System of preliminary scrutiny by CDSCO at the time of receipt of application for approval of Fixed Dose Combinations (FDCs)

1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations

API	Active Pharmaceutical Ingredient
BA	Bio-availability
BE	Bio-equivalence
CRF	Case Record Form
CT	Clinical Trial
FDC	Fixed Dose Combination
ICF	Informed Consent Form
IND	Investigational New Drug
INR	Indian National Rupee
LD	Lethal Dose
PK / PD	Pharmacokinetic and Pharmacodynamic
CV	Curriculum vitae
NOC	No objection certificate
QC	Quality control

3. GENERAL CONSIDERATIONS:

Fixed Dose Combinations (FDCs) refer to products containing two or more active ingredients used for a particular indication(s). As per Rule 122-E of Drugs & Cosmetics Rule, A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage form (including sustained release dosage form) and route of administration are considered new drugs. Further, a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier.

The development of FDCs is becoming increasingly high either to improve compliance or to benefit from the added effects of the two or more active drugs given together. They are being used in the treatment of a wide range of conditions and are particularly useful in the management of chronic conditions.

Appendix VI of Schedule Y to Drugs & Cosmetics Rules 1945, specifies the requirements for approval of various categories of FDCs. Such applications can be categorized as under:

1. FDC - Not marketed in India & one or more active ingredient(s) is a new drug not approved in India.

A. Sub Category I: One of the ingredients of the combination is an Investigational New Drug (IND).

B. Sub Category II: One or more of the ingredients of the combination is a New Drug not approved individually in the country however the same is approved in other country.

2. FDC - Not marketed in India but the active ingredients are approved/ marketed individually & it is likely to have significant PK/PD interactions

A. Sub Category 1: FDC - Marketed abroad

B. Sub Category II: FDC - Not marketed anywhere but individual components used concomitantly

C. Sub Category III: FDC - Not marketed and individual components are not used concomitantly

3. FDC - Marketed in India but some changes are sought

4. FDC - Only for convenience

5. FDC – Approvals of a FDC already approved in the country

Documents required for approval of a FDC varies widely depending on the category to which it falls, the nature of the drugs, disease for which it is indicated etc. Till date, applicants have used many different approaches in organizing the information and the differences in organization of data in each

application has made reviewing more difficult and can also lead to omission of critical data or analyses. Such omissions can result in unnecessary delays in approvals.

In order to streamline the submission of such application and their review, it has been decided to introduce a system of preliminary scrutiny of such applications at the time of receipt of these applications to determine the acceptability for review by CDSCO.

The preliminary scrutiny of the application will be done by CDSCO officer(s) based on checklists prepared for each of the above category of FDC, which are attached herewith. During the preliminary examination, the CDSCO officer(s) will scrutinize the application to ensure that it contains all the required administrative as well as technical information in proper manner as per the checklist. If application is not submitted in accordance with the format and the checklist, it will not be accepted by CDSCO for further review.

Once an application is accepted, the adequacy of the data will be reviewed by CDSCO as per the specified requirements and guidelines. In case the data submitted is not adequate or satisfactory, applicant will be requested to generate/submit adequate data for consideration and approval of the FDC.

The applicants are requested to prepare the applications in the following manner:

I. Before preparing the application, the applicant must categorize their proposal as specified above and submit information as per the checklist for that category.

II. Application in Form 44 should be complete in all respect and signed by the authorized person of the firm with name and designation.

III. The TR challan receipt submitted by the applicant should mention the name of the FDC including correct head of the account, payable at, bank clearance, etc.

IV. The documents must be submitted with indexing and page number. Without indexing or page number, no application will be accepted.

V. Clear and unequivocal information should be provided alongwith the application.

VI. Text and tables should be prepared using margins that allow the document to be printed clearly without losing any information and the left-hand margin should be sufficiently large so that information is not obscured by the method of binding. The documents printed on both sides of a page, can be submitted provided, however, one should take care that the information is not obscured when the page is placed in a binder.

VII. The proposed fixed dose combination should be based on therapeutic rationale. The applicant is required to justify the combination based on the rationale. While submitting the rationale for an FDC, the applicant must address the issues like drug-drug interaction between the ingredients, food effects and dosage schedule of individual active ingredients vis-a-vis that of the FDC. Further, the indication/claim for the FDC should be such that the individual active

ingredients makes a contribution to the claimed effect and the product should be formulated so that the dose and proportion of each substance in the FDC is appropriate.

