Do's & Don'ts

Thirteen Key Directives on Drug Development.

Directive 1. "***Write a clear SOP on drug development***". The goal of drug development is to present a quality rugged drug in the overall shortest development time. If your firm hasn't clear, concise drug development procedures and objectives on file, backed-up with all the necessary protocols, from cleaning, to process to analytical validation - don't start the project until this is done.

Directive 2.

"**Run pilot studies - never uncontrolled studies** -" uncontrolled studies like non-validated assays may seem cheaper at the time but generally give the wrong guidance. A pilot study to evaluate a potential bioequivalent product with a fully validated analytical assay/ metabolite/impurity procedure, prior to the main study - often works out more cost effective than plunging into a high cost study without a pilot evaluation. Never do uncontrolled studies!

Directive 3.

"**Write and Report Facts Faithfully**"

A failed result is a positive endpoint as it may well highlight a wrong development route. If the result stays 'failed' after a full investigation, then report its impact and conclusions on the study or process faithfully. Never average results in order to bring an out-of-spec-result into specification.

That's a GLP violation.

Directive 4.

"**Remember the 5C's of documentation"**

Each documentation page of a report, protocol, method, or submission file should be like the 5C's of a flawless diamond (cut, clarity, clear, carat, cost.)

Clear statements, aims, objectives conclusions and results inform the reviewer of where you are going.

Concise - a report that is succinct and to the point is all that's needed.

Compact , avoid any padding - period!

Controlled prospective protocols and procedures can be written for most studies or processes and will produce well-controlled documents.

Certify & check - review and audit every document your development unit produces. Sign, date and stamp documents that have passed a careful and thorough audit review process.

Directive 5.

"**Be innovative and creative**"

Get your research department to talk to the developers, the production people, regulatory affairs and lab. analysts. Do not compartmentalise your personnel. **C**ross departmental communication imparts development expertise and builds in genuine product value.

Challenge SOPs and procedures with the aim of producing a better product.

Documentation can always be made more attractive and user friendly. Writing procedures using attractive fonts and point sizes often invite readership.

Directive 6.

"**Be Open and Direct** "

Never hide a bad study or cover up a poor result. All test results are valid unless an appropriate investigation procedures proves otherwise. Review your firm's out-of-specification operational procedure, and check that there are no organization omissions…

Directive 7.

"**Investigate all abnormalities**"

Test results that are out-of-specification need formal written investigations based on a Out Of Specification Standard Operating Procedure. The result may well be a simple sampling or technician error. For example - an extraneous peak that suddenly appeared after many production manufactured lots

in an HPLC assay spectrum, was found on investigation to arise from a change in an inactive dye vendor (a new supplier) and not as was anticipated a new product impurity or degradant.

Directive 8.

"Run a mock PAI against your Application *just* before submitting."

The Drug Application will eventually be judged on the acceptability of the manufacture, control and testing facilities as documented in the agency file *and* in-house supporting data. Audit every facet of the development, manufacture, control and stability procedures of the drug product. Check and cross-reference each possible submission document against the manufacturing / control and laboratory files and equipment logs. Build in routine **self-inspection checks** during the development process. Formulate this quality development routine by SOPs and department audit checklists.

Directive 9.

"Make your Application really clear, concise and user friendly "

Well prepared and assembled print or electronic files and dossiers are a joy to read, review, and evaluate. Use all the desk top publishing tools to shape your firm's reports as attractive, stimulating, and interesting to read and review.

A document can entice or repel a reader simply by its construction - it can also be made a scientific work-of-art.

Directive 10.

"Treat regulators like your key personnel treat you"

Listen to regulators - they too have their story to tell and may know regulations that you don't. Listen to their concerns clearly - it's in your product's interest.

There is no greater achievement in satisfying a PAI inspector's requests in real-time and in producing the documentation/data requested - before he leaves the firms' premises.

That regulator won't forget you or your product line up for review!

Work with regulators - or they will work against you and your product may not get to the market place on time.

Treat regulators with respect - as you would like to be treated. Agency official are understanding, experienced professionals whose prime concern is product quality and safety.

In any regulatory meeting the only welcome outcome is a win-win scenario. Both parties get what they want.

Remember an agency never looses an argument - the product only suffers and gets delayed due to incomplete data or regulatory requirements.

Directive 11.

"Talk to the regulators regularly."

Allow regulators to review protocols prior to starting the work. Get their opinion and express your concerns openly. Regulators like openness and honesty - and work well with polite, respectful and professional personnel.

Directive 12.

"Take a hard look a your cGMP's "

The absence of GMP compliance simply adulterates your drug development pipeline. GMP compliance is targeted to play a more dynamic role in the drug review and PAI process.

(Establishment Evaluation System - FDA Drug Center and Office of Regulatory Affairs electronic data sharing)

Directive 13.

"Audit everything enthusiastically".

Leave no audit stone unturned. Establish consistent in-house audit self-inspection programs effective at *each* stage of the drug development pathway. At the end of every development report submission stage, (refer development checklist chapter 15), audit the department and relevant steps concerned.

End-of-study auditing is quite ineffective as early errors or omissions can not be corrected promptly and on-time.