, theranosticians, ethicists, and others, we can lead the way now in developing these interprofessional healthcare teams. Our learning institutions should take an aggressive role in implementing this interprofessional concept at the basic levels of training and, even more important, to extending and embedding this approach into healthcare delivery models at all levels. This is not a new theme – you've heard it for decades. But technology is available now that can make this concept a reality sooner rather than later. There really could be an iPHARM available to every patient and an iDOCTOR available to every physician within the next decade or two.

If we are bold enough to build a healthcare model that is truly patient-centered as we develop Personalized Medicine, one of the challenges for our profession will be to double, or maybe even triple, the skills and knowledge required for tomorrow's science and practice. Tomorrow's pharmacist will need a firm footing in the rapidly expanding biosciences: genomics, proteomics, and metabolomics, among others. As pharmacists become the chief communicators about the effects, benefits, cost effectiveness and complexities of these new personalized drugs, they will need language and counseling skills as finely honed as their scien-

tific knowledge. Our curriculum and experiential learning exercises will be required to support these skills even more than they do today.

But there are other stages where our profession can move to the front, and everyone here has a role to play. One of the areas where we can offer innovative leadership is in how new medications make it through the drug discovery pipeline. In the current dominant model, pharmaceutical companies spend close to one billion dollars and 12 or more years to research, develop and guide a new medication through the FDA approval process and then to market. Some of these drugs are developed because of immediate need. Some are developed by accident. Some are developed because marketing says if we advertise enough, people will clamor for the drug. The result is often an expensive drug designed for the widest possible population. This model does not serve the patient all that well, and it certainly will not support the notion of individualized therapies as genetics sciences move inevitably forward.

The typical randomized, double-blind clinical trial may no longer be the standard. In fact, possible alternatives to this model are already in place. The FDA's supported Critical Path Institute in Tucson [USA] is virtually re-engineering the process of drug design research with the goal of bringing effective new medications to market in shorter and shorter time periods. Like similar organizations in the U.S., the Critical Path Institute is experimenting on a variety of fronts to provide a system of checks and balances to assure the drug approval process is safe, efficient and cost effective.

Whether we are seeking to bring to market a blockbuster drug, or a genetically engineered therapy for just

one patient, we must always ask "What more can we do?" and "What can we do better?" If we move outside the box of our current standard operating procedures, we can find even more elegant solutions.

Another enterprise from Tucson also comes to mind as an example of out-of-the-box thinking. The University of Arizona is currently in the process of bringing a Mexican-developed anti-venom for brown-bark scorpion sting through the FDA approval process. The affected population of those who suffer severe reactions to the stings of this Sonoran Desert creature? Maybe as few as a hundred. The profit? Probably very little, and not for a U.S. company. Then why do it? Because the anti-venom works and we can relieve pain and suffering, maybe even death. Because one small effort now will make a difference in the quality of life for a child or an aging parent. Because it is the right thing to do.

Each of us here tonight can contribute something to solving the problems of health care in our country. Each of us can be a leader, even if we begin with small, local steps.

Are you a community pharmacist? You can bring change to your store now by instituting medication management therapy and increased patient counseling with more customers – the very essence of Patient-Centered Care. Only about 20 percent of pharmacies are now offering this important service, experts at my university estimate. And looking further down the road, I see you becoming a key link in translating new laboratory discoveries into everyday clinical practice, by virtue of your accessibility to patients and their trust in you. Much discussion is taking place currently about how we actually bring new knowledge out of the lab and not just to the bedside,





but all the way to the community – into the awareness and behaviors of patients, employers, and other consumers, and into common medical practice and public health policy. An example given in one article I read recently points out that administering aspirin to eligible patients might prevent more strokes than developing more potent antiplatelet agents. The article points out that we need to support not just more medical discovery, but we need to close the gaps in our systems that keep patients from benefiting from what we already know. As a pharmacist who sees patients daily, you are in a pivotal role to educate consumers and providers on best practices, and to help researchers collect important data about human behavior and medication usage that will speed the way we translate knowledge into practice.

Are you an executive in a pharmaceutical company? You may have to forsake traditional competitive behaviors, and look instead to sharing mass quantities of data with entities such as the Critical Path Institute. You may need to convince your company and others that the road to future success includes using those common databases to streamline research and new clinical trial models to develop and test novel therapeutics. Or maybe your contribution will be to partner with community pharmacists to improve post-market surveillance of your products by using new technologies to track the unexpected consequences of therapies developed with today's discovery and design models.

Are you a pharmacist in a medical center or health system? You are positioned to lead your organization in developing even better systems to reduce both medication and medical errors. Without a multitude of small steps taken collectively to improve safety and reduce human error in our

hospitals, we will never eliminate the shameful fact that U.S. hospitals average at least one drug error per day per patient. As we move forward in Personalized Medicine, your role as the vigilant and passionate protector of patient safety becomes even more important.

Are you associated with a health insurance company or Pharmacy Benefits Management company? You know that Personalized Medicine is already replacing other drug therapy in oncology and other specialty areas. You are crucial in leading the march to make sure patients have access to these new medicines and providers are reimbursed appropriately. I know one very large Pharmacy Benefits Management company whose board has already discussed business strategies regarding pharmacogenomics, and is planning their role in advancing this new therapy approach.

I am more hopeful than ever that our profession of pharmacy can be a major initiator of change in health care, health care that will benefit our country and humanity around the world. Within our ranks – within this room tonight – are those with the education, experience and interest to develop new lifesaving medications in the laboratory, to determine how to administer them, to conduct the clinical trials, to bring them to market, to assess their efficacy and cost effectiveness, and to deliver them to the patient at the right time, for the right reason. Within this room there is also the wisdom needed to diagnose the ills not just of the individual, but also of our entire healthcare system. We have the will and brainpower to find creative and lasting ways to make our system accessible, efficient, equitable, safe and truly patient-centered. Among us tonight are surely those ready to ask the hard questions: Why is our nation spending the most money on health care – around \$7,000 a ▶

year per citizen – and yet providing the lowest quality of care among developed nations? How do we get a better return on our healthcare dollar? Should health care be a right or a privilege in the United States?

This is just one more reason for our profession to take a leadership role in devising solutions. The bigger the challenge, the larger the opportunity to effect real change. I urge you all to take proactive roles in promoting solutions to one or more of the healthcare challenges I have outlined tonight, either at the local or national level. As a group, we can lobby and posture to provide expert, reasoned and cost-effective solutions. As action-leaders, we can develop demonstration projects that identify and develop quantifiable solutions to specific challenges. We must be listen to external influences – such as groups organized around specific diseases, cures, safety and hundreds of other points of view – that make themselves known to our community. If we are vigilant, and on the lookout for new opportunities, we can influence the national dialogue.

I have just skimmed the surface of all the work that begs our immediate attention. Please understand, I do not believe this future is too utopian to be realized. If there is any barrier, it will not be in our scientific and technical achievements, but in our inability or unwillingness to remake our systems and society.

Whether you are an educator, a clinician, a researcher or a captain of industry, I expect you all have stories similar to mine, and that you, too, started with a desire to make the future better than the present. My goal tonight was to remind you that as pharmacy professionals we are honor-bound to lead the way to that future. I challenge you to revisit those values that led you to this profession. I challenge you to recommit yourself to making the world safer and healthier.

I challenge you to unleash the power of your imagination in order to tackle the immense difficulties before us.

When you do, you might be the one who unlocks the genetics-based cure for diabetes for Hispanics. Or you might be the one who rewrites our Medicare policy so that when I really am 100, I'll be getting all the healthcare coverage I need. Or maybe you'll be the one who writes the pharmaceutical genomic protocols for that iPHARM device I so enjoyed using in my opening fantasy. Whatever your expertise, remember these other words of Steve Jobs, who really might make an i-PHARM for us someday: "Innovation distinguishes between a leader and a follower."

To my mind, one of the great Americans and leaders of the 20th century was Walt Disney. Disney intuited that there was a better way to tell stories, so he set out to discover new processes in animation that eventually set a new standard by which all cartoons would be measured. Disney knew that there was a better way to package entertainment for families, so he set out to build a new kind of amusement park – a theme park – that eventually set a new standard by which all amusement parks would be measured. Disney said, "Around here, we don't look backwards very long! We keep moving forward, opening up new doors and doing new things. Because we're curious, and curiosity keeps leading us down new paths."

Admittedly, it is more than curiosity that propels the pharmaceutical profession down new paths. We are in the business of relieving pain, suffering and illness. The stakes for our leaders are much higher than for Disney. But what interests me is Disney's perseverance to do things the right way – despite the cost, despite the work involved. Keep moving forward. Don't be satisfied with the status quo when there are so many possibilities ahead. Keep moving forward. Don't

pine for the good ol' days. Keep moving forward.

Ladies and gentlemen, the future needs you to be leaders. And the only way to get there is to keep moving forward. ■

J. Lyle Bootman, Dean of the University of Arizona College of Pharmacy, was awarded the **American Pharmacists Association's Remington Honor Medal** in March of 2008 to honor his lifetime achievement in pharmacy.

INTERVIEW WITH William Zellmer

Global Conference on the Future of Hospital Pharmacy

As part of the 2008 FIP Congress in Basel, Switzerland, the FIP Hospital Pharmacy Section will host the Global Hospital Pharmacy Conference, which will focus on The Future of Hospital Pharmacy. The meeting will identify opportunities for improvement in all aspects of the medication use process, including the procurement, preparation, distribution, prescribing and administration of medicines in hospitals. Consensus statements will be developed to offer guidance on the development of tools, timelines and tactics for achieving these advancements.

The IPJ has asked William Zellmer, Deputy Executive Vice President of the American Society of Health-System Pharmacists to comment on previous events that have served as the inspiration for this Conference and what is hoped to be achieved by bringing together these specialised practitioners on a global platform.

The first “Global” Conference on Hospital Pharmacy was held in Hilton Head, South Carolina, USA in 1985. What was the aim of the Hilton Head meeting? Who organised it?

WZ: The American Society of Hospital Pharmacists* (ASHP) and the ASHP Research and Education Foundation, in February 1985, conducted an invitational conference on “Directions for Clinical Practice in Pharmacy” at Hilton Head Island, South Carolina. Over the years, this event has come to be known as the “Hilton Head Conference” or, simply, “Hilton Head.” Reflecting on the first 20 years of the clinical pharmacy movement in the United States, the aim of Hilton Head was to assess progress in advancing clinical pharmacy education and practice and to identify practical ways to advance this facet of pharmacy. Hilton Head was organized as a consensus-building conference, with much of its work done in small discussion groups, and with participants voting on their level of

agreement with statements that were developed in the small-group discussions. Ideas espoused at the conference inspired many pharmacists in the U.S. to work for the advancement of clinical pharmacy.

Who was attending the Hilton Head meeting?

WZ: Approximately 150 pharmacy practitioners and educators were invited to the meeting, as well as observers from medicine, nursing, and hospital administration.

How were the results of the Hilton Head meeting being disseminated and implemented?