VIII. Trial batches of new drugs for test and analysis/clinical trial/BE study purpose should be manufactured after obtaining Licence in Form 29 from the concerned State Licensing Authority and copy of the licence should be submitted alongwith the application.

IX. While submitting reply to a query, the applicant should always enclose with the reply, a copy of query letter issued by CDSCO.

X. The applicant should submit stability data generated on 3 trial batches manufactured by them under Licence in Form 29 issued by State Licensing Authority (SLA). The stability data should be submitted as per the format attached at Annexure A.

XI. The clinical trial protocol should be submitted as per the format attached at Annexure B

XII. In case of clinical trial/ bioequivalence study NOC, the applicant should submit the adequate chemical and pharmaceutical information as per Annexure C attached.

XIII. The applicant should always submit certificate of analysis, dissolution data (in case of oral dosages form, as appropriate), stability study data etc. in respect of formulation, duly signed by the In-charge/Manager Q.C.

XIV. All items mentioned in the checklist of various categories of FDC may not be applicable to all drugs. The items not relevant to a particular new drug should be marked with "Not Applicable (NA)".

THIS SYSTEM OF PRELIMINARY SCRUTINY TO DETERMINE THE ACCEPTABILITY OF THE APPLICATION WILL COME INTO EFFECT FROM 01.01.2011.

4. CHECKLIST FOR ACCEPTABILITY OF APPLICATIONS PERTAINING TO FIXED DOSE COMBINATIONS (FDCs)

4.1. Category – I: FDC - Not marketed in India & one or more active ingredient(s) is a new drug not approved in India

4.1.1. Sub Category I: One of the ingredients of the combination is an Investigational New Drug (IND):

#	Documents required to be submitted	Status	
		Yes	No
1	**Application for: (permission for manufacture /import/clinical trial)**		
2	**Name of the applicant**		
3	**Name of the Fixed Dose Combination(FDC)**		
	a. Composition of the FDC		
	b. Dosage Form		
	c. Proposed indication for the FDC		
4	**Application in Form 44 complete in all respect duly signed and stamped by authorized person of the firm**		
5	**Treasury Challan of INR 50,000 duly signed and stamped by Bank of Baroda**		
6	**Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.**		
7	**Approval status of individual drugs in the country**		
8	**Copy of valid manufacturing license in Form 25/28 along with copy of form 29**		
9	**Source of bulk drugs. For those ingredients which are approved and consider new drug, copy of Form 46A.**		
10.	**Information on active ingredients which are considered as IND**		
	a) Physiochemical data (Chemical name and Structure, Physical properties etc.)		
	b) Analytical data (elemental analysis, NMR spectrum, IR Spectrum, UV spectrum etc.)		
	c) Complete monograph specification including identification, identity/quantification of impurities, enantiomeric purity, assay etc.)		
	d) Certificate of analysis		
	e) Validation [assay method, impurity estimation method, residual solvent/other volatile impurities(OVI) estimation method]		
	f) Reference standard characterization,		
	g) Material safety data sheet.		
11	**Data on Formulation:**		
	a) Master manufacturing formula		
	b) Details of the formulation (including inactive ingredients)		
	c) Finished product specification		
	d) In process quality control check		
	e) Excipient compatibility study		
	f) Process validation		
	g) Validation of analytical method		
	h) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.		
	i) Comparative evaluation with international brand(s) or approved Indian brands, if applicable.		
	j) Dissolution data in case of oral dosage forms as appropriate		
	k) Stability study evaluation as per requirements of schedule Y		

