



SUPAC-IR-PRINTING INK CHANGES

Recommendations for Implementation

SUPAC Requirements for Changes in Printing Inks

SUPAC-IR defines a change in a printing ink or its components as a "Level 1" change which means that prior approval from FDA is not required. Basically, FDA can be informed in the annual report and at least one batch of the product must be put into a long-term stability program. The FDA clearly stated in the guidance that the ink can be changed as well as the components of the ink provided the components are approved components.

FDA's Response to Industry Questions

In the FDA's February 18, 1997 letter to the pharmaceutical industry, they formally answered many of the SUPAC-IR questions which have come up since the guidance was implemented. This letter contained two questions related to changes in printing inks.

One question asked if a printing ink can be eliminated under SUPAC-IR as a Level 1 change. FDA's answer was "yes". The other question asked for clarification about changes in printing inks and their components. The question and answer was stated as follows:

Q: Can inks be changed under SUPAC-IR? If so, how?

A: If the new ink has been used in other approved products the change is allowed under SUPAC-IR as a level one change. Alternatively, if all of the components of the ink have been used in approved drug products, the switch also can be made under SUPAC-IR. A justification should be given; reference should be made to the approved product(s) where the ink and/or the components are already used.

Their answer indicates what is required but the wording may have added a bit of confusion as to what information needs to be submitted. Some companies have thought that you may need to reference a specific NDA or ANDA number as justification for changing to a new ink. We do not believe that this is required. Due to confidentiality concerns, this would not normally be possible unless you have another NDA or ANDA yourself where you use the ink. Colorcon cannot provide information to one customer concerning the use of a product by another customer.

Both in the wording of the guidance and the Q & A letter, the FDA states that the main requirement is to show that either the ink or the ingredients of the inks should have been previously approved. We believe that there are a number of ways in which this requirement can be adequately met.

A pharmaceutical company may want to change to a new ink for a number of different reasons (ie; better performance during the printing process, improved ink stability, improved global compliance of ink components, change in the color of the print, etc.). This may require new inks to be formulated, using previously approved components, which meet the particular performance criteria or it may simply require the use of a different ink which has been used commercially in the past for other applications. The SUPAC-IR guidance and the February 18th letter provide for making both of these types of changes.

Recommendations

Colorcon believes that the use of any one or more of the following recommendations should be acceptable to justify the ink change to the FDA.

A. REFERENCE TO OTHER SPECIFIC APPLICATIONS WHERE THE INK HAS PREVIOUSLY BEEN USED.

- If a company or affiliate already uses the new ink or an ink with the same components in another NDA or ANDA, the other submission can be referenced to show the use of the specific OPACODE[®] number
- Confidentiality prevents use of this approach in many circumstances where inks or components have been used by other companies.

B. JUSTIFICATION OF PRIOR USE OF INK COMPONENTS

FDA's Inactive Ingredient Guide

- Reference can be made to the FDA's "Inactive Ingredient Guide" which is available under Freedom of Information (FOI) requests. The FDA may soon be putting this guide on their internet site. This guide lists many excipients which have been used in NDA's and gives an "NDA Count" showing how many NDA's listed the component. This can easily demonstrate that the components have been previously used in various dosage forms. You must use caution, however, when using this list because it is not necessarily all-inclusive and does not contain all of the excipients used in certain inks that have been previously used. This is probably due to the start date of the database (old NDA's not included) and the way in which inks are specified in NDA's by various companies (some list actual OPACODE[®] formula numbers and some list components or a partial list of components). Also, we are not sure how this data has been updated and maintained over the years.
- For instance, you will note that there actually are many actual OPACODE[®] formulation numbers listed in the guide, however, by no means, does this represent the total number of OPACODES[®] used in NDA'ed products. Some customers list the components rather than the ink or may not have listed the minor components and solvents used in the ink since they are present at such a low level in the finished dosage form or "flash off" during the printing process. Additionally, sometimes companies utilize different nomenclature when referring to the components and this may get incorporated into the guide.
- This guide can, however, provide good back-up information regarding prior use of listed inks and ink components. For components not listed in the guide, there are other mechanisms which can be used.