WZ: ASHP published the proceedings in its journal, and officials of ASHP wrote articles about the event and spoke about the results at pharmacy meetings throughout the country. The ASHP Foundation also made grants available to groups of hospital pharmacists at the state and regional levels to conduct “mini-Hilton Head conferences.” In this way, a large number of pharmacists learned about the ideas discussed at Hilton Head and began to make commitments to change the way they practiced their profession, consistent with the principles of clinical pharmacy.

Have changes occurred in hospital pharmacy practice in the US as a result of the Hilton Head meeting and if yes, what are the most remarkable changes?

WZ: The remarkable aspect of Hilton Head was that it led many leaders in hospital pharmacy to re-conceptualize the purpose of the pharmacy department and of pharmacists. Whereas the traditional purpose of the department had been “to deliver the right medicine to the right patient at the right time” (with the “right medicine” defined as whatever the physician ordered), Hilton Head created a new paradigm. Now many hospital pharmacists began to see their purpose as ensuring that medicines are used appropriately for the optimal benefit of the patient. Clinical ►

* ASHP’s current name is American Society of Health-System Pharmacists

pharmacy was no longer thought of as an array of services added to the portfolio of the pharmacy department; rather, the inherent mission of pharmacy as a whole was seen as clinical. Once a pharmacist reaches this conclusion, it becomes a matter of deciding what needs to be changed in his or her practice to be true to this purpose.

Have other countries and regions benefitted from the Hilton Head conference?

WZ: Clinical pharmacy has captured the imagination of pharmacists and pharmacy educators around the world. They have often looked to the United States to learn how to implement the concept in their own countries. As they have studied the situation in the U.S., they have benefited, indirectly, from Hilton Head.

Where, when and how was the idea to organise a Global Conference on the Future of Hospital Pharmacy born?

WZ: Several years ago, ASHP officials began inviting leaders of national, regional, and international hospital pharmacy societies to a discussion session at the Midyear Clinical Meeting, which is conducted every December. As these leaders talked about common issues related to the advancement of the services of hospital pharmacists, they recognized that there would be great value in a program such as the Global Conference on the Future of Hospital Pharmacy. Participants in these meetings agreed that the FIP Hospital Pharmacy Section would be the logical group to organize the Global Conference.

Given that the Hilton Head Conference was invitational, will the Global Conference be open for anyone to participate? Why?

WZ: One official representative has been invited from each nation; these individuals are empowered to vote on the consensus statements that emerge at the Global Conference (GC). In this way, the GC will truly reflect a global perspective. Other persons may register for the GC and participate in all aspects of it except the voting on consensus statements. Because this will be an historic event, many pharmacists will be attracted to the program.

How will pharmacists globally benefit from the Global Conference the way US pharmacists benefited from Hilton Head?

WZ: Conferences of this nature become forceful by creating a widely shared vision about the preferred future and by motivating individuals to make changes that are consistent with that vision. The GC has been planned to achieve this result.

Are the objectives of the Global Conference the same as those of Hilton Head?

WZ: The key similarity between the two conferences is their design to yield a shared vision that serves as the

foundation for planning. There is immense potential for hospital pharmacists to be a much more powerful force in ensuring the appropriate use of medicines, and the GC will be an important factor in spreading this vision.

Given that the Hilton Head conference involved only Americans, the Global Conference will be challenged to incorporate much greater diversity of professional practice. How will that be accomplished?

WZ: Official country delegates at the GC will be asked to indicate whether a particular consensus statement is "foundational" (i.e., has application at all levels of development), intermediate, or advanced. The conference organizers believe that this will aid hospital pharmacy leaders in all countries in developing a sense of logical progression in the advancement of pharmacy practice as more resources become available.

How will the results be disseminated? How will the statements be implemented?

WZ: A summary of the GC will be published in many hospital pharmacy journals around the world. The complete proceedings will be published in the American Journal of Health-System Pharmacy and will be freely accessible on the World Wide Web. "Implementation" of the conference will depend on future efforts of the FIP Hospital Pharmacy Section and leaders in individual nations.

Will a follow-up meeting be organised?

WZ: This may well be desirable and will almost certainly be considered by the officers of the FIP Hospital Pharmacy Section.

What does this international work mean to you personally?

WZ: For me and many other pharmacists, involvement in organizational work on the international level is rewarding in terms of personal friendships, cultural enrichment, and broadened understanding of the world in which we live. It is not an exaggeration to say that the preservation and advancement of civilization depends on greater interaction and collaboration across national and cultural boundaries, which fosters trust and empathy. Pharmacists can contribute to this human imperative through their participation in FIP's efforts to align our profession with the need that people around the world have for a health profession that is dedicated to the appropriate use of medicines. This is exciting and fulfilling work! ■

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Pharmacy in Asia

Catching up to the future

Audrey Clarissa

The pharmacy profession is, and always should be, a dynamic healthcare profession. It has much potency that still needs to be developed so that we may best meet the needs of the community. This is the reason why over the past few decades, the role of pharmacist has evolved from that of a compounder and supplier of pharmaceutical products towards that of a provider of services and information and ultimately that of a provider of patient care. The contribution of pharmacists in community and hospital settings are recognised and are continually proven successful in reducing the cost of medicines use, improving health, reducing morbidity and mortality, reducing avoidable hospital admissions, reducing medication errors, improving rational use and prescribing of medicine and increasing access to healthcare and medicines. ►

The changes that are happening have made this profession recognised as part of multidisciplinary health care team. This global movement can be clearly seen in the community pharmacy world, where people are starting to discuss the importance of Good Pharmacy Practice (GPP), which is an integral and an inseparable part of this profession. Nevertheless, at the moment the recognition of the pharmacy profession in Asia is not evenly spread. There are a few countries that have stepped forward and given pharmacists and the profession its due recognition, but the reality is that in many countries pharmacists are still greatly underutilised and practicing below their capabilities.

There have been considerable efforts expended in Asia to keep up with these global changes. Many trainings and conferences have been conducted to prepare good community pharmacists, even though the results are relatively small at the moment. However, many Asian countries still do not require pharmacists to even be in the pharmacy, and worse yet pharmacists are often not even *expected* to be in the pharmacy. In many places, prescription drugs may be purchased and acquired without a prescription. Perhaps worst of all, there is still a widespread lack of knowledge that pharmacists are able to share drug information and give patient counselling. This has led many communities to misunderstand and misinterpret the pharmacy profession; some communities do not even know that this profession exists.

There are various reasons behind this situation in Asia. For example, the ownership issue has been one of the biggest problems. In some countries, pharmacies can be owned by non-pharmacists. Problems appear when the income of the pharmacy is relatively small, prodding owners to increase the income via extremely questionable pharmacy practices such as selling prescription drugs to patients even without prescription or by giving low salaries to pharmacist so that they are not supported for their continuing professional development – an essential component for continuous learning of a community pharmacist. Sometimes the salaries are so inadequate, living expenses are not covered.

In addition to this situation, the limited authority of pharmacists in the pharmacy – especially with respect to financial and human resources issues – cause another conflict of interest with the pharmacy owner. Both situations have pushed pharmacists to find additional income in other places, transferring most of their tasks to pharmacy technicians. This is extremely detrimental to both the functioning of the pharmacy and the reputation of the profession, as pharmacists' knowledge and expertise is very important as it extends to all aspects of preparation, distribution, and action and uses of drugs and medicines.

Therefore many times, we will be able to see the name and license of pharmacists in pharmacies without them being there.

When business and healthcare become a grey area, optimum health services to patients will never be achievable.

However, the ownership of pharmacies by non-pharmacist is important as it allows the investment of financial capital to build more and better healthcare centres to better meet community needs. Nevertheless, the investors should understand that the money they are investing to healthcare cannot be purely for business intentions as they are dealing with the health and safety of people and communities. Therefore, this "outside" investment should be supported by better and clear regulation that demands the maintenance or betterment of healthcare services. This regulation should also outline the distribution of pharmacies, as it is not evenly spread in urban, sub-urban and rural area.

System and regulation improvement should be done in two ways: external and internal. External means regulation from the government, created in a manner such that it may promote good development of pharmacy practice supported by proper logistic planning of pharmacies. For example, through proper regulation pharmacists would be more encouraged to improve their own practice and profession, as they would be assured financial support and license permits or are given full decision-making authority in the running of a pharmacy even if they are not the owner.

Internal means personal and professional improvement for pharmacists and their professional organisations. Pharmacist should be able to see and evaluate their profession so that they may know what they need to do in order to increase their competence. The competence is not only limited to new developments in pharmaceutical science and keeping pace with new treatments, but also in other fields such as entrepreneurship and communication. And it is the pharmacists' associations' responsibility to support and direct the development of pharmacists and ensure current and future professional competence. This is a philosophy which is at best misunderstood, if not altogether lacking.

Professional competency is one of the most important aspects of the profession and can not only be valued just one time upon graduation. Full competency consists of knowledge, skills, attitude, behaviour and value. Pharmaceutical science is developing rapidly nowadays and pharmacists should be updated with all new drug developments and how to prevent and ideally treat many diseases. Skills should be trained and developed. Good attitude and behaviour should also be developed, particularly consid-

ering the cultural and religious values within the community of practice. And a good pharmacist should greatly value healthcare professionals whom consider it imperative to deliver good pharmacy practice. This value should remain constant regardless of changing times.

Through this system and regulation improvement, the pharmacy profession will certainly grown in awareness and respect within Asian communities. Therefore, the social marketing of this profession will only get better, resulting in more and better opportunities for pharmacists to have a more significant, positive impact on the community and take their role in the healthcare world.

These appropriate roles will also certainly result in improved collaborative relationships with other members of the healthcare team. At the same time, patients will be able to see that pharmacists are the most accessible health professionals to the public; and that they can give proper consultations that meet their needs and expectations regarding their medication and treatment as diagnosed.

That perspective, and HOPE, for pharmacists in these communities may only be achieved if these improvements are done step-by-step and continuously. The implementation of these improvements needs strong commitment from every party involved – pharmacists, pharmacists' associations, regulatory bodies and community pharmacy owners. However, this implementation should not wait for the regulatory bodies or pharmacists' associations to take action – it can be started with us as pharmacy owners and pharmacists!

The first aspect of practice that I consider to be in need of revision is the current managerial and technical system. This so that the pharmacist may have a better opportunity to implement his/her tasks properly, including patient counselling. It certainly means an extra financial investment so that the pharmacists can work full time with a good salary and so they may continue their professional development. This also means some physical investment such as modern technical tools for preparing drugs, a patient counselling room and even a drug information centre in the future. These additional investments will certainly consider the pharmacy capacity and capability; therefore, to achieve it, a strategic plan for a certain period of time should be made.

