1 - Reasons for conducting a pre-approval inspection

The purpose of a PAI is to ensure that manufacturing, development and related control facilities meet current GMP, conform to the stipulations of the Code of Federal Regulations (CFR) parts 210, 211, 820 and 11 and are in line with commitments to verify the authenticity and accuracy of data contained in the submitted application file. The inspectors must ensure that product development is carried out in a way that produces reliable process attribute ranges. They must also make sure that all key GMP systems (» FDA system approach) at the development and commercial sites are up to current GMP standards.

New Drug Application (NDA)
The New Drug Application is the registration file sent to the FDA for the marketing of a new drug product in the U.S.

Biologics License Application (BLA)
The Biologics License Application is the equivalent of an NDA for biopharmaceutical and biotechnology products.

Marketing Authorization Application (MAA)
The Marketing Authorization Application is the registration file submitted to the relevant national authorities of EU member states or the EMEA (European Medicines Evaluation Agency) as part of an application to market a new product in the European Union.

2 - Pre-Inspection Activities

Proper preparation work is vital for ensuring that your company successfully passes a PAI. It is highly recommended that preparation work starts at least 12 months before the date when you plan to contact the relevant authority.

An initial PAI meeting should be held to define the responsibilities of individual PAI team members and milestones must be set in order to monitor the progress of preparation work. Our website offers a range of tools and guides that help ensure your preparations for a PAI run smoothly. PAI protocols for drug products and active pharmaceutical ingredients have been created to systematically identify the strengths, opportunities, weaknesses and threats associated with organization, personnel, quality systems, facilities, utilities, water systems, clean steam, HVAC, gases, equipment, key raw material suppliers, manufacturing process synthesis, sieving, milling, micronisation, analytical testing, test method validation, method transfer, stability, laboratory equipment, microbiological testing, contractors/suppliers and inspection issues (» checklists). These protocols enable you to identify any potential shortcomings during the early stages of preparation work, usually 6-12 months before the submission of a new drug, and give you the opportunity to resolve the issues or finalise pending work and reports in good time.

The FDA is also increasingly focusing on the validation of computer and/or computerised systems and compliance with 21 CFR Part 11 on a risk-based evaluation. It is vital that you are well prepared in these areas (» checklists)!

Companies should be aware that preparing for a PAI is not a last-minute activity. It is clear from current warning letters that SOPs are still extremely important. One of the most likely reasons for this is the FDA's new systematic approach. Common observations for SOPs relating to key issues such as deviation, OOS, change control and training are that they are often too convoluted or general and sometimes workers are not given sufficient training in how to implement them. Many warning letters also cite incomplete document history files or outdated SOPs. Generic SOPs are available on our website to help you avoid such pitfalls and only need to be adapted slightly to suit your company (» SOP's).

It is also advisable to organize comprehensive training for the personnel who are to participate in a regulatory authority inspection. Indeed, it is widely recognised that personnel who behave in an inappropriate manner or provide misleading information can cause inspectors to look into areas where they previously had no concerns. The same applies to the misinterpretation of questions and the use of phrases that should be avoided such as "I think", "I suppose", "I guess", "normally", "usually", "occasionally", or "mostly". It is vital that all personnel who could potentially come into contact with an FDA investigator undergo proper training on how they should conduct themselves during an inspection. It is important to remember that there is a whole range of do's and don'ts that must be followed in all circumstances.

Troubleshooting and Gap analysis conducted by the PAI team provides a further useful tool. This "organized brainstorming" meeting is designed to list all potential strengths, opportunities, weaknesses and threats. Everyone taking part in the meeting must be able to speak openly and honestly when discussing where they personally see potential risk areas or weaknesses. Senior management are often surprised by how much is already known within an organisation, but is not communicated to the people who are able to change and improve issues that may have caused problems in the past but were never resolved.

It is crucial that you closely examine the findings of any previous inspections and the commitments that were given to the agency as inspectors often use these as a starting point for their work.

Shortly before the inspection, a key contacts list should be compiled detailing the names, positions, phone numbers, mobile numbers and e-mail addresses of the most experienced personnel. This will ensure that information flows rapidly and smoothly during the hectic inspection period.

