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Regulatory Highlights

Regulatory Highlights for September 2008 to February 2009

New FDA Validation Guidance

The main highlight of the period under review is FDA's draft of a new guideline on Process Validation, which appeared in November. It is now over 20 years (1987) since the original "Guideline on General Principles of Process Validation" was issued by the agency; experience gained during the intervening years has now allowed them to update their recommendations in the light of more modern regulatory attitudes.

The new guideline is more sharply focussed than its predecessor. The 1987 guidance contained a lot of information and examples relating to medical devices, but this new document is aimed specifically at drug manufacturing processes − including biological products and active ingredients.

A new definition of validation is given: "the collection and evaluation of data, *from the process design stage throughout production*, which establishes scientific evidence that a process is capable of consistently delivering quality products." This signals a fundamental break from the previous approach, which encouraged the view of validation as a single precommercialisation event. In contrast, the new emphasis is on a lifecycle approach, comprising three interlinked stages:

1. Process Design
2. Process Qualification
3. Continued Process Verification

Traditional validation studies have concentrated on the "Stage 2" activities, but it is increasingly recognized that unless these are based on sound process understanding, they will not lead to a "qualitatively safe product" − hence the new emphasis on process design. Similarly, a once-for-all validation cannot take account of all sources of future variability − for example in raw material quality, equipment deterioration or evolving operating practices; thus, ongoing process and product scrutiny, combined with statistical analysis and trending, are equally important.

The new guideline provides more specific recommendations than its predecessor, for all three stages. Stage 1 involves the building and capturing of process knowledge and understanding, and the use of this to establish a strategy for process control. The functionality and limitations of the commercial manufacturing equipment should be considered at this stage, as well as the variability contributed by different component lots, production operators, environmental conditions, and measurement systems in the production setting. Design of Experiments (DOE) studies are especially recommended for revealing relationships, including multifactorial interactions, between the input variables. Computer-based or virtual simulations of certain unit operations or dynamics can also provide process understanding and avoid problems at the commercial scale. It is essential that these activities and studies be documented, so that the results can guide strategies for the process qualification and continued verification stages.

Stage 2 (process qualification) is conceived as comprising two elements: (1) design of the facility and equipment; (2) performance qualification. (Previously, this second element would have been considered as the entirety of validation.) Success at this stage − demonstrating that the commercial manufacturing process performs as expected − signals an important milestone in the product lifecycle, and needs to be completed before any commercial distribution of the drug product. Performance qualification requires a written, and approved, protocol − which should discuss the following (*inter alia*):

- the manufacturing conditions, including operating parameters, processing limits and raw material inputs
- the data to be collected and how it will be evaluated
- tests and acceptance criteria for each significant step
- a sampling plan which will provide statistical confidence of quality
- criteria that provide for a rational assessment of consistency in product quality
- design and qualification of equipment, as well as of personnel training and material sources
- validation of analytical methods
- review and approval by appropriate departments and the quality unit

After execution of the protocol, a report should be prepared which discusses all aspects, summarizes and analyses the collected data, evaluates any unexpected observations and additional data, any deviations or aberrant test results, and describes any corrective action or changes indicated. As in the 1987 guidance, there is no discussion of how many validation runs are required; this remains to be decided on a case-by-case basis.

The goal of the third validation stage is to continually ensure that the process remains in a state of control during commercial manufacture. Systems should be put in place to detect any *process drift*. It is recommended that a person with adequate statistical training should develop the data collection plan and the statistical methods used to evaluate process stability. A high level of sampling and monitoring should be maintained until sufficient data is available to estimate normal variability, after which the scrutiny may be reduced to a statistically appropriate level.

Whereas the 1987 guidance discussed the use of *retrospective* validation, this option is no longer mentioned. However, the *concurrent* release of performance qualification batches can still be acceptable under some circumstances; FDA expects that this will be used only rarely, and that its use will be coordinated with the agency.