Through these continuous improvements, I hope that in the next three years there will be more pharmacies with good pharmacy practice in Asia and hopefully more than 70% of the total number of pharmacies in the next ten years. This will emphasise the pharmacists as a purveyor of good healthcare services, and the pharmacy as a real healthcare centre and no longer only as a drug shop or

drug storeroom. This is what I feel to be the main target to be achieved. There is no ideal minimum hours or minimum number of pharmacists involved as it will depend on the size and location of the pharmacy, financial capital and the evolution of public expectation and pharmacists' own willingness to expand in service, keeping in the balance of pharmacist working hours and the number of pharmacists so that each practitioner still has time to learn and develop professional skills and knowledge.

These noble notions continue to be basic challenges for community pharmacy in Asia. Once these challenges are accepted by all of us and in turn met, with the help of all stakeholders, only then we may move forward in expanding pharmacy regulation and practices to the levels already being tested and adopted by so many of our international colleagues. ■

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Balancing Brazil

Tipping the access balance analysis of availability of medicines versus health needs in Brazil

Carlos Vidotti *and* Lia Castro

In Brazil, the trend for launching of new medicines and their influence on the treatment of diseases is not known, despite the existing burden of disease. The research and development of medicines done by research groups and industries have not been able to launch new medicines for the treatment of diseases of the poor. Improving quality of life may solve significant part of burden of diseases, but when medicines are required, they must be available and accessible.

In such a scenario, characteristics of new drugs launched into the market should be known by policy makers, managers and researchers from public and private institutions, so that they could approach the issue of availability of new drugs taking into account current health needs. In the USA and Europe, 1393 New Chemical Entities (NCE) were introduced from 1975 to 1999, but only 16 are indicated to treat tropical diseases and tuberculosis (1). Additionally, there has been a systematic decrease in launching new drugs as it happens in the USA (2) and Europe (3), and, also in India (4) and Brazil (5).

In the last 10 years in Brazil, several public policies to improve availability and accessibility of medicines were approved, namely National Medicines Policy – PNM (1998), Health Fund (1999), Pharmaceutical Productivity Chain Competitiveness Forum (2003), Support Program for the Development of the Pharmaceutical Productive Chain – PROFARMA (2004), National Policy for Pharmaceutical Assistance (2004), National Policy for Medicinal Plants (2006), National Policy for Basic Care – PNAB (2006). Research and development of new drugs to treat diseases with public health impact has become a significant strategy. The PNAB focuses its efforts and resources on four priority diseases: hypertension, diabetes, tuberculosis and leprosy (5).

Objectives

The purpose of this study is to describe new drugs intended to treat the PNAB diseases, marketed in Brazil over a period of eleven years (1994-2004) and to describe the burden of these diseases.

Materials and Methods

We identified new drugs that were granted authorization to be marketed in Brazil by the Brazilian National Health Surveillance Agency (ANVISA) in the period 1994-2004 searching ANVISA database. We excluded diagnostic products, radiological contrasts, vaccines, insulines, hemodialysis products, drug combinations, blood derivatives, and immunoglobu-

lins. We described the indication for those drugs (5). Information on the most prevalent diseases in Brazil was obtained from DATASUS, the official information system of Unified Health System (SUS) (6, 7).

Results

Forty-seven new drugs were registered in Brazil for the treatment of PNAB diseases. Thirty-five (74.5%) new drugs are indicated for hypertension treatment, nine (19.1%) for diabetes, three (6.4%) for tuberculosis –rifapentine, rifabutine and terizidone – and none for leprosy.

For hypertension, in Brazil the estimated prevalence is 35% of inhabitants over 40 years old, which accounts for more than 40 million people with hypertension. The mortality rate for circulatory system diseases has been increasing. In 1998, the rate was 158.4 deaths per 100 thousand inhabitants. This year, the cardiovascular diseases were the leading cause of deaths, with 381,202 deaths.

The prevalence of Type-2 diabetes mellitus (DM) in Brazil was estimated to be 7.6% in the overall population and 17.4% in the population aged 60 to 69. In a study, almost half (46.5%) of diabetes patients did not know their own diagnosis.

The Ministry of Health estimates that by 2010 Brazil will have 10 million cases of Type-2 DM and one million of Type-one DM. In 2003, 81,053 new cases of tuberculosis were registered in the country, but sub-notification is estimated to be approximately 30%. Deaths caused by tuberculosis are estimated to be five thousand a year. In Brazil, the prevalence rate of leprosy, in 2005, was 1.48 cases per 10,000 inhabitants, and 38,410 new cases were notified.

Discussion

There is a great difference between the number of new drugs registered to treat PNAB diseases, with hypertension being subject to 35 new drugs and leprosy none. It is theorized that as leprosy affects mainly poor populations, commercial interests could be

to blame for the direction of research and development of new drugs.

The five leading causes of deaths in Brazil in 1999, were, in decreasing order, cardiovascular diseases, cancer, infectious and parasitic diseases, chronic respiratory diseases and perinatal problems (6). Only one (2,8%) of 35 new drugs indicated to treat hypertension was selected by the National Essential Drugs List – RENAME. Out of nine new drugs to treat diabetes, none was selected by RENAME. In both cases, one can consider that one of the criteria adopted by the selection process is that the drug must not be under patent protection. On the other hand, there might be a lack of therapeutic innovation in the new entities; if the new drug represented a real advance, it could be selected (5).

Three (6.4%) new drugs for the treatment of tuberculosis were identified, rifapentine, rifabutine and terizidone, but infectious and parasitic diseases were the third cause of death, with 83,791 deaths in 1998, tuberculosis nearly 6% of these(6). Nitazoxanide and eflornithine were introduced to treat parasitic diseases (5). Eflornithine is indicated for the treatment of infection caused by *Trypanosoma brucei gambiense* sleeping sickness, that does not occur in Brazil. Eflornithine was registered in Brazil to reduce women unwanted facial hair, which could classify it as a lifestyle drug.

The three levels of government – federal, state and local – buy 35% of the national pharmaceutical market and they are the biggest customer; in 2004, they spent nearly 2.1 billion American dollars on medicines. In the face of that, the government could develop initiatives with the purpose of improving research and development of new medicines driven by diseases that have great impact on public health and negative socio-economic influence. The governments have legal liability, power and financial resources to design and set up public policies to bring new and better medicines – in terms of safety, efficacy, cost, therapeutic innovation and use ▶

convenience – for the treatment of diseases that affect people (5).

The public sector of developing countries has a role to play, which is quite different from that in wealthy countries. In the former countries, the biggest part of health research is financed and done by the public sector and, thus, health research should be driven by public health needs (8-10).

Conclusion

There are diseases that now and in the future demand strategic control from SUS which are not being covered by the adopted new medicines. As previously theorized, it is speculated that new medicines launched follow mainly a commercial direction.

There is a gap between the burden of diseases and the research funding for reducing it. Market forces are not strong or interested enough to look for development of medicines to treat diseases that affect poor populations, which cannot afford their own treatment.

We propose a model for research and development which takes into account health needs, articulates competencies and has the participation of users in its management. ■

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A picture worth a thousand words

The use of pictograms for medication labelling

Elena Pascuet, Jane Dawson and Régis Vaillancourt

As technology advances beyond expectation, it may remain useless if its use is not communicated properly. This philosophy is leading us to return to a most basic form of communication in order to effectively get the message across.

Introduction

Individuals with limited literacy or language barriers face greater difficulty when attempting to interpret pharmaceutical drug labels and instructions, and therefore may unintentionally misuse a medicine. This poses unnecessary barriers for the treatment and management of chronic and acute diseases and contributes to poor adherence to prescribed drug therapy. In the 2004 Institute of Medicine report, *Health Literacy: A Prescription to End Confusion*, it was stated that “health literacy is fundamental to quality care,” and is an instrumental factor in assessing a patient’s capacity for comprehending and executing treatment plans and adhering to medication regimens (1). Health literacy is defined as the degree to which individuals have the capacity to obtain, process, and understand basic information and services, and is most often measured by reading comprehension of health-related information (1). A lower level of health literacy in patients can serve as a strong predictor for a poorer health status and well-being, increased utilization of health services, and less likelihood of receiving preventive care and services (2).

A key step to improve the level of health communication understood by patients and their families is by providing adequate patient counselling material and tools to children and their families. However, there are a number of barriers that need to be overcome in order to clearly convey counselling messages. Some patients do not understand

how to take their medications because they are unable to read the instructions, or in the case of multiple medications, remember them all. Currently, the majority of adult and paediatric drug and disease education information available is mainly in text format. To make matters worse, this text is written at a level too high for even the general adult population, when it is recommended that it should be written at the 8th-grade level or lower (3, 4). The problems associated with patient comprehension of medical instructions is difficult even in developed countries with higher levels of literacy, and are even more compounded when healthcare providers are faced with illiteracy or differences in language.

These obstacles highlight the importance of accurate and effective communication between healthcare providers and patients to ensure comprehension of pharmacotherapy, thereby promoting compliance and ensuring positive patient health outcomes. The use of pictograms can help reduce the risks related to poor patient understanding of health care information and improve comprehension among patients across all literacy levels and cultures (5).

Pictograms

Pharmacists in the Military and Emergency Pharmacy Section (MEPS) of the International Pharmaceutical Federation (FIP, www.fip.org) are involved in providing human- ▶

Name: Patient A		Patient's ID: 5555	
Medication: Drug X		Date: Feb 27, 2008	
Directions: Take 2 tablets twice a day for seven days			
Organisation: Q-EO			
	Indication 	Dose/Route Take 2 tablets with water 	
	Frequency 	In the morning and night 	
	Precautions Keep out of reach of children and infants  		

Figure 1) Pictogram storyboard concept

itarian care for patients, often where they do not have a language in common. For these reasons MEPS developed a project to design and develop pictograms to label medications. Pictograms are descriptive symbols that help convey information regarding medication and health, and can be incorporated to emphasize key counseling points. Their use helps to reduce the amount of reading required and motivates patients to follow medication instructions, therefore leading to a positive effect on the patient's ability to recall and retain medication instructions (6). In addition, they can be used to help bridge communication barriers due to varying levels of health literacy, language differences, and cultural variations.

The objectives of the MEPS pictogram initiative are to:

- To design, validate, and evaluate pictograms for labeling medications in different cultures.
- To identify culture-specific pictograms based on the continent of origin for labeling drugs.
- To provide practice tools to enable the use of pictograms.

Pictographic storyboard

Previous studies and observations have shown that low literacy adults, much like children, are not systematic in scanning visuals and lack precision in aiming, resulting in small steps of drifting eye movements around a picture. Therefore, MEPS proposed to create a unique pictographic storyboard concept to separate the fundamental aspects of a medication counselling session into four separate components flowing as a story. The use of a vertical column containing an outline of the human body serves to highlight the indication, with three separate rows to indicate dose and route of administration, frequency, and auxiliary information.

This enables key points of a counselling session to be emphasized with a less demanding and better-suited visual

format to set the foundation for complementing medication counselling and to increase patient comprehension and compliance.

Healthcare providers can now easily apply the storyboard concept in their clinical practice, either in low-technology environments (as a paper format using pictogram stamps), or in high-technology environments where computers are largely available. The online version (Figure 1) can be accessed through www.fip.org and is also available at the authors' institution internal server for fellow healthcare professionals. The storyboard concept is easy-to-use and is both patient and culture-specific in that pictograms are selected based on those most easily understood by the patient.

