

Getting the Right **Documentation** from

'If there is no documentation it's a rumor; If it's well documented - it's a fact.- FDA



SOP CONTROL

Standard Operational Procedures for a generic development unit are the documentation first essential requirements.

Without a functional set of standard development procedures, developing generic drugs will follow a haphazard non-reproducible process. SOPs are efficient and useful instructional and working tools.

AII pharmaceutical companies conducting drug research and development must have understandable SOPs. The primary purpose of the SOP is to translate the various regulations and guidelines, which are open interpretation, into clear and concise sets of instructions.

> Don't Do Without Development SOPS

Essentially generic development can distilled into standard be development procedures which any development scientist could apply. procedures These may electronically circulated as a readdocuments. Master

By: Brian Brice & Jan Kay MSc. Contact e-mail journal@locumusa.com

authorized and stored by QA using electronic new signature procedure (e-sig rule of 20 October 1997)

Standard Operating **Procedures** should meet six basic and functional requirements and where possible be e-SOPs

- SOP Index system (on PC)
- an intelligent numbering system.
- standardized format
- approval signatures
- a rapid distribution procedure (e-SOPs)
- Annual biannual or reviews (electronic)

The SOP index is a list consisting of a SOP reference numbers and the procedure titles.

The SOP number ideally has four components, the department code (P for pharmaceutics etc.), the SOP number e.g. (001 to 999), the edition number (01, 02) and the last review or the editorial date. (e.g. P-000-01-0100).

Do's and Don'ts

Do - make the SOP index an actual Standard Operating Procedure and change the edition # for each new SOP modification during the course of the year.

Do - have both electronic and a Master SOP manual in a spiral bound book form for all key departments e.g. Pharmaceutical, Analytical, Stability, Microbiology, Quality Assurance Metrology Engineering, Administration and Regulatory Affairs, for ease of updating and removing superseded (old) editions.

Do - write brief and to the point SOPs so that they can be read and understood quickly. Use forms or checklists for extra information and attached to the SOP.

Don't - have loose lying SOPs gathering dust on the shelf.

Don't - write a SOP that cannot be followed - routinely, by all concerned.

Don't - write long SOPs (about 1 to 5 pages is sufficient for the average SOP).

Don't - write SOPs just to comply with GMP - use them frequently as operational and training tools.

Don't - allow SOPs to become static documents - review and amend them regularly as procedures are optimized.

SOPs & Protocols are living entities...

Describing daily operations...

DEVELOPMENT SOPS

The Standard Operation Procedures chosen, must fully represent a cross-section of the SOPs needed for a drug development unit to operate efficiently and to produce drug products on time.

A researcher conducts work according to a documented set of procedures - which hopefully represents the best and most current

methods available i.e. drug development via "state-of-the-art" techniques.

A drug researcher must keeps a record of every detail of the product development - both the advances and the failures of the experimental batch lots.

SOPs also demonstrate that you are following a key rule of a good researcher - that the research procedures are fully described so that they can be replicated where necessary.



A development SOP is a protocol or summary of the overall generic drug development process. It acts as a guideline or road map for the development team to follow to ensure complete product development.

Development SOPs are not a CFR requirement. They are designed for rapid and complete generic drug development and are significant aids to agency staff during pre-approval inspections (PAIs).

DEVELOPMENT NOTEBOOKS

Similar to printed SOPs or better still electronic SOPs, numbered and bound printed analytical pharmaceutical development notebooks (do not use electronic workbooks) are essential tools and records for a structured generic or innovative development program to succeed. Patent data (formula or processes) must be fully traceable and needs to follow precise rules to assure authenticity and possible data challenge. Well structured pharmaceutical analytical and workbooks meets these needs.

> CHECK LIST 4

CL # HPGD-02-0100

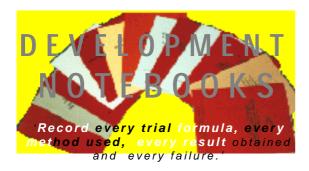


SOP CONTROL

"... failure to follow your SOPs adulterates the product..."

Yes	No
Yes	No
	Yes

Footnote: Bold letters in checklist indicate that this work must be checked and approved before pre-formulation work starts.