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One controversial aspect of the 1987 guidance was the suggestion to use "worst case" conditions during validation runs. The new guideline makes it clear that the commercial manufacturing process and routine procedures must be followed for the performance qualification batches, and it is not typically necessary to explore the entire operating range at the commercial scale − if assurance can be provided by other data (i.e., data generated during the process design stage).

Curiously, although the new guidance is supposed to be in harmony with recent ICH guidelines (Q8, Q9 and Q10 are all specifically mentioned), there is no discussion of how the "design space" concept would fit into the validation lifecycle. Another aspect which active pharmaceutical ingredient (API) producers in particular may want further clarification on is the recommendation that CGMP conditions be employed for certain stage 1 activities − specifically for "viral and impurity clearance studies". Would this really apply, for example, to the development of crystallization processes to remove process-related impurities from an API?

The full text of the draft guideline can be obtained from the FDA Web site: www/fda/gov/cder/guidance/8019dft.pdf). Discussion articles have also appeared, for example by S. Pommeranz, on behalf of the European Compliance Academy (www.gmp-compliance.org/eca_news_1402_5699-6013_n.html).

Genotoxic Impurities

The other significant development on the FDA front in this period is the long-awaited release, in December, of the agency's first draft guideline on Genotoxic and Carcinogenic Impurities (www.fda.gov/cder/guidance/7834dft.pdf). It is now two years since the European Medicines Agency's (EMEA's) guideline on this subject came into force. Despite the controversies surrounding certain aspects of the EMEA approach (see, for example, Snodin, D. *RAJ Pharma* **2008**, 593−598 and 663−670), FDA have now proposed essentially the same recommendations − specifically, adopting a default exposure limit of NMT 1.5 μg per day for those genotoxic impurities where there is no evidence of a threshold-related toxicity mechanism. This is regarded as a "virtually safe dose", estimated to increase the lifetime risk of cancer by no more than 10^{-5}. FDA have rejected recommendations from the Pharmaceutical Research and Manufacturers of America (PhRMA) to allow higher daily exposures for drugs administered over very short periods − on the grounds that a drug may be used multiple times by the same individual, or may be used outside of its approved indication. They suggest, however, that lower exposure limits may be required for paediatric drugs − perhaps down to 0.15 μg per day, citing evidence of increased susceptibility to toxins in infants and children.

Unlike the EMEA guideline, this present draft specifically addresses drugs undergoing clinical development as well as those seeking marketing authorizations. In the case of clinical drugs, some allowance for the duration of medication can be made to justify higher exposure limits. Extrapolating from a 10^{-6} lifetime increased cancer risk, permitted daily exposures (PDEs) of up to 120 μg can be acceptable for genotoxic impurities in clinical drugs administered for no more than 14 days. The limit then reduces in stages down to 5 μg/day for up to 12 months treatment − with the standard 1.5 μg/day applying thereafter. The recommendation is to evaluate any identified impurity in a clinical drug by means of structure−activity relationships, with *in vitro* mutation assays being applied to any impurities with an identified alert. However, there is no discussion of what would be an appropriate identification threshold for impurities in clinical drugs. (The threshold of 0.10% or 1 mg daily exposure is well-established by ICH guidelines for commercial drugs.)

Any testing for genotoxicity should, wherever possible, be conducted on the isolated impurity itself − rather than on typical or spiked batches of drug substance, as has traditionally been accepted for qualifying ordinary process-related impurities. This reflects the low sensitivity of the available assays. However, it is also recognized that it may not always be possible to synthesize the impurity in sufficient quantities.