Culture-specific pictograms

Perceptions and opinions of health, disease and medicine may differ substantially due to cultural attitudes and beliefs. A lack of cultural specificity in the design of pictograms can be a barrier to comprehension. Therefore, one must be aware of cultural attitudes to medicine and provide culturally appropriate medication information that can be used in an acceptable way. For example, the auxiliary instruction 'take with food' requires the food of the culture to be depicted.

The MEPS working group recommended that prior to pictographic use, sources with knowledge of the country of intended use were to be consulted regarding culturally specific elements. Locally designed pictograms are often preferred by patients and result in greater comprehension than generic or international pictograms because cultural and technological differences are incorporated into their illustrations (7, 8).

Development and pre-testing of culture-specific pictograms

In collaboration with the International Federation of Pharmacy Students, culture-sensitive pictograms were submitted to student-led focus groups from various geographical regions, including Ghana, Egypt, Singapore, Hungary, Finland, India, Indonesia, Serbia, United Kingdom, Taiwan, and Australia. The pictograms submitted for their appraisal included the following: 1) take with water; 2) take with food; 3) do not drink alcohol; and 4) frequency (once a day, twice a day) for their approval. A total of 8 pictograms were originally submitted to the students under 7 categories. These pictograms were then modified by the students for usage in those specific cultures, with the addition of new ones based on suggestions made during testing.

Testing of pictograms for comprehension and practicality In association with Pharmacists without Borders (PSF) Canada, Canadian Forces, and the MEPS, pictographic instructions were given to pharmacy aides administering medications during daily use in clinical settings in Benin and Gabon, Africa with the objective of determining the ease of use and practicality of pictographic instructions.

Pictogram			
Continent of residence	n (%)	n (%)	n (%)
North America	17 (9,7)	95 (54,3)	63 (36,0)
Latin America + The Carribean	18 (18,2)	66 (66,7)	11 (15,2)
Europe	31 (8,3)	222 (59,2)	122 (32,5)
South-East Asia	3 (17,6)	12 (70,6)	2 (11,8)
Africa Region	14 (26,4)	34 (64,2)	5 (9,4)
Oceania	1 (4,8)	11 (52,4)	9 (42,9)
Eastern Mediterranean	2 (20,0)	8 (80,0)	0 (0,0)
Western Pacific	13 (12,7)	72 (70,6)	17 (16,7)
p<0,001			

Table 1) Online survey question #6: Take medication in the morning

In Gabon, the patient comprehension of the pictogram elements and storyboard concept both at the time of dispensing and upon short-term follow-up was assessed in an operational context. A large majority of the pictograms tested reached the European Commission (EC) Standard and the International Standards Organization (ISO 3864) comprehension criterion of at least 80% or 67% correct, respectively, for pictorial symbols (9).

In Benin, the acceptability and practicality of using supplementary pictographic instructions for medications by local African health care workers was tested. Pictographic labels were prepared for the most common dosing frequencies. Precautions such as 'keep out of reach of children/babies', and auxiliary instruction stickers were provided to 'stick on' as required and pre-printed on each sachet.

Validation of culture-specific pictograms

The pictograms were thus further modified based on feedback received from international collaborators. To validate the culture-specificity of these pictograms, an online survey was made available on the FIP website that asked respondents to select a single pictogram from a group of pictograms that they believe would be best understood by people from the respondent's continent of residence. A total of 845 respondents worldwide completed the survey, presented in either English or Spanish. For example, the pictogram instructing to take medication in the morning was included on the online survey (Table 1).

The results of the survey are being used to modify the online pictogram program. If a single pictogram was not understood by 80% of the population, then a combination

of a second or third pictogram will be made available for a sum of $\geq 80\%$ selection for that continent of cultural origin. Samples of pictograms most often selected in various continents are presented in Figure 2. It should be noted that each pictogram was not necessarily equally chosen by all areas of cultural origin, demonstrating cultural specificity. By specifying the continent of cultural origin for a given pictogram will allow for it to be best understood by that individual, and may help reduce interpretation errors. ►

Medication instruction	Pictogram(s)
Take medication in the morning	 
Take medication in the evening	
Take medication at night	 
Take medication with food	 
Do not drink alcohol with your medication	
Take medication with water	

Figure 2) A sample of pictograms generally preferred by most continent subgroups.

Conclusion and practical implications

The use of culturally sensitive pictograms, either presented individually or in a storyboard concept, in conjunction with written and verbal instructions can produce positive results in the comprehension of drug information. This initiative responds well to the world's changing diversity and the need to find supporting tools of communication. Pictograms have been recognized as serving an integral component of medication labelling program framework. Further studies are warranted in order to determine the acceptability by healthcare providers and therefore the usability and applicability in other real life situations. ■

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Historical non-involvement
and future opportunities:

Pharmacy and TB

International Pharmaceutical Federation (FIP) Collaborating Centre



The International Pharmaceutical Federation (FIP) and the School of Pharmacy, University of London is pleased to announce the establishment of the first FIP Collaborating Centre (FIPCC). The purpose of the FIPCC for Pharmacy and Health is to serve as a conduit for expertise, research, capacity building, innovation and development in collaboration with key stakeholders including FIP Member Organisations, WHO and UNESCO. The FIPCC will provide expert institutional support through research, policy analysis and technical advice to enable and catalyse FIP's expanding global activity in medicines and public health policy, human resources for health and education. This paper on Pharmacy and the prevention and treatment of Tuberculosis is the first of a series of papers from the FIPCC. ►

Summary

Tuberculosis has prevailed for thousands of years but control of this disease has never been more critical – the last decade saw the greatest number of TB cases than in any other decade in history. Why is it, then, that there has been so little pharmaceutical development in this disease over the last forty years? Why have pharmacists historically taken a ‘back seat’ in TB control? This report, the first of a series of reports to be released by the International Pharmaceutical Federation (FIP) Collaborating Centre hosted by the School of Pharmacy, University of London, presents these questions in the current global context – with specific examples – and attempts to bring together evidence of what is being done and what could be better done by pharmacists for global TB control.

Background

Tuberculosis has been globally endemic for thousands of years. Evidence of TB has been uncovered in Egyptian mummies three thousand years old (3) and in Incas up to 26,000 years ago (5). More recently, industrialisation and the resulting urbanisation has resulted in the various epidemics observed today. For example, the TB epidemic in Europe in the 19th and early 20th century preceded the epidemics now being observed in sub-Saharan Africa and parts of Southeast Asia.

It has been argued that sociological improvements, such as better sanitation and housing, have resulted in the greatest reduction in TB prevalence in the United Kingdom. Rates of TB mortality were decreasing long before the advent of antituberculous medicines or vaccination and even before the identification of the TB bacillus by Robert Koch. Figure 1 displays the reduction in TB mortality in England and Wales before and after the introduction of medical interventions in the mid-20th century. Nevertheless, many thousands of people have benefited from the introduction of both medicines and vaccination

and, therefore, medicine can be seen to have ‘added value’ in terms of TB eradication.

In the light of advances in diagnoses, vaccination and medicines, it is a valid question to ask why we have not achieved the same success with eradicating TB that we have with other diseases, such as smallpox. Several characteristics of TB and TB treatment challenge this degree of efficacy. TB is a mycobacteria, inferring that it has a thick waxy cell wall and as such is relatively impenetrable to medicines and therefore difficult to treat. In addition, bacterial growth of *M.tuberculosis* is relatively slow such that bacteria are less likely to be dividing when they are most susceptible to anti-bacterial drugs. It took almost 15 years from the discovery of penicillin (which is used widely for many types of infections) before the first efficacious anti-TB drug (streptomycin) was isolated. Even with the introduction of newer and more efficacious medicines such as isoniazid and rifampicin, the duration of treatment of TB is a minimum of six months.

A number of anthropic factors contribute to the prevalence of TB globally, with estimates of one-third of the world's population being infected (7). The HIV/AIDS epidemic has greatly impacted on the incidence of TB. Deterioration of the immune system and reduction of CD4+ cell count results in the progression of TB (9). However, TB and HIV interact pathophysiologically, clinically and epidemiologically (11;12) – See Box 2. Concurrent infection with HIV in those already infected with TB increases the risk of development of overt TB disease (6). The increased risk of infection may also be due to re-infection which is of greater consequence in areas such as sub-Saharan Africa (Figure 2), where the prevalence of both TB and HIV is high (13;14).

In terms of treatment, TB appears to have been a victim of its own success – if the correct medications are taken

BOX 1: TB BASICS

AETIOLOGY AND TRANSMISSION

Tuberculosis (TB) is caused in humans by the bacteria *Mycobacterium tuberculosis*. TB is not particularly virulent, as compared with influenza for example, but prolonged exposure will lead to infection. Infection progresses to disease in approximately 10% of individuals over their whole lifetime. Factors such as malnutrition, impaired immunity or concomitant disease increase the likelihood of disease progression.

DIAGNOSIS

Includes chest X-Ray, sputum smear microscopy and cultures of sputum or a biopsy.

TREATMENT

The World Health Organisation (WHO) recommends the treatment of drug-susceptible pulmonary TB using two phases. The initial two-month phase involves a regimen of rifampicin, isoniazid, pyrazinamide and ethambutol. The four-month continuation phase is a regimen of rifampicin and isoniazid.

PREVENTION

Includes primary prevention of infection and secondary prevention of disease. Primary prevention involves reducing exposure and transmission with the BCG vaccination available to aid this. Secondary prevention may involve treatment of latent TB infection (LTBI) using antituberculous drug regimens.

STRATEGY

Six-point Global WHO Stop TB Strategy:

1. Pursue high-quality Directly Observed Treatment, Short-course (DOTS) expansion and enhancement
2. Address TB/HIV, MDR/XDR-TB (Multi-drug and Extensively Drug-Resistant Tuberculosis) and other challenges
3. Contribute to health system strengthening including health workforce capacity
4. Engage all care providers
5. Empower people with TB, and communities
6. Enable and promote research

BOX 2: TB AND HIV

- Immunosuppression associated with HIV infection will jeopardize any immune defence against TB, and may also affect clinical or radiological characteristics, for example, the tuberculin skin test (4). Evidence suggests a symbiotic association between TB and HIV; HIV infection enables greater replication of *M.tuberculosis* and this may augment replication of HIV (before treatment).
- Risk of reactivation of latent TB is increased by HIV infection. Some reports suggest a 24 times greater risk in tuberculin positive HIV infected patients (6). Development of TB disease from primary infection is also more likely in patients with HIV infection and may be a significant contributing factor to the increase in TB (8).
- Due to the ubiquitous nature of global TB infection and the epidemic levels of HIV and AIDS, cross-over infection (co-infection) between the two is immense, estimated at 11 million people (10).