12	**Animal Pharmacology including summary of the study, general pharmacological actions, specific pharmacological actions, follow-up and supplemental safety Pharmacology Studies, Pharmacokinetics including absorption, distribution; metabolism; excretion**		
13	**Animal toxicology data as per Schedule Y.**		
	a. systemic toxicity studies,		
	i. single dose toxicity		
	ii. repeated dose toxicity		
	b. Male Fertility Study		
	c. Female Reproduction and Developmental Toxicity Studies		
	d. Local toxicity		
	i. Dermal toxicity		
	ii. Ocular toxicity		
	iii. Inhalation toxicity		
	iv. Vaginal toxicity		
	v. Photoallergy or dermal phototoxicity		
	vi. Rectal tolerance test		
	e. Genotoxicity		
	f. Allergenicity/Hypersensitivity		
	g. carcinogenicity		
14	**Human / Clinical pharmacology (Phase I) including summary of the study and reports**		
	i. Summary		
	ii. Specific Pharmacological effects		
	iii. General Pharmacological effects		
	iv. Pharmacokinetics, absorption, distribution, metabolism, **v. excretion**		
	vi. Pharmacodynamics / early measurement of drug activity		
15	**Therapeutic exploratory trials (Phase II) including summary of the study and reports**		
16	**Therapeutic confirmatory trials (Phase III) including summary of the study and individual study reports with listing of sites and Investigators.**		
17	**Regulatory status in other countries, as appropriate.**		
	a) Names of the countries where the drug is marketed/approved		
	b) Names of the countries where the drug is approved as IND, withdrawn,		
	c) Names of the countries where the drug is withdrawn, if any, with reasons		
	d) Free sale certificate (FSC) or Certificate of Pharmaceutical Product (COPP), as appropriate.		
18	**Copy of proposed Package Insert which should include generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.**		
19	**Draft specimen of the label and carton**		

Note:

1. **All items mentioned above may not be applicable to all drugs. The items not relevant to a particular new drug should be marked with "Not Applicable (NA)".**

2. **In case the application is for clinical trial permission , adequate chemical and pharmaceutical information should be provided to ensure the proper identity, purity, quality & strength of the investigational product, the amount of information needed may vary with the Phase of clinical trials, proposed duration of trials, dosage forms and the amount of information otherwise available.**

4.1.2 Sub Category II: One or more of the ingredients of the combination is a New Drug not approved individually in the country however the same is approved in other country:

#	Documents required to be submitted	Status	
		Yes	No
1	**Application for: (permission for manufacture /import/clinical trial)**		
2	**Name of the applicant**		
3	**Name of the Fixed Dose Combination(FDC)**		
	a. Composition of the FDC		
	b. Dosage Form		
	c. Proposed indication for the FDC		
4	**Application in Form 44 complete in all respect duly signed and stamped by authorized person of the firm**		
5	**Treasury Challan of INR 50,000 duly signed and stamped by Bank of Baroda**		
6	**Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.**		
7	**Copy of valid manufacturing license in Form 25/28 along with copy of form 29**		
8	**Approval status of individual drugs in the country**		
9	**Source of bulk drugs. For those ingredients which are approved and consider new drug, copy of Form 46A.**		
10	**Information on active ingredients which are considered as IND**		
	a) Physiochemical data (Chemical name and Structure, Physical properties etc.)		
	b) Analytical data (elemental analysis, NMR spectrum, IR Spectrum, UV spectrum etc.)		
	c) Complete monograph specification including identification, identity/quantification of impurities, enantiomeric purity, assay etc.)		
	d) Certificate of analysis		
	e) Validation [assay method, impurity estimation method, residual solvent/other volatile impurities(OVI) estimation method]		
	f) Reference standard characterization,		
	g) Material safety data sheet.		
11	**Data on Formulation:**		
	a) Master manufacturing formula		
	b) Details of the formulation (including inactive ingredients)		
	c) Finished product specification		
	d) In process quality control check		
	e) Excipient compatibility study		
	f) Process validation		
	g) Validation of analytical method		
	h) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.		
	i) Comparative evaluation with international brand(s) or approved Indian brands, if applicable.		
	j) Dissolution data in case of oral dosage forms as appropriate		
	k) Stability study evaluation as per requirements of schedule Y		
12	**Animal Pharmacology including summary of the study, general pharmacological actions, specific pharmacological actions, follow-up and supplemental safety Pharmacology Studies, Pharmacokinetics including absorption, distribution; metabolism; excretion**		
13	**Animal toxicology data as per Schedule Y.**		
	a. systemic toxicity studies		