Improved Testing Standards for Heavy Metals

The United States Pharmacopoeia (USP) has announced the phasing out of their traditional wet chemistry test for heavy metals in drugs, and its replacement with more modern instrumental methods. (*Chem Eng. News 86*(49), 32−34, Dec 8, 2008). The current test involves precipitating the metal sulfides and comparing the colours obtained with those from a lead sulfide standard. However, this method fails to quantify individual metals and has long been recognized as unreliable even for total metal content. Front runners for its replacement would be inductively coupled plasma spectrochemistry or atomic absorption spectroscopy, but manufacturers will be able to use whatever method they wish so long as it is validated to an appropriate standard. Any procedure that provides measurement values within ± 20% of the correct concentration for each element will be considered acceptable.

In a *stimuli* article, USP have proposed a preliminary set of limits for 31 individual elements (*Pharmacopoeial Forum* **2008**, *34*, 1345−1348). This is more comprehensive than the equivalent guidance from EMEA (www.emea.europa.eu/pdfs/human/swp/444600.pdf), which considers only 14 metals; but for those 14, USP are now proposing the same limits. Additional elements of particular interest to process chemists include boron (PDE 10,000 μg), mercury (PDE 15 μg), and tin (PDE 30,000 μg !). Some industry commentators worry that such an extensive list could pose problems and confusion for raw material suppliers, who are unlikely ever to have tested for many of these elements before, and recommend concentrating in the first instance on those metals that are known to pose the greatest health and environmental threats. (*Pharm. Technol.* **2009**, *33*(2), 36−42) However, manufacturers will not be requested to test for every element in the list, but rather to make a risk-based selection, considering potential contributions from their raw materials and processing methods.

It is expected that a new draft chapter of USP-NF will be published in the summer of 2009, and finalized one year later. Actual implementation will take several years beyond that to allow manufacturers and suppliers sufficient time to acquire the new, more expensive, analytical equipment, and perhaps adjust

their processes to reduce individual metal levels, without adversely affecting drug supply.

Drug Substance Starting Materials

The designation of a regulatory starting material for a drug substance synthesis continues to be a contentious issue, requiring case-by-case negotiation with regulatory authorities to obtain a balance between appropriate regulatory control and sustainable economic manufacture. FDA previously proposed detailed guidelines on the topic in 2004, but withdrew them a short time later, leaving the ICH Q7A GMP Guide for APIs as the principal benchmark. Nevertheless, while this guideline defines what may by considered a starting material, it offers no advice on how to select the starting materials from the list of all raw materials and intermediates.

A recent article by global regulatory affairs managers at AstraZeneca (Illing, G. T.; Timko, R. S.; Billett, L. *Pharm. Technol*. **2008**, *32*(12), 52−57) proposes a strategy to justify starting materials based on the control of three key aspects: process control, analytical control, and change control. Traditionally, manufacturers have relied mainly on analytical controls, defining and maintaining tight specifications for the starting materials, to compensate for their limited knowledge of how they were synthesized. This article proposes that consideration of the other two aspects could create a "design space" where starting materials are selected based on scientific understanding of the synthesis and analytical control mechanisms, of the source, formation and fate of impurities, and of how changes to the synthesis of the starting material may influence the drug substance impurity profile. This knowledge should facilitate risk-based decisions regarding regulatory flexibility. (For example, a shorter registered synthesis would likely require more analytical controls, whereas a longer synthetic route could have a reduced level of analytical controls.)

In terms of process control, a distinction is made between starting materials which are commodity chemicals and those which have been custom-synthesized. The former are likely to have been made by well-documented methods in large scale for use in several industries, and so are unlikely to present unexpected risk to patients. The latter will have been made by only one or two custom manufacturers in varying scales throughout the drug's development, so further scale up could present increased risk. This, however, can be mitigated by the increased process information that would be available *vis-à-vis* a commodity material. A regulatory filing should disclose sufficient synthetic stages (including pre-GMP stages) to explain how the important structural elements are assembled into the drug substance. The filing should also discus the fate of any impurities present in the starting material, and how variation in the process affects the removal of those impurities.