BOX 3: GLOBAL BURDEN – THE FACTS (2)

- Over 14 million cases of TB in 2006; over 9 million new cases of TB in 2006
- 8% of new cases were HIV-positive; over 11% deaths from TB were in HIV-positive cases
- The highest incidence rate per capita is in the African Region (363 per 100,000 population)
- The African, South-East Asia and Western Pacific regions accounted for 83% of total case notifications
- Approximately 0.5 million cases of multidrug-resistant TB (MDR-TB) in 2006

as prescribed, current treatment can achieve cure rates of over 97% (15). In addition, the World Bank has considered the WHO “DOTS” strategy to be one of the most cost-effective of any health intervention (16). This may explain why there have been no newly developed first-line drugs since rifampicin in 1966.

Certainly, TB eradication has been hindered by the long duration of treatment, making it more difficult for patients to tolerate the full treatment. In this sense patient adherence to treatment presents a significant obstacle and is a reason for the direct observation of consumption of medications advocated by WHO in high prevalence countries. Poor adherence is partly responsible for the rise in drug resistance. This was apparent very soon after the introduction of streptomycin (17). In using a combination of three medicines, the probability of resistance occurring is negligible (18) and therefore would not be observed in current practice if medicines were used appropriately. Medicines must be prescribed judiciously and patients given the support needed to ensure completion of treatment, particularly when the regimen is complex and/or protracted.

Finally, it is pertinent to also consider how national infrastructure impacts on global TB incidence. For example, Afghanistan has experienced decades of war and also exhibits incidence of TB in excess of 300 cases per 100,000. Similarly, the collapse of the Soviet Union and the resulting breakdown of healthcare infrastructure was likely responsible for increases in TB incidence in the 1990s in Eastern Europe. It is noteworthy that two peaks in TB notifications and deaths were observed in the UK after the respective World Wars (Figure 1) although commentators suggest this may also be due to reporting issues as well as the influence of war and infrastructure (19).

Targets, strategies and policy

A number of targets have been set in

the light of the global burden of TB. Tuberculosis is included as a Millennium Development Goal (target 6) which aims to ‘halt and begin to reverse the incidence of malaria and other major diseases’ by 2015 (20). In addition to this, the ‘Stop TB Partnership’ introduced two targets to halve TB prevalence and death rates from 1990 to 2015 (see Box 4). In order to meet these targets, the newly introduced Stop TB Strategy (2006) sets out interventions which include six specific components (see Box 5). This builds on the previous WHO DOTS strategy (1991) with DOTS being one of the key components.

To meet the various specific targets, the Stop TB Partnership has instituted strategic action plans. Around these actions a number of working groups have been convened to enable DOTS expansion, DOTS-Plus for multidrug-resistant TB, TB/HIV, new TB diagnostics, new TB drugs, new TB vaccines, and advocacy, communications and social mobilization. This appears to have resulted in an increased output in both pharmaceutical development and local, national and global action to combat TB.

New pharmaceutical interventions in TB control

Following the resurgence of TB (predominantly due to HIV and increasing rates of resistance) there has been a renewed interest. This has resulted in greater funding both by the World Bank, from which most funding is obtained, and pledges from the Bill and Melinda Gates Foundation amounting to \$900 million (US). Consequently, there are a number of pharmaceutical interventions involving vaccination, diagnoses and treatment currently being developed and evaluated. However, if there is to be a significant impact on global TB control, any new technologies must be applicable in resource-poor developing country settings where the greatest burden of TB lies. With this in mind it is vital to develop interventions that are valid and effective in HIV-infected populations. ►

Vaccination

The BCG vaccination is controversial with evidence suggesting efficacy ranging between 0 and 80% (21). Efficacy appears to vary according to latitude with lower efficacy in countries nearer the equator. In addition, although the vaccine prevents TB meningitis in children, evidence is weaker for its efficacy in adults. This may relate to a waning effect that occurs over time. Finally, the BCG interferes with the immune-response dependent tuberculin skin test for latent tuberculosis (for example, Mantoux and Heaf tests) and is also contraindicated in immunocompromised individuals.

However, with 2-3 billion people vaccinated globally the BCG certainly has its advocates; administration is relatively simple (and can even be given orally) and the vaccine is cheap. Nevertheless, it is clear that there is a need for a new vaccine that is not only efficacious but also prevents infection of TB and eradicates established infection. In addition, it would be desirable to have a vaccine that is easily administered and prevented all forms of TB, including resistant strains, in both children and adults whether immunocompromised or not. A number of candidates are in various stages of development (Table 1) and these include methods of boosting the response to, or enhancing, the immunogenicity of BCG itself, and whole cell preparations that may act as an adjunct to drug treatment of TB and latent TB infection (LTBI) (22).

Diagnosis

Current diagnostic techniques can be broadly grouped into diagnoses of TB and LTBI. The former include a variety of very different methods, including clinical diagnoses, chest X-ray, sputum smear microscopy, and culture of sputum or biopsy for confirmation of diagnoses and for susceptibility testing of resistant TB forms. In general, the quicker tests, such as X-ray and sputum smear microscopy, lack sensitivity and specificity; whereas the more sensitive and specific culture

and susceptibility tests take much longer (up to 6 weeks) and treatment must be started provisionally before these results confirm TB.

The ideal tool for TB diagnosis should include a number of features:

- Be able to confirm bacterial sensitivity (resistance) and TB type (pulmonary or extra-pulmonary; TB or LTBI) while excluding non-tuberculous mycobacteria;
- Give an indication of severity of disease and demonstrate high sensitivity and specificity in immunocompetent and immunocompromised patients;
- Be quick and give rise to fewer patient visits;
- Relatively inexpensive.

There are a wealth of tests in development and under evaluation, some of which show promise in resource-poor settings (Table 1). One example is the microscopic observation drug-susceptibility assay (MODS) which uses simple light microscopy to detect growth of mycobacteria in media with or without the presence of antimicrobial drugs to conduct sensitivity testing (23). Essentially, growth/no growth of mycobacteria, as seen under the microscope, indicates a result and is considerably quicker than current methods – 8 days compared with 4-6 weeks. This method is inexpensive and simple demonstrating good sensitivity and shows promise for resource-poor countries.

For LTBI, the immune-based tuberculin skin tests (TST, for example, Heaf and Mantoux) are available and work on the principle that by injecting a small amount of TB protein antigen under the skin, the body will elicit an immune response if the antigen has been encountered before. Therefore, this test is only reliable in immunocompetent individuals and as such may exclude not just HIV-infected individuals but also the very young or old. There are also other reliability problems with the TST. There is no conclusive evidence that TST can be

BOX 4: STOP TB PARTNERSHIP TARGETS (1)

Established in the year 2000 the Stop TB Partnership ultimately aims to eliminate TB through the collaboration of various international organizations, countries, public and private donors, governmental and nongovernmental organizations and individuals.

- By 2005, and to be sustained or exceeded by 2015: At least 70% of people with infectious TB will be diagnosed (under the DOTS strategy) and at least 85% of those diagnosed will be cured.
- By 2015: the global burden of TB disease (disease prevalence and deaths) will be reduced by 50% relative to 1990 levels. Specifically, this means reducing prevalence to 155 or fewer per 100,000 population, and reducing deaths to 14 or fewer per 100,000 per year by 2015, including people coinfecting with TB and HIV. The number of people dying from TB in 2015 should be less than 1 million.
- By 2050: TB will be eliminated as a global public health problem. Using the criterion for TB elimination adopted in the USA, this means that the global incidence of TB disease will be less than 1 per million population.

BOX 5: SIX COMPONENTS OF THE STOP TB STRATEGY (1)

1. PURSUE HIGH-QUALITY DOTS EXPANSION AND ENHANCEMENT

- Political commitment with increased and sustained financing
- Case detection through quality-assured bacteriology
- Standardized treatment with supervision and patient support
- An effective drug supply and management system
- Monitoring and evaluation system, and impact measurement

2. ADDRESS TB/HIV, MDR-TB AND OTHER CHALLENGES

- Implement collaborative TB/HIV activities
- Prevent and control multidrug-resistant TB
- Address prisoners, refugees and other high-risk groups and special situations

3. CONTRIBUTE TO HEALTH SYSTEM STRENGTHENING

- Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery, and information systems
- Share innovations that strengthen systems, including the Practical Approach to Lung Health (PAL)
- Adapt innovations from other fields

4. ENGAGE ALL CARE PROVIDERS

- Public-Public, and Public-Private Mix (PPM) approaches
- International Standards for Tuberculosis Care (ISTC)

5. EMPOWER PEOPLE WITH TB, AND COMMUNITIES

- Advocacy, communication and social mobilization
- Community participation in TB care
- Patients' Charter for Tuberculosis Care

6. ENABLE AND PROMOTE RESEARCH

- Programme-based operational research
- Research to develop new diagnostics, drugs and vaccines

reliably used more than once and may actually boost or prime the immune system by stimulating a response itself. These tests may also render false positive results if an individual has either been infected with non-tuberculous mycobacteria or has previously been inoculated with BCG. Finally, the result must be read 72 hours after the test has been performed. This requires the individual to visit the TB service twice and this bears inherent limitations. These limitations suggest that there is a need for a reliable, sensitive, specific and quick test that is easy to administer and read.

In part, at least some of these criteria have been met with the interferon gamma release assays (IGRAs) including the QuantiFERON® – TB Gold and the T-SPOT® TB tests. These work on the principal of the immune 'communicator' cytokine – interferon gamma – being produced in the presence of a specific antigen. The interferon is either quantified itself or the resultant effects are quantified. On limited evidence, these tests appear to compare well with the TST in terms of sensitivity and specificity, the fact that they can be reliably performed more than once and show promise in the immunocompromised with fewer patient visits. The main drawback, however, is that they are considerably more expensive (although savings are made in reduced patient visits) and are therefore not ideal in resource-poor settings.

Treatment

Treatment is technically separated into treatment of TB and LTBI although the medicines used and the limitations to these are similar. Treatment of TB takes a minimum of six months but for extra-pulmonary TB, drug-resistant TB or co-infection with HIV, treatment is longer and more complex. It is worth mentioning that approximately half the cases of TB in London, for example, are extra-pulmonary representing a significant burden (rates of extra-pulmonary TB in new TB cases in 2006 varied between 1 and 36%, average 15.3%, in the twenty-two

WHO-defined 'high burden' countries (2)). The initial regimens used in treatment include a minimum of four medicines, each of which, although highly efficacious, has characteristics that can compromise patient tolerability. For example, rifampicin is a powerful enzyme inducer and consequently interacts with many other medicines including the oral contraceptive pill and, notably, some anti-retroviral therapy. It is also excreted in body fluids imparting orange/red discolouration to urine, tears, etc. and can cause liver toxicity requiring ongoing liver function tests. Hence, treatment for TB, from the patients' perspective, is at best unpleasant especially considering the duration of treatment. This may explain why resistance occurs as a consequence of non-adherence and signifies a need for much shorter regimens with an improved side effect profile.