	i. single dose toxicity		
	ii. repeated dose toxicity(In case of injectable formulation, sub-acute toxicity data generated with the applicants' product has to be provided).		
	b. Male Fertility Study		
	c. Female Reproduction and Developmental Toxicity Studies		
	d. Local toxicity		
	i. Dermal toxicity		
	ii. Ocular toxicity		
	iii. Inhalation toxicity		
	iv. Vaginal toxicity		
	v. Photoallergy or dermal phototoxicity		
	vi. Rectal tolerance test		
	e. Genotoxicity		
	f. Allergenicity/Hypersensitivity		
	g. carcinogenicity		
14	**Human / Clinical pharmacology (Phase I) including summary of the study and reports**		
	i. Summary		
	ii. Specific Pharmacological effects		
	iii. General Pharmacological effects		
	iv. Pharmacokinetics, absorption, distribution, metabolism, **v. excretion**		
	vi. Pharmacodynamics / early measurement of drug activity		
15	**Therapeutic exploratory trials (Phase II) including summary of the study and reports**		
16	**Therapeutic confirmatory trials (Phase III) including summary of the study and individual study reports with listing of sites and Investigators.**		
17	**Regulatory status in other countries, as appropriate.**		
	a) Names of the countries where the drug is marketed/approved alongwith package insert circulated in those countries		
	b) Names of the countries where package insert		
	c) Names of the countries where the drug is approved as IND, withdrawn,		
	d) Names of the countries where the drug is withdrawn, if any, with reasons		
	e) Free sale certificate (FSC) or Certificate of Pharmaceutical Product (COPP), as appropriate.		
18	**Copy of proposed Package Insert which should include generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.**		
19	**Draft specimen of the label and carton**		

Note:

1. **In case, such a combination is not marketed anywhere in the world, clinical trials data right from Phase I as appropriate may be required to be generated and submitted to this office. If such FDC is marketed abroad Phase III clinical trials data generated in India are required to be submitted.**
2. **All items mentioned above may not be applicable to all drugs. The items not relevant to a particular new drug should be marked with "Not Applicable (NA)".**
3. **In case the application is for clinical trial permission , adequate chemical and pharmaceutical information should be provided to ensure the proper identity, purity, quality & strength of the investigational product, the amount of information needed may vary with the Phase of clinical trials, proposed duration of trials, dosage forms and the amount of information otherwise available.**

4.2 Category II : FDC - Not marketed in India but the active ingredients are approved/ marketed individually & it is likely to have significant PK/PD interactions

4.2.1 Sub Category I- FDC - Marketed abroad:

#	Documents required to be submitted	Status	
		Yes	No
1	**Application for: (permission for manufacture /import/clinical trial)**		
2	**Name of the applicant**		
3	**Name of the Fixed Dose Combination(FDC)**		
	a. Composition of the FDC		
	b. Dosage Form		
	c. Proposed indication for the FDC		
4	**Application in Form 44 complete in all respect duly signed and stamped by authorized person of the firm**		
5	**Treasury Challan of INR 50,000 duly signed and stamped by Bank of Baroda**		
6	**Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.**		
7	**Approval status of individual drugs in the country**		
8	**Names of the countries where the FDC is approved and marketed .(*Names of the countries where the FDC is Approved / Marketed / Withdrawn etc should be clearly stated in the covering letter also)***		
9	**Copy Package Inserts, promotional literatures of FDC circulated in those countries where it is marketed**		
10	**Copy of valid manufacturing license in Form 25/28 along with copy of form 29**		
11	**Source of bulk drugs along with current regulatory status of the source with copy of Form 46A in case of new drug.**		
	Information on active ingredients		
12	a) Brief Chemical & pharmaceutical data		
13	**Data on Formulation:**		
	a) Master manufacturing formula		
	b) Details of the formulation (including inactive ingredients)		
	c) Finished product specification		
	d) In process quality control check		
	e) Excipient compatibility study		
	f) Process validation		
	g) Validation of analytical method		
	h) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.		
	i) Comparative evaluation with international brand(s) or approved Indian brands, if applicable.		
	j) Dissolution data in case of oral dosage forms as appropriate		
	k) Stability study evaluation as per requirements of schedule Y		
14	**Free sale certificate/ certificate of pharmaceutical product from the country of origin (in case of import of the finished form of the FDC).**		
15	**Clinical trials data showing safety and efficacy of the FDC in the same strength (that has been carried out in other countries) including published data.**		
16	**Summary of Drug-Drug-Interactions (known and/or expected) among the active ingredients present in the FDC, along with its implications. This should be prepared and signed by a competent person on behalf of applicant.**		
17	**Animal toxicology study data, as appropriate (In case of injectable formulation,**		

	sub-acute toxicity data generated with the applicants' product has to be provided).		
18	**Copy of proposed Package Insert which should include generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.**		
19	**Draft specimen of the label and carton**		