3 - During the Inspection

To a large extent, success or failure is dependent on the skills and capabilities of the PAI coordinator / moderator and the standard of a company's backroom organisation. It is important to have at least two separate rooms set aside for the inspection. The front room is used by the inspectors and the second room, often referred to as the "war room" or backroom, is used to ensure that documents are quickly and efficiently retrieved and guarantee the smooth flow of both personnel and documents to the inspection room.

The war room / backroom coordinator and his or her assistant must have clearly defined roles. The same applies for the inspection front room, where the coordinator moderates the inspection and the inspection observer (scriber) takes notes. Each individual request from the inspec-

tor should be written down on an inspection request form that notes the date, time, inspector's name, subject and the requested information. This form should then be taken to the backroom for preparation or investigation by a designated person (runner). Documents such as validation master plans, protocols and reports, batch records, SOPs and other key quality documents should be collected prior to the inspection and made available in the backroom.

It is extremely important that documents are brought to the attention of the inspectors in their original form only (with original signatures) or alternatively as copies that are officially sanctioned in line with your document control procedure.

4 - Pre Approval Inspection - The Exit Meeting

The exit meeting should be attended by the inspection coordinator, plant/site manager and other key management personnel including QA/QC managers. Tact, responsiveness and thorough note-taking are essential.

During the exit meeting, the inspector verbally concludes the inspection and may leave a 483 (483 is the number assigned to the form that includes the citations found by FDA inspectors) if potential violations have been observed. Any misunderstandings or misinterpretations relating to the presented facts should be cleared up at this point. It is important to remember that only facts can be discussed and it is too late to support misunderstandings with further documentation or data during the meeting.

If you dispute any of the findings that are presented, you can communicate your concerns to the FDA district office. However, it is important to remember that a good inspection coordinator should have been able to resolve such issues during the inspection, thereby avoiding confrontation during the exit meeting. If measures have already been taken or put in place to rectify any observations, these should be brought to the attention of the inspector by asking for the observations to be annotated. There are four common terms used to annotate a 483: "Reported corrected, not verified"; "Corrected and verified"; "Promised to correct" and "Under consideration". However, the FDA inspector is under no obligation to add these comments to the 483 form observations. The site is also permitted to ask if the inspector will recommend the approval of the inspected product or site (Cover letter by the district office to the establishment inspection report – EIR).

The company should speak with a single voice, usually through the inspection coordinator or the most senior executive present at the exit meeting. At the end of the meeting, this person should also make some concluding remarks (stating, for example, that the inspection was fair, that all verbal and written findings will be taken seriously, that the inspection has been of great value to the site, that the site will maintain this high GMP level, that inspection motivates personnel) and thank the inspector for his or her time and effort.

5 - Post-Inspection Acitvities

A formal response to all 483 items should be sent to the FDA district office within 10-15 days after completion of the inspection, even if this is not legally required. Issuing a formal response can help to reassure the agency of the company's good intentions and thereby minimise the potential for further regulatory action. It is important that responses to individual 483 observations are not only product related but also system related.
Each observation should be accompanied by a detailed, scientifically justifiable plan with reasonable timelines for implementation and finalisation as a minimum requirement. Show evidence of implementation and do not make the mistake of writing general statements such as "We will fix this problem", "This will not happen again next time". These statements will not be accepted.

If missing documentation such as SOPs has been cited, it may be worthwhile writing, approving and implementing relevant SOPs and attaching authorised copies to the first response (a translation may be necessary).

In the April 2002 edition of the Gold Sheet, FDA inspector Kim Trautman recommends that it may occasionally be advisable to exceed the 15 day first-response period if you have been unable to compile, specify or scientifically formulate plans or corrective measures within this timeframe. A native speaker should review the final response. If you have missed the deadline for implementing corrective measures, you should inform the FDA and explain what has happened and what your new timeframe is.

The company can request that the 483 responses are filed together with the 483 report and that the responses are released along with the 483 report if access to the documentation is requested in line with freedom of information legislation.

The FDA inspector will write an EIR (establishment inspection report) that includes the 483 observations, further details on the site's operations and additional GMP comments. This report is placed in the company's file and is also available under freedom of information legislation. This is the main difference between the FDA and most other regulatory bodies, where inspections are considered confidential and are only discussed between the government and the company. It is vital for the company to have a copy of the FDA establishment inspection report, to read all of the inspector's additional comments and concerns and to use this material for subsequent inspection preparations.

It is crucial that the progress of corrective measures is closely monitored. It is inevitable that there will be another inspection…