The drug substance manufacturer's change control system should cover the starting material suppliers' activities as well as its own, through vendor assurance programs. In particular, changes to a starting material should be subject to detailed assessment for the presence of new impurities, and a determination of their fate during subsequent processing steps.

Bulk Material Sampling

Taking samples for analysis is one of the most critical aspects of quality control, but one which is fraught with difficulties (often compounded when the task is assigned to junior employees with little training). The problems are discussed and analyzed in depth in a series of articles by Patricia L. Smith, a statistician and process improvement specialist, of which three have so far appeared. (*J. GXP Compliance* **2008**, *12*(4), 60−65; **2008** *12*(5), 69−76; **2009** *13*(1) 67−73) The statistical evaluation of analytical data relies on an assumption of randomness in the sampling procedure. A sample is random when every unit in the whole batch has an equal chance of appearing in the sample. A "grab" sample, taken for convenience from the top layer, clearly would fail this criterion. True randomness in this sense is impossible to achieve when sampling bulk materials such as batches of drug substance, since individual particles cannot be identified. In these cases, the author recommends adhering to principles of *correct sampling*, where the batch is spatially divided into appropriately sized smaller units, which are then sampled *randomly*. Even this may be physically impossible with a three-dimensional container, but the problem can be somewhat overcome by reducing the dimensionality of the batch.

Four main sources of sampling variation are identified: material variation, sample identification and collection, sample handling, and process variation. These give rise to seven distinct types of error, which will combine to inflate the overall variation in the analytical results, and potentially lead to wrong conclusions being drawn. Suggestions are offered on how to reduce the influence of each error, although it may not be possible to eliminate them completely. General advice includes:

- for solids sampling, grind the material before sampling (except when determining particle sizes)
- increase the mass of the total physical sample
- collect several random increments from the lot and combine them to form the sample
- mix the material and ensure it stays mixed during sampling
- monitor results over time and look for patterns and anomalies

Cleaning and Contamination Control in API Plants

A number of articles have been published recently which relate to the general topic of contamination control. David Bornett, director of regulatory affairs at SAFC Pharma, has written about the containment and handling issues surrounding high-potency APIs (*Pharm. Technol.* **2008**, *32*(September)). While not saying anything new, this gives a useful overview of current standards and practices. Compounds are assigned to one of four risk categories (1- lowest risk to 4 - highest risk) according to criteria such as dosage level, occupational exposure limits, acute/chronic toxicity, existence of warning symptoms, genotoxicity, mutagenicity, etc. The recommended levels of protection then depend on the category assigned and the amount of the substance to be handled in a typical operation. Engineering controls should be the primary source of containment, with personal protective equipment (PPE) playing only a secondary role. The potent compound handling systems should ideally incorporate five levels of cascading protection: process isolation,

containment equipment, facility design, PPE, and procedures (including training and health monitoring). Emphasis is placed on proper design of the facility, with a recommendation for independent third-party certification.

The more general issue of protecting the products (as opposed to the operators) from contamination is addressed in a "white paper" from the International Society of Pharmaceutical Engineers (ISPE) (Newberger, S.; Melton, T. *Pharm. Eng.* **2008**, *28*(6), 32−42). This develops a concept of "Briefly Exposed" operations, which was first introduced in ISPE's 2007 revised *Baseline Guide on APIs*. Traditional advice has been to perform critical API operations in a Level III (Controlled) environment, unless the equipment itself is completely closed, when a less onerous Level I (General) environment would suffice. Noncritical operations may be run in open equipment in a Level II (Protected) environment. The revised guide recognizes that the level of risk depends upon the duration of exposure to the open environment; exposures of very short duration can thus constitute a valid intermediate category. The authors illustrate how this could work in practice by analyzing the common situation where a crystallizer hand-hole needs to be open for a short period in order to add seed crystals. Using a variety of formal risk-assessment tools, a number of measures were identified which could mitigate the contamination risk and thus justify operating the equipment within a Level II environment. The authors believe this could save up to 30% in construction and operating costs.