4.2.2 Sub category II: FDC - Not marketed anywhere but individual components used concomitantly

#	Documents required to be submitted	Status	
		Yes	No
1	**Application for: (permission for manufacture /import/clinical trial)**		
2	**Name of the applicant**		
3	**Name of the Fixed Dose Combination(FDC)**		
	a. Composition of the FDC		
	b. Dosage Form		
	c. Proposed indication for the FDC		
4	**Application in Form 44 complete in all respect duly signed and stamped by authorized person of the firm**		
5	**Treasury Challan of INR 15,000 duly signed and stamped by Bank of Baroda**		
6	**Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.**		
7	**Copy of valid manufacturing license in Form 25/28 along with copy of form 29**		
8	**Approval status of individual drugs in the country**		
9	**Source of bulk drugs along with current regulatory status of the source with copy of Form 46A in case of new drug.**		
10	**Information on active ingredients**		
	a) Brief Chemical & pharmaceutical data		
11	**Data on Formulation:**		
	a) Master manufacturing formula		
	b) Details of the formulation (including inactive ingredients)		
	c) Finished product specification		
	d) In process quality control check		
	e) Excipient compatibility study		
	f) Process validation		
	g) Validation of analytical method		
	h) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.		
	i) Comparative evaluation with international brand(s) or approved Indian brands, if applicable.		
	j) Dissolution data in case of oral dosage forms as appropriate		
	k) Stability study evaluation as per requirements of schedule Y		
12	**Summary of available pharmacological, toxicological and clinical data on the individual ingredients**		
13	**Summary of Drug-Drug-Interactions (known and/or expected) among the active ingredients present in the FDC, along with its implications. This should be prepared and signed by a competent person on behalf of applicant.**		
14	**Clinical data showing safety and efficacy of the FDC / Concomitant use of the ingredients, in the same strength, including published data. If enough supportive literatures are not available, then 'adequate evidence' on safe and effective concomitant use of the ingredients should be provided**		
15	**Animal toxicology study data, as appropriate (In case of injectable formulation, sub-acute toxicity data generated with the applicants' product has to be provided).**		
16	**Copy of proposed Package Insert which should include generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.**		
17	**Draft specimen of the label and carton**		

4.2.3 Sub Category III: FDC - Not marketed and individual components are not used concomitantly

#	Documents required to be submitted	Status	
		Yes	No
1.	**Application for: (permission for manufacture /import/clinical trial)**		
2.	**Name of the applicant**		
3.	**Name of the Fixed Dose Combination(FDC)**		
	a. Composition of the FDC		
	b. Dosage Form		
	c. Proposed indication for the FDC		
4.	**Application in Form 44 duly signed and stamped by authorized personal (Application for manufacture and market New FDC, BA/BE study and clinical trial application)**		
5.	**Treasury Challan of INR 15,000 if all active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year duly signed and stamped by Bank of Baroda**		
6.	**Approval status of individual drugs in the country**		
7.	**Source of bulk drugs /raw materials (for those ingredients which are considered new drugs)**		
8.	**Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.**		
9.	**Information on active ingredients:**		
	a) Brief Chemical & pharmaceutical data		
10.	**Data on Formulation:**		
	a) Master manufacturing formula		
	b) Details of the formulation (including inactive ingredients)		
	c) Finished product specification		
	d) In process quality control check		
	e) Excipient compatibility study		
	f) Process validation		
	g) Validation of analytical method		
	h) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.		
	i) Comparative evaluation with international brand(s) or approved Indian brands, if applicable.		
	j) Dissolution data in case of oral dosage forms as appropriate		
	k) Stability study evaluation as per requirements of schedule Y		
11.	**Summary of available pharmacological, toxicological and clinical data on the individual ingredients**		
12.	**Summary of Drug-Drug-Interactions (known and/or expected) among the active ingredients present in the FDC, along with its implications. This should be prepared and signed by a competent person on behalf of applicant.**		
13.	**Clinical study protocol as per Annexure attached**		
	a. Patient Information Sheet and Informed Consent Form (ICF) as per Appendix V of Schedule Y,		
	b. Copy of 'Ethics Committee' approval letters (if available) ,		
	c. Case Record Form (CRF), Certificate of analysis of study drug(s)		
	d. Undertaking by Investigator(s) as per Appendix VII of Schedule Y and CV,		
14.	**BA/BE study protocol (when applicable), and**		
	a. Patient Information Sheet and Informed Consent Form (ICF) as per Appendix V of Schedule Y,		
	b. Copy of 'Ethics Committee' approval letters (if available) ,		
	c. Case Record Form (CRF), Certificate of analysis of study drug(s)		
	d. Undertaking by Investigator(s) as per Appendix VII of Schedule Y and CV,		