In the case of LTBI treatment, or chemoprophylaxis, the same issues are apparent. In the UK, 6-month daily isoniazid or 3-month rifampicin plus isoniazid are recommended for routine use (24). However, as only one in ten individuals infected with TB will progress to disease, the emphasis of treatment is on safety and must be balanced against the serious consequences of hepatotoxicity. Adherence rates to preventive treatments are lower than with TB treatment, perhaps due to the absence of symptoms, the long duration of treatment and the consequences of non-adherence not being seen as significant. Chemoprophylaxis may not be utilised in high burden resource-poor settings where the emphasis on TB control is likely to be in treating TB.

A number of medicines have shown some promise. These include novel agents as well as existing chemotherapies (Table 1). Existing drug classes such as the fluoroquinolones, including moxifloxacin and gatifloxacin (already licensed for other indications) are currently used outside their licence as second-line antituberculous drugs and are under continuing eval- ▶

Table1: Emerging technology in response to limitation in TB control

	Existing technology	Desired features	Emerging technology/ innovation
Prevention (Vaccination)	BCG: Widespread use; simple administration; low cost; waning effect; variable efficacy; no proven efficacy in adults; contraindicated in immunocompromised	<ul style="list-style-type: none"> • Prevent invasion of pathogen • Eradicate established infection • Simple administration (oral?) • No waning effect 	<ul style="list-style-type: none"> • Boost response to BCG (e.g. viral vectors, protein in adjuvant) • Enhance immunogenicity of BCG (e.g. altered BCG) • Whole cell preparations (e.g. environmental mycobacteria)
Diagnosis			
LTBI	TST, e.g. Mantoux, Heaf	<ul style="list-style-type: none"> • Improved sensitivity and specificity • Reproducibility (no boosting phenomena) • Instant/quick and simple results • No cross-reactivity with BCG or NTM • Low administration costs: training, laboratory requirements • Effective in immunosuppressed (HIV, children, elderly) 	Interferon gamma release assays (IGRAs), e.g. T-SPOT®. TB, QuantiFERON®
TB	<ul style="list-style-type: none"> • Clinical • Radiology (chest X-ray) • Sputum smear microscopy • Sputum/biopsy culture and sensitivity testing 	<ul style="list-style-type: none"> • Highly sensitive and specific • Detect resistance • TB type (include extrapulmonary; exclude NTM) • Severity of disease • Immunocompromised patients (HIV, children, elderly) • Low administration costs: training, laboratory requirements, patient visits, Instant/quick and simple results 	<ul style="list-style-type: none"> • Nucleic acid amplification tests (NATs) • Immunologic tests (IGRAs) • MPB64 Skin patch test – differentiates TB/LTBI • Rapid culture systems – sensitivity testing • Rapid detection of drug resistance: <ul style="list-style-type: none"> – Line probe assays – Bacteriophage-based assays – Molecular beacon assays – Microscopic observation drug-susceptibility assay (MODS)
Treatment			
LTBI & TB	<p>LTBI: Short and safe regimens</p> <p>TB: Short and relatively safe regimens</p> <ul style="list-style-type: none"> • Work concomitantly with HIV therapy • Treat MDR-TB 	<p>LTBI: 3-month rifampicin plus isoniazid regimen (UK guidelines; not advocated in the US); 6-month isoniazid regimen (UK guidelines)</p> <p>TB: 6-month regimen including, 2-month initial phase – rifampicin, isoniazid, ethambutol plus pyrazinamide regimen; 4-month continuation phase – rifampicin plus isoniazid regimen</p>	<p>Existing drugs: Fluoroquinolones – moxifloxacin and gatifloxacin (already licensed for other indications)</p> <p>Related drugs: Rifamycins – rifabutin (use in HIV) and rifapentine (long t1/2 but limiting contraindications, e.g. use in HIV+)</p> <p>Oxazolidinones: e.g. linezolid</p> <p>New drugs: PA-824 (nitroimidazole, Phase I trials in 2005); disrupts protein synthesis and ability to make a fatty acid (cell wall) – targets non-growing bacteria, effective against resistant strains?</p> <p>TMC207 (Diarylquinoline): yields culture conversion within 2 months in animal model when substituted into existing drug</p>

Note: LTBI=Latent TB infection; MDR-TB=Multi-drug resistant TB; HIV=Human immune-deficiency virus; BCG= Bacillus Calmette-Guérin; NTM=Non-tuberculosis mycobacteria; TST=Tuberculin skin test

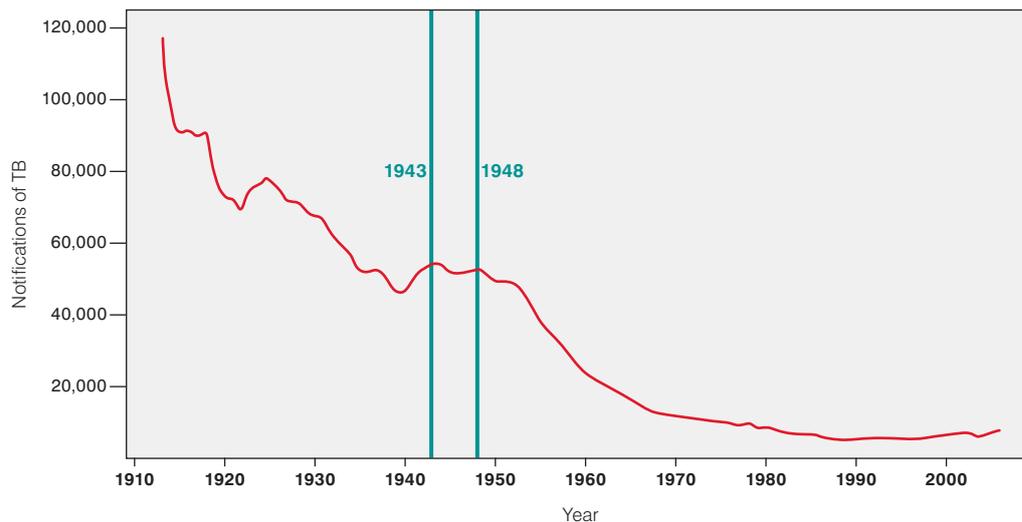


Figure 1: Notifications of TB in England and Wales before and after medical interventions (data source: Notifications of infectious disease (NOIDs), Health Protection Agency, 2008)

uation in clinical trials. Although they may prove useful as an adjunct to existing regimens, or potentially displacing pyrazinamide, for example, they are not the 'magic bullet' treatment that will significantly reduce duration of treatment or reduce the number of medicines used in anti-TB regimens. However, they may allow a greater degree of choice of treatments that is currently lacking.

Another group of existing drugs, the rifamycins of which rifampicin is a member, also show promise, for example, the use of rifabutin in HIV infected individuals, or rifapentine which exhibits a long serum half-life. However, both are less efficacious than rifampicin.

Two novel agents, among a growing number, potentially show promise: the nitroimidazole PA-824 and the diarylquinoline TMC207 (25). PA-824, which was entered into Phase 1 clinical trials in 2005, disrupts mycobacterial protein synthesis, disabling its ability to make fatty acids essential in cell wall construction. This agent also appears to target non-growing (dormant) bacteria, an essential sterilising property, and may also be more efficacious against resistant forms. When substituted into existing regi-

mens TMC207 has yielded complete culture conversion within two months in animal models (Phase 1 clinical trials)(22). If successful, these two agents, along with others, may have a significant impact on reducing durations of current treatment, although it will certainly be some years before this is realised.

TB formulations

Oral liquid preparations are not readily available: Currently in the UK only isoniazid and rifampicin are manufactured (26) and in India rifampicin, pyrazinamide oral suspensions and isoniazid syrup are currently available on the market (MS Gharat, personal communication, 2008). If liquid preparations are required for first-line TB medicines, they can be specially ordered and manufactured but the shelf-life is much reduced and they are expensive. In addition, combined anti-tuberculous preparations exist with the aim of improving adherence but none incorporate ethambutol. While evidence from Indonesia does not appear to support a four-drug combination of TB medications (27), a logical first step would be to improve the range of drug formulations available to allow greater concordance between healthcare professionals and patients, improve the supply of

medicines that are available to children and an alternate choice for non-adherent patients.

There are a number of novel drug delivery systems that are being investigated that may improve both the delivery of medicines and their administration (28). These include microspheres, microparticles, nanoparticles, and liposomes that may be administered as inhaled, depot, implant and aerosol preparations.

Pharmacy and TB

Pharmacists have long been involved in many aspects of TB control. For example, pharmacy has been used as a resource in many countries to provide TB surveillance from the dispensing records of antituberculous medicines (29-33). Similarly, adherence has been monitored through pharmacies in terms of patient timeliness of medicines collection, and adherence to notification of TB to public health authorities (34-36). Interventional roles for pharmacists are also reported. These include management of treatment of LTBI, TB patient counselling, active participation in a multidisciplinary TB teams, on-site TB drug preparation, providing medication profiles, and facilitating therapeutic drug monitoring (37-41). However, it is in the area ►

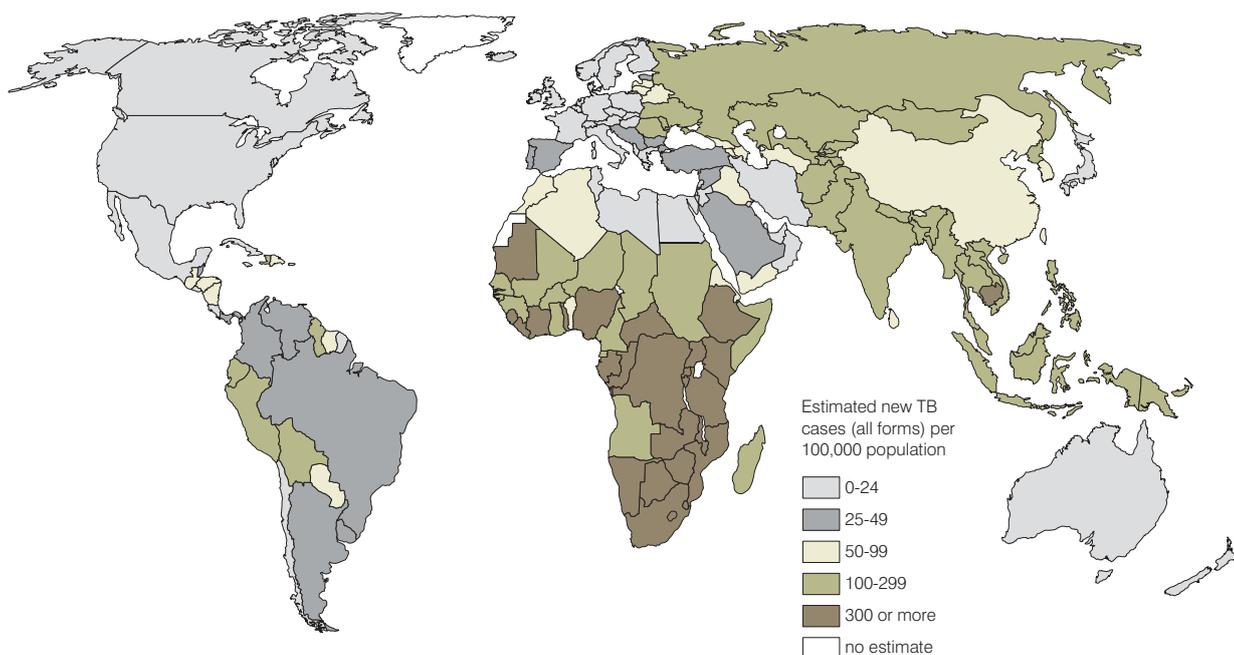


Figure 2: Estimated global incidence of TB (WHO, 2008)

of providing DOT that pharmacists have, perhaps, demonstrated greatest promise.