C. ACCEPTABILITY OF THE COMPONENTS FOR DRUG USE

Compliance of the Components to USP/NF, CFR, or FCC Standards

- Many of the components used in inks have compendial or CFR status for drug and/or food use which indicates their acceptability as a component of drugs or foods. Colorcon can provide this information for the inks of interest. An example for a typical Opacode Ink is listed below:

QUALITATIVE LISTING FOR OPACODE[®] S-1-17764

Pharmaceutical Glaze (modified) *
Synthetic Black Iron Oxide (21 CFR)
FD&C Blue No. 2 Aluminum Lake 30%-36% (21CFR)
Isopropyl Alcohol (USP/NF)
Propylene Glycol (USP/NF)
Ammonium Hydroxide (Reagent)
Simethicone Emulsion (USP/NF)

- Pharmaceutical Glaze (modified) has been a component in many OPACODE[®] formulations which have been previously used in approved drug applications. An example is OPACODE[®] S-1-8100HV which is actually listed in the FDA's Inactive Ingredient Guide. Pharmaceutical Glaze (shellac dissolved in ethanol) is made, then esterified to create the modified glaze. This is defined in Colorcon's Drug Master File.

Colorcon Certification

If necessary, Colorcon can provide, where appropriate, a certification letter which states that all components of the new ink have been used in previously approved drug products based on our understanding of our customer's applications and commercial usage patterns.

Based on Colorcon's interpretation of FDA's SUPAC-IR guidance and the February 18, 1997 Q & A letter, we believe that providing this type of information to FDA should be adequate to justify conversions to a new OPACODE[®] ink from an existing ink.

March 2008

World Headquarters

Colorcon

415 Moyer Blvd., P.O. Box 24, West Point, PA 19486-0024

Tel: 215-699-7733 Fax: 215-661-2605 Website: www.colorcon.com/pharma

e-mail: info@colorcon.com

Locations	Telephone	Facsimile	Locations	Telephone	Facsimile
<i>United States</i>			<i>Asia/Pacific</i>		
Santa Ana, California	714-549-0631	714-549-4921	Singapore	65-6438-0318	65-6438-0178
Indianapolis, Indiana	317-545-6211	317-545-6218	Fuji-gun, Shizuoka, Japan	81-5-4465-2711	81-5-4465-2730
Humacao, Puerto Rico	787-852-3815	787-852-0030	Shanghai, China	86-21-5442-2222	86-21-5442-2229
Stoughton, Wisconsin	608-887-8970	608-887-8984	Goa, India	91-832-288-3434	91-832-288-3440
			Gyeonggi-do, Korea	82-31-296--2173	82-31-296-2178
<i>Canada</i>			<i>Latin America</i>		
St. Laurent, QC, Canada	514-337-8341	514-337-9159	Buenos Aires, Argentina	54-11-4552-1565	54-11-4552-3997
<i>Europe</i>			Cotia, Brasil	55-11-4612-4262	55-11-4612-3307
Dartford, Kent, England	44-1322-293000	44-1322-627200	Bogota, Colombia	571-418-1202	571-418-1257
Massey, France	33-1-6447-9750	33-1-6932-5983	Caracas, Venezuela	58-212-237-9842	58-212-238-2259
Idstein, Germany	49-6126-9961-0	49-6126-9961-11	Santa Fe, México	52-55-3000-5700	52-55-3000-5701 /02
Gallarate, Italy	39-0331-776932	39-0331-776831			
Budapest, Hungary	36-1-200-8000	36-1-200-8010			
Istanbul, Turkey	90-216-465-0360	90-216-465-0361			
Barcelona, Spain	34-9-3589-3756	34-9-3589-3792			

The information contained herein, to the best of our knowledge is true and accurate. Any recommendations or suggestions are made without warranty or guarantee, since the conditions of use are beyond our control. Any information contained herein is intended as a recommendation for use of our products so as not to infringe on any patent.