15.	**Reports of clinical trial carried out with the FDC in the country as per appendix II of Schedule Y. In case , the application is for market authorisation,**		
16.	**Reports of Bioequivalence study carried out with the FDC in the country. In case , the application is for market authorisation,**		
17.	**Animal toxicology study data, as appropriate In case of injectable formulation, sub-acute toxicity data generated with the applicants' product has to be provided).**		
18.	**Copy of proposed Package Insert which should include generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.**		
19.	**Draft specimen of the label and carton**		

4.3 Category III : FDC - Marketed in India but some changes are sought (i.e. change the ratio of active ingredients or to make a new therapeutic claim or a new dosage form etc.)

#	Documents required to be submitted	Status	
		Yes	No
1.	**Application for: (permission for manufacture /import/clinical trial)**		
2.	**Name of the applicant**		
3.	**Name of the Fixed Dose Combination(FDC)**		
	a. Proposed Composition of the FDC		
	b. Proposed Dosage Form		
	c. Proposed indication		
4.	**Details of the approval of the FDC in the country**		
	a. Approved Dosage Form		
	b. Approved composition		
	c. Approved indication		
	d. Copy of earlier approval obtained from CDSCO (if any)		
5.	**Application in Form 44 duly signed and stamped by authorized personal**		
7.	**Treasury Challan of INR 15,000 if all active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year duly signed and stamped by Bank of Baroda**		
8.	**Rationale for new proposed claim(s) along with therapeutic justification with supporting literature.**		
9.	**Copy of valid manufacturing license in Form 25/28 along with copy of form 29**		
10.	**Source of bulk drugs along with current regulatory status of the source with copy of Form 46A in case of new drug.**		
11.	**Information on active ingredients:**		
	a) Brief Chemical & pharmaceutical data		
12.	**Data on Formulation:**		
	a) Master manufacturing formula		
	b) Details of the formulation (including inactive ingredients)		
	c) Finished product specification		
	d) In process quality control check		
	e) Excipient compatibility study		
	f) Process validation		
	g) Validation of analytical method		
	h) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.		
	i) Comparative evaluation with international brand(s) or approved Indian brands, if applicable.		
	j) Dissolution data in case of oral dosage form as appropriate		
	k) Stability study evaluation as per requirements of schedule Y		
13.	**Clinical trials data showing safety and efficacy of the FDC with the proposed new claims including published data.**		
14.	**Regulatory status of the drug with the proposed new claims in other countries, as appropriate:**		
	a) Names of the countries where the drug is marketed/approved alongwith package insert circulated in those countries.		
	b) Names of the countries where the drug is withdrawn, if any, with reasons		
15.	**BE study protocol and /or Clinical study protocol as per Appendix X of Schedule Y, as appropriate**		
	Report of BE study and /or Clinical trial conducted in the country as appropriate(In case the application is for marketing authorisation)		
16.	**Toxicity data as per Schedule Y, as appropriate. In case of injectable formulation, sub-acute toxicity data generated with the applicants' product has to be provided).**		
17.	**Copy of proposed Package Insert which should include generic name of all active ingredients; composition; dosage form/s, indications; dose and method**		

	of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.		
18.	**Draft specimen of the label and carton**		