The same issue of the magazine also reports on an interesting exercise to decontaminate a Japanese β-lactam-producing facility, to make it suitable for general API processing. (Takahashi, H.; Sakai, H.; Gold, D. H. *Pharm Eng.* **2008**, *28*(6), 24−30) A plan of action was developed and discussed with the FDA (U.S.), along with agreed acceptance criteria. All buildings on the site were assigned to one of three risk levels; those buildings in which β-lactam products had been handled or where there was a risk of contamination (e.g., from air-flows or personnel movements) were decontaminated by wiping or spraying with dilute sodium hydroxide/sodium hypochlorite/surfactant solution. In many cases fittings (including electrical wiring) were completely replaced. After decontamination, certain surfaces were given a coat of impermeable epoxy paint. Over 1600 swab samples were then taken and assayed for the presence of the previous β-lactam products at detection limits of 1 ng/cm^2. Twenty-six positive results were obtained (overwhelmingly from the former synthesis factory), and in those cases the room involved was completely decontaminated all over again, after which a more thorough sampling exercise (278 samples) gave no positive results. Once general API manufacture commenced, monitoring was continued for a further 60 months. Additionally, the first three batches of API produced post-decontamination were analyzed for the presence of the previous β-lactam products, with detection levels of 5 − 20 ng/g.

On the more general topic of cleaning API equipment, an article by N.A. Fletcher (Foster Wheeler Energy, U.K.) discusses retrofitting Clean-In-Place (CIP) systems into plant equipment. (*Pharm. Eng.* **2008**, *28*(4), 50−58) CIP is gaining increased acceptance in the API industry because, as a fully automated process, it facilitates cleaning validation, leading to improved product quality. It can also reduce downtime between different product campaigns by removing the need for manual cleaning, which may involve some disassembly. It is a particularly attractive option for highly potent APIs, since there is no need to open the contaminated equipment, thus reducing operator exposure. The ideal situation would be to incorporate CIP facilities in the original plant design, but retrofits can also be successful − especially when existing nozzles or access points can be utilized, and when the retrofit can be performed during a campaign turnaround or during a short shut-down. This article highlights the problem areas typically associated with reactor heads, Nutsche-type filters, centrifuges and dryers, and describes the design of suitable components which may overcome the difficulties.

The logical extension of automating the cleaning process is to augment it with an online verification system. In recent years Total Organic Carbon (TOC) analysis has been increasingly used for cleaning validation in pharmaceutical plants, and its suitability as an online PAT application is discussed in an article by engineers from Hyde Engineering and Consulting Inc., of Colorado. (Bader, K.; Hyde, J.; Watler, P.; Lane, A. *Pharm. Eng.* **2009**, *29*(1), 8−-20) The article describes a cleaning study in a biopharmaceutical plant to remove a representative protein soil (bovine serum albumin) from a reactor. At the end of the CIP sequence, residual TOC was determined by an installed online analyzer, and the results compared with off-line analysis of manually obtained samples of the final rinse, and of surface swab samples. The study was repeated over nine consecutive runs, with strong correlations between the results obtained from all three methods. (The online analysis provided consistently higher determinations than the offline rinse samples, but lower than the swab samples.) The economic benefits of the online sampling were mainly in the reduced time involved. On a per-run basis, preparations for online analysis and sampling required approximately 20 min. In comparison, each run required nearly 10 h of labor for manual sample collection and analysis. The authors conclude that, although integrating online TOC measurements into CIP system automation will result in added capital costs, operating costs can be significantly reduced and will likely justify the investment. Of course, TOC may not be the ideal analytical method for use with API equipment, especially if organic solvents are used in the later cleaning stages, but the general principles outlined in the article would presumably apply to other PAT methods, such as IR or UV, as well.