DEVELOPMENT NOTEBOOKS

Pharmaceutical development notebooks are essential tools for successful generic drug development.

Spiral bound or loose leaf lab books are not permitted

The Development notebooks are bound, numbered, 100 page, hard cover notebooks suitable for a development laboratory environment. It is important to accept that entries to the laboratory notebook need to be completed from page one to pages 100 in a chronological order as the work was performed.

No blank pages may be left for later completion and no page may be left blank to be 'filled-in' at a later time or date.

Every page must be fully utilized... Leave no blank spaces

The issue and control of the development notebooks and the signing procedures after each work section is complete is an important audit control check.

The development notebooks are used to record all pre-formulation and product development procedures. All failed procedures must be recorded. No product was ever developed without a number of reject lots.

Laboratory equipment printouts and HPLC printer spectra and data must be well pasted or firmly taped onto the relevant pages of the notebook (use 3M non aging non yellowing tape).

The paste-in are signed and dated in ink with the signature split across edge of the paste-on and the actual page itself.

Avoid printers with heat sensitive paper as data rapidly fades

Paste-on pint-outs should be affixed in such a manner that a reviewer or auditor examining the data months or years later will feel comfortable that the all the print-outs and data was entered and fixed at the actual time of analysis.

Where a print-out uses heat sensitive paper it should be photocopied the same day and the original and copy ink-signed and permanently pasted onto the working page. With time the original heat sensitive paper will fade, however the copy with signature will remain as the permanent record.

Heat sensitive paper printers should be strongly discouraged and changed where ever possible.

Laboratory notebooks prepared in this manner become swollen and bulky - which is the proper appearance a reviewer expects.

Always co-sign all copies of original print-outs

Where (in rare cases) the amount of print-out material is much too large and bulky to affix to the notebook page, it is essential to carefully annotate the print-out with the lab book issue and page number and in turn reference the print-out on the actual lab book page with the number of spectra and total pages of the print-out.

Its storage location should be annotated on the relevant page as well to allow for rapid retrieval at a later date or when archived. Most modern laboratory equipment indicate the date and time of printing and this time stamp should carefully be synchronized with the experimental data, calculation and results.

Fix graphs and print-outs in a secure permanent manner

Key data recorded in notebooks include:

- All ingredient lot # and expiry dates
- Active and excipient sources (supplier)
- all pre-formulation formula
- all manufacturing methods used
- Equipment used, speeds and times
- All in-process controls
- all results and observations
- all tentative specifications
- All finished product controls
- proposed stability specifications
- all failed data, and abnormal results
- investigations and conclusions
 Each stage and page of the notebook
 is signed by a supervisor and then dated.

Corrections to notebooks follow the Correction SOP. All deletions must be readable and no correction fluids (Tipex Fluid[™] or White-out[™]) are permissible.

All ingredient weights and measures require a *check signature* at the time of measurement. Late signatures are invalid and are neither GMP or professional.

Development of pre-formulation and development lots do not require *strict* GMP procedures, however good GMP development practices enhance the scientific validity of results obtained.

Non-calibrated equipment and poor process techniques produce questionable development reports and generic products.

ANDAs derived from inadequate development procedures may certainly fail in the market place.

DEVELOPMENT QUALITY ASSURANCE

A well documented, and controlled generic development unit permits for rapid generic drug development at the lowest cost.

Meticulously prepared development documentation aids in the timely production of rugged generic products within the allocated development time frame.

Good documentation is a cost-andtime saver and allows for rapid data review during pre-approval inspections (PAIs), a blessing for agency inspectors, as well as a proven training record for further successful generic product development.

Lab Notebooks are the key source of data in PRE-APPROVAL INSPECTIONS

The development notebook is the raw data source for the 'Development Report' and is an important review document from a pre-approval and regulatory viewpoint.

Up to 10% of development and research time should be allocated to fine-tuning development SOPs, notebooks, auditing correct documentation and team training in their correct use.

>CHECK LIST<



CL # HPGD-02-0100

DEVELOPMENT NOTEBOOKS

"... Sign every stage not every page - check every page and every stage...."