Category IV : FDC - Only for convenience

#	Documents required to be submitted	Status	
		Yes	No
1.	**Application for: (permission for manufacture /import/clinical trial)**		
2.	**Name of the applicant**		
3.	**Name of the Fixed Dose Combination(FDC)**		
	a. Composition of the FDC		
	b. Dosage Form		
	c. Proposed indication for the FDC		
4.	**Application in Form 44 duly signed and stamped by authorized personal**		
5.	**Treasury Challan of INR 15,000 if all active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year duly signed and stamped by Bank of Baroda**		
6.	**Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.**		
6.	**Copy of valid manufacturing license in Form 25/28 along with copy of form 29**		
7.	**Approval status of individual drugs in the country**		
8.	**Source of bulk drugs along with current regulatory status of the source with copy of Form 46A in case of new drug.**		
9.	**Information on active ingredients**		
	a) Brief Chemical & pharmaceutical data		
10.	**Data on Formulation**		
	a) Master manufacturing formula		
	b) Details of the formulation (including inactive ingredients)		
	c) Finished product specification		
	d) In process quality control check		
	e) Excipient compatibility study		
	f) Process validation		
	g) Validation of analytical method		
	h) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.		
	i) Comparative evaluation with international brand(s) or approved Indian brands, if applicable.		
	l) Dissolution data in case of oral dosage form as appropriate		
	j) Stability study evaluation as per requirements of schedule Y		
11.	**Toxicity data as per Schedule Y, as appropriate. In case of injectable formulation, sub-acute toxicity data generated with the applicants' product has to be provided).**		
12.	**Summary of available pharmacological, toxicological and clinical data on the individual ingredients**		
13.	**Data showing safety, efficacy and convenience in use of the FDC has to be provided. If enough supportive literatures are not available, then 'adequate evidence' on its convenience to users has to be demonstrated.**		
14.	**Summary of data showing NO significant PK/PD interaction among the ingredients. This should be prepared and signed by a competent person on behalf of applicant.**		
15.	**Regulatory status in other countries, as appropriate.**		
	a) Names of countries where the drug is marketed/approved		
	b) Names of countries where the drug is approved as IND, withdrawn,		
	c) Names of countries where the drug is withdrawn, if any, with reasons		
16.	**Copy of proposed Package Insert which should include generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.**		
17.	**Draft specimen of the label and carton**		

Category V: FDC – Approvals of a FDC already approved in the country

#	Documents required to be submitted	Status	
		Yes	No
1.	**Application for: (permission for manufacture /import/clinical trial)**		
2.	**Name of the applicant**		
3.	**Name of the Fixed Dose Combination(FDC)**		
	a. Composition of the FDC		
	b. Dosage Form		
	c. Proposed indication for the FDC		
4.	**Details of the approval of the FDC in the country**		
	a. Approved Dosage Form		
	b. Approved composition		
	c. Approved indication		
5.	**Application in Form 44 duly signed and stamped by authorized personal**		
6.	**Treasury Challan of INR 15,000 if all active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year duly signed and stamped by Bank of Baroda**		
7.	**Copy of valid manufacturing license in Form 25/28 along with copy of form 29**		
8.	**Source of bulk drugs along with current regulatory status of the source with copy of Form 46A in case of new drug.**		
9.	**Information on active ingredients:**		
	a) Brief Chemical & pharmaceutical data		
10.	**Data on Formulation**		
	a) Master manufacturing formula		
	b) Details of the formulation (including inactive ingredients)		
	c) Finished product specification		
	d) In process quality control check		
	e) Excipient compatibility study		
	f) Process validation		
	g) Validation of analytical method		
	h) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.		
	i) Comparative evaluation with international brand(s) or approved Indian brands, if applicable.		
	j) Comparative Dissolution data in case oral dosage form as appropriate		
	k) Stability study evaluation as per requirements of schedule Y		
11.	**In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product.**		
12.	**BA/BE study protocol (in case of oral dosage form as appropriate as per Appendix X of Schedule Y**		
	a) Patient Information Sheet and Informed Consent Form (ICF) as per Appendix V of Schedule Y.		
	b) Copy of 'Ethics Committee' approval letters (if available)		
	c) Case Record Form (CRF)		
	d) Undertaking by Investigator(s) as per Appendix VII of Schedule Y and CV		
13.	**Copy of proposed Package Insert which should include generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contraindications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.**		
14.	**Draft specimen of the label and carton**		

5. ANNEXURES:

5.1 Annexure- A: FORMAT FOR SUBMITTING THE RESULTS OF STABILITY STUDY OF NEW DRUGS

Stability testing: Summary sheet

Results of stability testing should be presented as shown below.