Stainless Steel in GXP Processing

Stainless steel is one of the most common materials of construction for API processing equipment, especially at commercial manufacturing scales. Yet although it has been standard for many decades, it remains a mystery to many process chemists, who tend to take its desirable properties for granted. While it may not be necessary for the chemist to have the same in-depth knowledge as an engineer or material scientist would, a little more background information would not go amiss. To this end, a recent article by T.W. Miller (*J. GXP Compliance* **2009**, *13*(1), 10−22) can be recommended for those of us concerned particularly with the GMP compliance aspects. The

article discusses the different grades of stainless steel generally available (e.g., 304, 304 L, 316, 316 L) in terms of their elemental composition and fabrication details, and the different surface finishing processes (grinding, polishing, electropolishing) applied. Regulators expect that process-contact steels be properly specified and installed, and also properly maintained and cleaned. 316 L stainless steel is the gold standard for wetted components, but other alloys may be more appropriate in some circumstances, depending on the nature of the process streams and on the anticipated cleaning media. 304 stainless steel is a better choice for noncontact surfaces, such as the frame of a skid or the exterior of a cabinet in a cleanroom. While the material is, by definition, corrosion-resistant (resulting from a passive layer of chromium oxide covering the surface) corrosion problems, such as rouging or pitting, can occur if the equipment is improperly maintained or exposed to inappropriate media. Aggressive chemicals such as strong acids are well-known to be incompatible, but halide salt solutions can also cause problems if not promptly and completely rinsed. Depending on the severity of a corrosion problem, remediation measures could involve acid-washing, passivation, electropolishing, grinding, or pickling. From a compliance point of view, the specification and testing of steel should be managed as part of the commissioning, qualification, and validation processes. For example, a profilometer should be used to confirm the desired degree of surface roughness. Any remedial actions also need to be managed by a change control process. Corroded metal surfaces pose the potential for particulate and microbial contamination. There should be no rouge or rust in cleanrooms, and corrosion in unclassified areas should be minimised. All equipment should be inspected routinely − externally as well as internally. Checks should be made for corrosion issues as well as for cleanliness before every use.

New API Sourcing Guide

The increasing presence of counterfeit and substandard APIs in the drug supply chain has given rise to various initiatives by the FDA, the European Commission, and the World Health Organization (WHO). A new "quick guide" to API sourcing was published in September 2008 by APIC, the interest group of European API manufacturers, with the aim of helping drug manufacturers ensure their APIs come from legitimate and reliable sources. The document focusses on the interaction between the API and medicinal product manufacturers. It does not address in detail the entire vendor qualification process, rather concentrating on those aspects which increase confidence that API batches received are what they purport to be. For example, vendor audits should ideally be performed when an actual production campaign is underway, and rescheduled if necessary, even at short notice. A walk-through of the warehouse could be an opportunity to check for the presence of API (or intermediates) purchased elsewhere which could be subject to relabelling. Review of equipment-use log books and their correlation with batch records and analytical data can bring to light any production inconsistencies. It is recommended that the API manufacturer provides examples or templates of the labelling used on API containers, so that the customer can easily detect any inconsistencies on receipt. The use of tamper-resistant closures can provide additional assurance. And −as a general principle − the shorter the supply chain, the more secure it will be. Any agents, brokers, distributors, repackers, or relabellers involved will need to be assessed as well as the original manufacturer of the API. The complete document can be viewed at http://apic.cefic.org/pub/APIC%20Quick%20Guide%20for%20API%20Sourcing_September08final.pdf.