Final comment

Pharmacists have demonstrated their use in provision of DOT both in a high-burden developing world setting and a low-burden developed world setting. The ubiquity of pharmacies globally provides a means for delivering a safe, convenient and accessible service in the heart of communities. If safe and structured systems could be effected, as in India, to allow the expansion of pharmacy DOT globally, there would likely be improved adherence to treatment with greater professional involvement and consequently safer delivery of care.

Pharmacists' contribution to TB control should not be limited to DOT. Certainly, through their public health role they can actively participate in TB screening programmes. As screening for disease is notoriously inefficient, providing a 'walk-in' service, within community pharmacies, could dramatically improve the efficiency of current systems such as the Port of Arrival screening and mobile X-ray units. Members of the public in high prevalence areas could be encour-

aged to access screening through community pharmacies. Pharmacists and pharmacy technicians could be trained to perform Mantoux or IGRA testing 'in-house', or refer individuals to TB services on a risk-assessment basis.

In addition, as treatment of LTBI is essentially an exercise in supplying medicines and monitoring side effects, pharmacists are well placed professionally to take on this role. One model could see patients initiated on treatment by a TB service and then referred to collect their medicines regularly from their local community pharmacy.

It is important that pharmacists and pharmacies are recognised as a valuable resource in the battle against TB both in high and low prevalence areas. However, it is perhaps more important that pharmacists themselves recognise that they have the necessary skills and infrastructure to deliver aspects of TB services for the safe and effective delivery of patient care and contribute to TB control.

This year is the 30th anniversary of the Alma Ata declaration that focuses on primary health care with the

increased attention of policy makers on the potential the private and community sectors hold in providing a broader outreach for preventative and curative services to scale up public health interventions. If pharmacists are proactively prepared they are well positioned to operationalise the medicines centred and patient focused vision for pharmacy practice. ■

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Pharmacy DOT – A tale of two countries

The London experience

Community pharmacy-provided DOT (termed P-DOT) has recently been commissioned in North East London and is currently being implemented and evaluated. As the UK is a low prevalence setting, DOT is not routinely provided and reserved only where adverse factors present, such as a history of non-adherence. Previously, DOT was provided in TB services as an intermittent treatment given thrice-weekly. However, this may not have provided the most convenient access of care for patients (although those with significant social needs may have benefited from concurrent case-worker involvement that some TB services in North East London provide). There are five TB services

in North East London serving the seven Primary Care Trust (PCT) areas. Within each PCT there are roughly 60 community pharmacies. A fraction of community pharmacies providing DOT within these PCTs would likely provide better access for TB patients both geographically and from the extended opening hours that most pharmacies provide. In addition, patients would benefit from expert pharmaceutical advice and patient advocacy that could be provided for non-English speaking individuals given that pharmacy staff are likely to be from the surrounding area (North East London includes areas of high proportions of ethnic minorities and also immigration). P-DOT is also a politically

good direction following the release of the interim report by Lord Darzi (42) which suggested greater provision of healthcare in the community, rather than in the acute sector. In addition, this is favourable in terms of the Stop TB Strategy in several ways: Pursuing high-quality DOTS expansion and enhancement; engaging all care providers; empowering people with TB and their communities. Finally, this service is more easily deliverable under the new Pharmacy contract in England and Wales whereby pharmacists are rewarded more for the services they provide rather than the number of prescriptions they dispense. P-DOT is currently being implemented and evaluated in North East London.

The Indian experience

Pharmacies in India are recognised as a healthcare resource. However, the risk of the over-availability of medicines is also an acknowledged concern with individuals able to purchase TB medications with or without prescription (43). In addition, TB patients were reported to experience stigmatisation in queuing up at and attending public health TB programmes where it would be obvious they had TB – confidential care, however, can be provided in pharmacies. It is partially for these reasons that pharmacists in the State of Maharashtra – an area representing a population of 13 million and 77000 registered pharmacists – have actively engaged with public authorities to act as partners in TB control. Pharmacists were keen to

demonstrate their public health role in contributing to improve TB patient outcome through their outreach activities and by providing a safe and more convenient access for patients to TB medications. Educational workshops were designed and facilitated: The Educational programme was part of the “TB Fact Card Project”, a collaborative project of the Indian Pharmaceutical Association with Commonwealth Pharmaceutical Association & International Pharmaceutical Students’ Federation, implemented in 2005-2006 in Mumbai. Subsequently, pharmacists were invited from high burden districts of Mumbai (State of Maharashtra) to participate in the training. In addition, participant pharmacists were encouraged to use the

Good Pharmacy Practice Manual developed by the Indian Pharmaceutical Association, Central Drugs Standard Control Organization, and the WHO India Country Office. This led to a number of outcomes. The training provided education about TB and also information regarding DOTS. In addition, a pilot project involving fifty pharmacists in the district provided various TB services and monitored patient outcomes. Finally, a project allowing DOT-provider pharmacists, has followed the TB Fact Card Project (44). This included training by the Government TB Control Department about provision of DOT treatment (Figure 3) and is currently being monitored.

Interprofessional Collaboration as a Catalyst for Change

A Personal Opinion Paper

Steven J. Hoffman

Healthcare is changing. Gone are the days of isolated professional silos and provider-centricity. The consumers of health care are now demanding quality services from a range of health professionals, delivered by those who they believe are best qualified to provide it. Today's patients have little patience for hierarchy, turf wars or miscommunication among the various health professionals they consult, and the research evidence shows that any of these aggravations may also affect their health care outcomes.

The future will undoubtedly feature changes to the way health professionals practice. The world simply does not have enough of them, nor are they mixed or distributed evenly (or equitably) among the places where they are needed. According to the World Health Organization, we currently lack 4.3 million health workers worldwide; 36 of the 57 countries with severe shortages are on the African continent (1). While the global health community is largely focused on “scaling-up” the production of health workers, the sheer numbers dictate that a quick resolution to this crisis may not be possible without changes to the way we educate health professionals or the way in which they practice. Indeed, the 59th World Health Assembly in 2006 called for the development of “innovative approaches to teaching [health professionals]” (2), and many groups – such as the Global Health Workforce Alliance – have been tasked with meeting this challenge.

One innovative strategy recently endorsed by the World Health Organization (3) is interprofessional collaboration, which is a patient-centred, team-based approach to health care delivery that synergistically maximizes the strengths and skills of each contributing health professional (4). The goal of this approach is to optimize both the quality and efficiency of health care systems. Research shows that successful interprofessional care can result in fewer errors, lower patient mortality rates, fewer hospitalizations, enhanced patient satisfaction (5), and increased staff motivation, well-being and retention (6). While teamwork in health care is not a new idea, perhaps advances in communication technologies (e.g., electronic health record) and our understanding of organizational behaviour (e.g., on issues related to power and hierarchy) will help us achieve a level of collaboration that had previously been impossible. Regardless, it is clear that this paradigm is the future face of

health care as it has the potential to radically transform health professional practice for the better so that upcoming health needs can be met efficiently and effectively with quality health care services.

This radical transformation in health care delivery, however, will not only take place in the practice setting. Great changes to every system-level structure supporting health professionals will be necessary to foster and facilitate this fundamentally different way of providing health care. Changes will soon be seen in the regulatory and accountability systems, as well as in the leadership, governance and remuneration of health care teams. Institutional processes and medico-legal liability systems will also have to adapt to a future with collaborative decision-making where all team members are jointly responsible for their own mistakes and those of their colleagues. But perhaps the greatest changes will take place in the education sector, where interprofessional education will increasingly be mandated to ensure that the next generation of health professionals have the knowledge, skills and behaviours necessary to work collaboratively. In many places it is these health professional students who are advocating for change and championing this approach (4).

Several countries have already taken bold steps to move toward this direction. Governments in Canada and the United Kingdom, for example, have recently invested millions of dollars to create an interprofessional workforce and make the necessary changes to support it. International networks of educators, researchers and policymakers now exist in several countries and regions (including Australasia, Canada, Europe, Scandinavia and the United Kingdom), and numerous centres of excellence in interprofessional education have been established at universities in every part of the world. The World Health Organization has also recently launched a study group on this issue to advance interprofessional education and collaborative practice internationally (3). Global momentum has already taken hold.

Interprofessional collaboration will be the future face of health care and will catalyze revolutionary changes to the various structures that support it. This is indeed an exciting time for health care and health professionals. Let us work together for better health and make collaborative practice a reality. ■

Author's Information

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Launch of the Action Plan: Dr Manuel Dayrit, Director, Human Resources for Health Department and Dr Kamal Midha, President, FIP

Launch and implementation of the Pharmacy Education Action Plan 2008-2010

Moving Forward

WHO UNESCO FIP Pharmacy Education Taskforce

The unique partnership between the UN agency for Health (WHO) and the UN agency for education (UNESCO) together with FIP, launched the Pharmacy Education Action Plan 2008 – 2010. The launch was held at the Global Health Workforce Alliance Global Forum for Human Resources for Health on the 6th of March 2008, Kampala, Uganda. This summary provides an update of the progress of the Taskforce and plans for the near future.



Kampala launch (from left): Prof Ian Bates, Project Lead Vision and Competency – Tana Wuliji, Project Manager, FIP – Dr Tina Brock, Communications Liaison – Alawi Sebalu, Uganda Pharmacy Student's Association – Nomvula Mapule Mabuza, International Pharmaceutical Students Federation – and Prof Claire Anderson, Project Lead Capacity.

Launch of the WHO UNESCO FIP Pharmacy Education Action Plan 2008 - 2010

The Pharmacy Education Action Plan was launched in the spirit of the FIP President Dr Kamal Midha's call for participants to take a proactive and constructive role to address gaps and use innovative and participatory means to develop education. The Action Plan focuses on addressing bottleneck issues in pharmacy education such as academic and institutional capacity, quality assurance, vision and competency. The joint effort of these organizations facilitates a more effective, efficient and concrete approach as well as enabling a multisectoral platform for dialogue, learning and sharing of evidence and experience at global, regional and local levels.

The launch affirmed the need to harness the mutual interests, expertise and efforts of education and health sectors and professional bodies towards tangible steps that build education capacity. In a shifting environment of professional roles and challenges, it is crucial to enable progression towards a pharmacy

workforce that is relevant to providing services that meet local needs. In order to move beyond the current paradigm of stand-alone content driven educational systems, educational investment and development must be needs-based and integrated into broader health workforce and service planning.