A separate form should be completed for each pharmaceutical preparation tested:

Accelerated/real-time studies
Name of drug product
Manufacturer
Address
Active ingredient (INN)
Dosage form
Packaging

Batch Number Date of manufacturing Expiry date
1.
2.
3.
Shelf-life

Batch Size Type of batch (experimental, pilot plant, production)
1.
2.
3.

Samples tested (per batch)

Storage/test conditions: Temperature C Humidity %

Results:
1. Chemical findings
2. Microbiological and biological findings
3. Physical findings
4. Conclusions

Signature of competent / authorized personnel
Name:……
Designation:……
Date:……

Note: Detailed stability study data / results in tabular form should also be enclosed along with the above summary sheet.

5.2 Annexure B: CHECKLIST FOR CLINICAL TRIAL PROTOCOL

#	Particulars
1	**Title Page**
	(a) Full title of the clinical study,
	(b) Protocol / Study number, and protocol version number with date
	(c) The IND name/number of the investigational drug
	(d) Complete name and address of the Sponsor and contract research organization if any
	(e) List of the Investigators who are conducting the study, their respective institutional affiliations and site locations
	(f) Name(s) of clinical laboratories and other departments and/or facilities participating in the study.
2	**Table of Contents (A complete Table of Contents including a list of all Appendices)**
	Background and Introduction
	Study Rationale
3	**Study Objective(s) (primary as well as secondary) and their logical relation to the study**
4	**Study Design:(** Overview of the Study Design, f low chart of the study, brief description of the methods and procedures to be used during the study, Discussion of Study Design etc.)
5	**Study Population:**
6	**Subject Eligibility:**
	(a) Inclusion Criteria
	(b) Exclusion Criteria
7	**Study Assessments –** Plan, procedures and methods to be described in detail
8	**Study Conduct stating the types of study activities that would be included in the study viz.** (a)Medical history, type of physical examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function tests, symptom measurement, dispensation and retrieval of medication, Subject cohort assignment, adverse event review, etc. (b) Each visit should be described separately as Visit 1, Visit 2, etc., (c) Discontinued Subjects, describes how protocol violations will be treated, including conditions where the study will be terminated for non-compliance with the protocol, (d) Describes the circumstances for Subject withdrawal, dropouts, or other reasons for discontinuation of Subjects, (e) Describe the method of handling of protocol waivers, if any
9	**Study Treatment**
	(a) Dosing schedule
	(b) Study drug supplies and administration
	(c) Dose modification for study drug toxicity
	(d) Possible drug interactions.
	(e) Concomitant therapy
	(f) Blinding procedures:
	(g) Unblinding procedures
10	**Adverse Events (As per Appendix XI of schedule Y)**
11	**Ethical Considerations**
	(a) Risk/benefit assessment
	(b) Ethics Committee review and communications
	(c) Informed consent process.
	(d) Statement of Subject confidentiality including ownership of data and coding procedures.
12	**Study Monitoring and Supervision:**
13	**Investigational Product Management**
14	**Data Analysis**
	(a) Details of the statistical approach to be followed including sample size, how the

	sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints
	(b) Statistical analysis
	(c) Statistical considerations for Pharmacokinetic (PK) analysis, if applicable
15	**Undertaking by the Investigator as per Appendix VII of schedule Y**
17	**Appendices**
	(a) study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); CRF and other data collection forms

5.3 ANNEXURE C: CHEMICAL AND PHARMACEUTICAL INFORMATION FOR CLINICAL TRIAL PERMISSION

Information on active ingredients:

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight
ii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification
iii. Stability Studies: Data supporting stability in the intended container closure system for the duration of the clinical trial.

Data on Formulation:

i. Dosage form,
ii. Composition,
iii. Master manufacturing formula,
iv. Details of the formulation (including inactive ingredients),
v. In process quality control check,
vi. Finished product specification & Method of Analysis,
vii. Excipient compatibility study,
viii. Validation of the analytical method.
ix. Stability Studies: Data supporting stability in the intended containerclosure system for the duration of the clinical trial.

Note: While adequate chemical and pharmaceutical information should be provided to ensure the proper identity, purity, quality & strength of the investigational product, the amount of information needed may vary with the Phase of clinical trials, proposed duration of trials, dosage forms and the amount of information otherwise available.