1. D oes the Development Unit have bound & page numbered notebooks?				
2. Are the printed development notebooks signed on every stage & page?	Yes	No		
3. Has each completed section been signed with a check signature ?				
4. Has correcting fluid been used to cover up data?				
5. Are data corrections performed according to the SOP ?	Yes	No		
6. Are all pre-formulation and development formula numerically recorded ?	Yes	No		
7. Do the notebooks record successful <i>and</i> failed development product formula?	Yes	No		
8. Do all calculations have check signatures which are dated.	Yes	No		
9. Has the Product Development SOP been complied with during the product development phase?	Yes	No		
10. Is a process of formula, specifications and process optimization evident?	Yes	No		
11. Do all specifications have an appropriate range, where absolutely needed?	Yes	No		
12. Have critical upper <i>and</i> lower range limits been qualified?	Yes	No		
13. Are out-of-specification results <i>investigated</i> and documented?	Yes	No		
14. Are the lot #'s, expiration dates and source of each active and non-active ingredient used during <u>routinely</u> recorded in workbooks?	Yes	No		
15. Does the development notebook appear suitable as a scientific <i>basis</i> for the generic drug product 'Product Development Report'?	Yes	No		
16. The Product Development Report comprises of both pharmaceutical and analytical development reports.	Yes	No		

Footnote: Bold letters in checklist indicate that this work must be checked and approved before pre-formulation work starts.

STANDARD OPERATING PROCEDURE



SOP # HPGD-02-01YY

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SOP CONTROL AND DEVELOPMENT NOTEBOOKS

The following Standard Operating Procedures are recommended for a generic development unit and should be in place prior to initiating product development: Electronic, computer based, SOPs are rapidly becoming a common place phenomena in pharmaceutical environments.

Electronic updating and distribution and removal of superseded SOPs is greatly simplified by using an internal network system (intranet) for SOP distribution and viewing. An appropriately signed 'Master SOP' collection is held by the firms archive or library system, while electronic copies for staff use displayed in a PDF™ format are viewable on firms numerous internal desk computer screens.

SOP CONTROL

HPGD-02-01YY Indexing procedure for pharmaceutical development SOPs
HPGD-02-01YY Index for pharmaceutical development SOPs
HPGD-02-01YY Signing procedures of pharmaceutical development SOPs
HPGD-02-01YY Standard Operating Procedures - number and format
HPGD-02-01YY Circulation of pharmaceutical development SOPs
HPGD-02-01YY Annual review of pharmaceutical development SOPs
HPGD-02-01YY List of FDA guides and Guidelines impacting on product development dosage form and type (IR)

DEVELOPMENT NOTEBOOKS

HPGD-02-01YY Issue and use of pharmaceutical development notebooks.

HPGD-02-01YY Signing procedures for development notebooks.

HPGD-02-01YY Development notebooks - review and audit procedures.

HPGD-02-01YY Standard procedures in generic product development.

HPGD-02-01YY Pharmaceutical development notebooks - disposition.

ED. N0: 01 Replaces NEW	Effective Date:	APPROVED:			
Ed. Status :	DD/MM/YY				
UI		Department	R&D	RA	QC/QA



Designed for: Pharmaceutical Researchers: Pharmaceutical & legal Consultants **Generic** Drug Development Firms and **CMC Innovative** & Research-based Units.

IAGIM - Drug Development Association.

IAGIM supplies new drug pipeline of generic CMC technology via joint ventures partnership with Pharmaceutical Manufacturing Companies, Pharmaceutical Associations, drug development units and research & university affiliations worldwide.

♦ The Association's Objectives

Provides an International flow of know-how Technology on Innovative and Generic Drug Development.

♦ The Association's Publications

Member's *technical* bimonthly Drug Letter *"Development Do's and Don'ts"*24 volume authoritative Handbook *Series* on Generic Drug Development.

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US ANDA *Electronic* Template Drug Registration System free to three year members.

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♦ The Association's Archives

The Association maintains a working Drug Development Archive on the World Wide Web dealing with all aspects of drug development, process validation and analytical aspects. Keep informed of the important regulations, FDA will adopt this year, so you can plan your drug development pipeline and manufacturing operations ahead.

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International Journal of Generic Drugs

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