Participants from diverse backgrounds including students, research councils, Ministries of Health, health agencies, hospital management, professional bodies and higher education institutions voiced their support for and agreement with the objectives and approach of the WHO UNESCO FIP Pharmacy Education Action Plan. Amongst them Dr Steve Kimatu, Pharmacy and Poisons Board, Ministry of Health, Kenya, emphasized the importance of intersectoral collaboration between professional bodies, education and health ministries in an effort that led to a ten-fold scale up in the production of pharmaceutical technologists in Kenya. Dr Lungwani Muungo, Head, Pharmacy Depart-

ment, School of Medicine, University of Zambia, described the needs driven approach to the development of the first pharmacist training degree in the country and emphasized that without collaboration between the regulatory and professional bodies and ministries of health, education and finance, it would not have been possible.

Dr Manuel Dayrit, Director, Human Resources for Health, WHO, acknowledged the important role of FIP in bringing the two UN agencies for education and health together in this collaboration. In strengthening the relationships at the global level between WHO and UNESCO, the potential to build closer dialogues between ministries of health and education is enhanced at a national level. In the process of the action plan, Dr Dayrit urged participants to act, reflect and undertake further action and examine practical steps to move forward at the country level with hopes that other professions will be engaged in the process. ►



Members of the Pharmacy Education Taskforce (Prof Ian Bates, Prof Claire Anderson, Tana Wuliji) with Prof Richard Odoi Adome (centre), Head and academic faculty of the Department of Pharmacy, Faculty of Medicine, Makerere University, Kampala, Uganda.

Pharmacy Education Action Plan Implementation and Activities

A Terms of Reference to operationalise the Taskforce with a new structure fit to implement the Action Plan was developed and adopted by the FIP Executive Committee in March 2008. The Terms of Reference will establish a regionally representative Taskforce Advisory Group, Project Leads, Project Teams, network of pharmacy schools and partners to support the implementation of the Action Plan. The FIP Bureau and Executive Committee will continue to oversee the progress of the Taskforce and Prof Henri R. Manasse Jr., FIP Professional Secretary, will serve as the Bureau Liaison to the initiative.

Project Team Leads to steer activities in each priority domain were appointed in March 2008. Mr Mike Rouse, convener of the International Forum for Quality Assurance in Pharmacy Education was appointed Project Lead for quality assurance. Professor Claire Anderson, past president FIP Academic Section will be the Project

Lead for academic workforce and institutional capacity. Professor Ian Bates, Vice-President European Association of Faculties of Pharmacy will be the Project Lead on developing a vision for pharmacy education and competency framework. These Project Team Leads have developed Project Plans within each domain and are in the process of forming Project Teams comprised of active expert contributors.

A proposal was developed to establish a network of schools of pharmacy (representative of all regions) to participate in the Action Plan process, contribute towards consultations, share experiences and resources, provide data and assist with field testing of tools and frameworks. Such a network will be open and participatory and it is intended that the network will broaden over the course of the Action Plan. Expressions of interest from over 20 universities who have participated in the global consultations and Taskforce activities thus far were received. An application from this network was

submitted to UNESCO as part of the university network program UNITWIN in April 2008.

Country case studies are a key component of the Action Plan and preparations are underway for the development of evidence, tools and guidance in countries with the greatest pharmacy workforce shortages. With an initial focus on countries in sub-Saharan Africa, the tripartite taskforce will hold a series of workshops with interested countries in late 2008 to undertake stakeholder analysis and develop a case study methodology that facilitates needs-assessment and catalyses pharmacy education development. Based on the paradigm of needs-based education arising from the 2nd Global Pharmacy Education Consultation in Beijing, China held in September 2007, the country case studies will explore strategies and test a process of education development that is geared towards needs (health, market), oriented towards the provision of services that are relevant to these needs, matched to required

competencies to provide services and integrated to human resource plans.

Interactive sessions and consultations in 2008

The Taskforce has planned several interactive sessions and consultations for 2008. Among these is a session held by the Taskforce during the American Association of Colleges of Pharmacy (AACCP) in Chicago in July 2008 entitled 'First do no harm: collaboration vs colonization' to align with the conference theme of 'global pharmacy' which will explore scenarios for international cooperation in education development. There will also be a focus group workshop on culture and competency to be held during the International Social Pharmacy Workshop in New Zealand in July 2008: 'Competency – towards a culturally inert understanding'. This is aimed at better understanding what 'competency' means to different cultures and how to overcome barriers associated interpreting and applying the concept.

The 3rd Global Pharmacy Education Consultation will take place at the 2008 FIP congress in Basel at a parallel session on Wednesday 0900-1200 September 3rd as an open consultation.

The purpose of this consultation is to:

- To engage and consult with a wider stakeholder group to gain input into the implementation process of the Action Plan 2008-2010.
- To provide an update on the progress of the Taskforce and outline further plans for development.
- To report on the outcome of the Country Case Study Taskforce Workshops
- To seek the interest of potential contributors and develop an inventory of resources and contacts to facilitate the development of a web-based Taskforce global platform for pharmacy education.

The reports from these events will be made available on the FIP website. All participants in the FIP Congress in Basel are invited to take part in the 3rd Global Pharmacy Education Consultation. The outcomes of the 3rd Global Pharmacy Education Consultation will be published in the next edition of the International Pharmacy Journal (IPJ). The dedication, expertise and support of all contributors to the Pharmacy Education Taskforce has been instrumental to the progress thus far, particularly the voluntary efforts of the Taskforce members, Universities and global, regional and national stake-

holders who have provided valuable input at each stage. The continued support of stakeholders in the implementation phase of the Action Plan is greatly appreciated and the tripartite partnership of WHO, UNESCO and FIP looks forward to realizing the outcomes of the Action Plan. ■

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The Pharmacy Education Taskforce is convened by the FIP as a collection of stakeholders representing various global, regional and national networks with the goal of coordinating and catalyzing action to develop pharmacy education. www.fip.org/education

For more information about the Pharmacy Education Taskforce please contact Tana Wuliji, Project Manager, FIP: tana@fip.org

IPJ TALK

The Future of Medicines...?

In light of this issue's topic, the IPJ Editors thought it would be quite fitting to speak to some individuals who, likely more than all of us, will be the ones to experience the future of medicines use. So, we gathered together Emma and Stijn, ages 9 and 11, to talk about what they know about pharmacists and medicines and what they think the FUTURE will and should hold for all the things that "make us better".

Do you know what a pharmacist is?

This is a shop that has medicines for people and kids.

S: I went there once for medicines for my dad and then another time when my ball was on the roof.

E: I had antibiotics from there once but I can't remember what they were for.

Did you talk to the pharmacists in the pharmacy? What do you think pharmacists do?

E & S: We really didn't need to talk to anyone there.

I think they sell the medicines to people. They get the medicines from the factories or companies.

Do you guys take any medicines?

E & S: Well we took antibiotics that time...and we also have our 'puffers' (Ventolin) that we take.

What kinds?

S: There are different kinds...round ones and "L" shaped ones

Is it easy to take, or icky, or not nice?

E: It's ok...just tastes normal, not nice but not bad either. This one time I had an allergy pill and it went on my tongue but it was really BURNING and my whole mouth filled up with saliva and I had to spit it all out.

How often do you have to take it?

S: Sometimes every day, not always.

Does it make you feel better?

E: Yup it helps me cough less

S: I get more air

So do you think that medicines are a good thing?

E: Well the taste of the antibiotics was good...strawberry or peach. Yum!

S: I like cough syrup!

Ok well what about just medicines in general...do you think they help people?

S: Yeah and there should be a pharmacy in every neighbourhood because if you're coughing and you are in Delft ►



but your pharmacy is in The Hague you might not make it to the pharmacy to get your medicines. *[this interview was on location in The Netherlands, ed.]*

Do you know other people who take medicines? (Do they like it?)

S: Our mom has a puffer too, or medicines for headaches. One of our friends probably takes a lot of medicine because he was in the hospital [with meningitis] but now he's home, so he probably has a lot of medicines.

Do you guys like sciency stuff like chemistry...biology...etc

E: No...not yet really. We did some stuff in art class with colours but we don't really know much about medicines.

S: But we watched Brainiac once and they did this experiment with wine, beer and

Well there are tons and tons of scientists and pharmacists working on trying to discover new medicines to make it easier and safer for people who take them. What do you think they should do to make medicines easier and nicer to take?

E: Antibiotics should taste better!! Like with strawberries or peach!

S: They should make smaller aspirins. Or make some that can be put in water.

E: Sometimes our dad breaks up the paracetamol and puts it in the water and we drink it but then the water tastes horrible.

S: Oh they could put little bits of the medicine in cookies! *[they were eating cookies, ed.]*

Why do you think that they don't do that now – make it taste nicer or put medicine in cookies?

S: Well then people would go to the pharmacy and if they had money they would buy lots and eat too much.

E: Yeah I had this stuff and it was sugar free but I just ate more of it but if they do that with medicines people really could eat too much.

How long do you think it takes to make medicines?

E: Hmmm one or two weeks...

S: Well first you need to have the ingredients and they may be hard to find. If they have to come from America then they have to land in France or Holland and if there's a problem then it would take more hours...

Then when you have the ingredients maybe they didn't make it right the first time so they have to start again, so maybe it takes 5 years or so...

It takes a really long time to make new and different kinds of medicines – sometimes 20 years or MORE just to create one brand new medicine! If you could start now and make ANY kind of medicine, what would it be? ANYTHING at all!

S: Really small medicines! Small aspirins! Make it smaller so it would be easier to take! Oh and more yummy cough syrups. And I would make the puffer handier, smaller so it would fit in your pocket.

E: It already does fit in your pocket!

S: Well maybe I would have a really small pocket one time...

E & S: Medicines so you never have to brush your teeth, or turn you into a fly or spider and back again.

What about for at school?

E: Yeah pills that make you smarter!

S: Or more medicines for cancer, or meningitis. And we have a classmate who fell off a trampoline and is now brain damaged and can't remember things. Maybe they could make medicines that would bring the memory back.

E: Yeah or medicines that keep you young! "Fountain of Youth" medicines so you can stay younger!

How do you think TAKING medicines will change?

E: Well you could break a capsule and the medicine could go on your tongue.

S: Or they could make this stuff for people who are burnt very badly that would heal the skin

E: INSTANTLY!

S: Or this spray that you could spray onto plants that are dead and they would come back to life!

E: People too! And it would be cheap, just one euro!

What about the inhalers – how do you think that could be different later on?

S: Put the medicine in a really yummy cough candy!

E: Sugar free! But tastes good! Or you could put the medicine right into a strawberry, then squish the juice out of the strawberry and just take the medicine!

What do you think if you could download your medicines off the internet to your mobile, do you think that would be a good idea?

S: Hmm I don't think it would be so handy because it could have a virus and you'd take it and die

E: Then you could use the spray!

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