Pharmaceutical Quality Systems

The ICH's Q10 guideline on Quality Management Systems was finalized last year, and its content was reviewed previously (*Org. Process Res. Dev.* **2008**, *12*, 819−820). It has given rise to a flurry of discussion in the industry, particularly on how to integrate it with regional CGMP requirements. A webcast entitled "Quality Systems in the Global Marketplace" took place last June, with panelists from the FDA, the European Commissariat, and several major pharmaceutical companies. Some highlights of the discussion have been summarized in the August edition of *Pharmaceutical Technology* (Drakulich, A. All Roads Lead To Quality Systems. *Pharm. Technol.* **2008**, *32*(8), 42−47) The article deals with six topics: Evolution and concepts of Q10, FDA expectations, Outsourced activities and purchased materials, Quality systems for R&D, Change management and CAPA systems, and Global quality inspections. A short accompanying article in the online version of the magazine highlights some of the current misconceptions about Q10, and the panelists' attempts to counter these "myths". It also presents a 48-point Q10 gap analysis checklist.

Postapproval Management Plans

A relatively new concept which is being actively discussed in the United States is the Regulatory Agreement, also known as the CMC Postapproval Management Plan (PMP). The idea has been floated by the FDA in the context of Quality-by-Design submissions using the ICH Q8 framework. The agency has yet to provide firm guidelines on how PMPs could be used, but a short article by regulatory scientists at Eli Lilly offers some suggestions (Hudson, P. S.; Baker, D. D. *Pharm. Technol.* **2009**, *33*(1) 82−86). A PMP would be product-specific and based on sound scientific knowledge of that product and the manufacturing processes. Submitted alongside the relevant marketing application (e.g., NDA, BLA), it would propose change control protocols and associated acceptance criteria for manufacturing changes that might be desirable in the future. Using risk management principles, the applicant may be able to propose reduced reporting requirements for certain parameter changes. For example, the widening of a Proven Acceptable Range (PAR) would traditionally require the submission of a Prior Approval Supplement (PAS) to the agency, with inevitable long delays in implementation; but the applicant could instead use the PMP to propose testing and acceptance criteria, based on product knowledge (e.g., design space) by which they would demonstrate that the widened range did not negatively affect the product downstream. This might then justify the submission of such a change in the future as a CBE-30 (change to be effected in 30 days) supplement. The drafting of a PMP would require significant up-front effort on the applicant's part, and it

would itself require FDA's specific approval, but thereafter, it could reduce some of the hurdles to continuous improvement currently experienced in the pharmaceutical industry, with advantages in both product quality and cost reduction.

Priority Review Vouchers

Chemical and Engineering News (Jarvis, L. M. *Chem. Eng. News* **2009**, *87*(3), 38−40) reports on a new FDA initiative which aims to encourage companies to spend more effort developing drugs for tropical diseases such as tuberculosis, malaria, blinding trachoma, buruli ulcer, cholera, Dengue fever, etc. Although these diseases are relatively rare in the United States at the moment, the agency is concerned that intercontinental jet transport, immigration, tourism, and military operations may make them a more serious threat to the health of Americans in the future. Under legislation approved in 2007, companies submitting marketing applications for new chemical entities to treat such diseases can at the same time apply for a Priority Review Voucher (PRV), which will, on payment of additional review fees, expedite the FDA's review of another product. The PRV can be applied to any other drug in the company's pipeline; alternatively, it can be auctioned off, traded, or sold to a competitor, thus potentially benefiting small as well as large pharma companies, also nonprofit organizations and public−private partnerships. The agency has set a target to review 90% of applications with "priority" status within 6 months. It is estimated that the use of a PRV to get a potential blockbuster product to market faster could be worth up to $300 million to a drug company. *C&EN* reports that Novartis is set to become the first company to receive a PRV for their antimalaria treatment Coartem. This, though, calls into question the value of the program in encouraging innovation in the tropical diseases area. Coartem, an artemisinin-based drug, has actually been available in developing countries since 2001. However, since none of its active ingredients have been previously approved in the United States, it does qualify for the PRV program. Also, the award of a PRV is not contingent on the company actually marketing the drug in the United States. The agency published a draft guideline on the use of PRVs in October 2008 (www.fda.gov/cder/guidance/8329dft.pdf).

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