Attention:
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Rm. 1061
Rockville, MD 20852

September 23th, 2010

RE: Docket No. FDA-2010-D-0283

Draft Guidance for Industry on CMC Postapproval Manufacturing Changes Reportable in Annual Reports

Dear Sir/Madam:

Colorcon Inc. appreciates the opportunity to provide comments on the above referenced Draft Guidance for Industry *on CMC Postapproval Manufacturing Changes Reportable in Annual Reports*.

Colorcon commends the Food and Drug Administration for the development of this important guidance document which utilizes the principles of ICH Q8 and Q9 to provide a scientifically sound, low risk pathway for facilitating various types of postapproval manufacturing changes where there has been significant experience showing that these types of changes stand limited potential for impacting drug performance. This will allow for proactive management of limited resources both within FDA review divisions as well as throughout industry and should help to expedite continuous quality improvement projects which will enhance drug quality.

Company Background

Colorcon, Inc. is a global pharmaceutical excipient formulation company with operations in the United States, Canada, Latin America, Japan, India, China and Europe. Our products include immediate release and modified release film coatings, that when applied to solid dosage forms, provide a protective interface between the drug and its environment. We also produce various excipients such as Pregelatinized Corn Starch, Sugar Spheres, Polyvinyl Acetate Phthalate, FD&C/D&C Aluminum Lake pigments and printing inks used on pharmaceuticals.

General Comments

The guidance is very helpful in providing clarity to industry related to how certain types of low-risk changes should be filed with the FDA. Colorcon is very supportive of the flexibility provided by this guidance to expedite these type of changes and manage resources.

However, Colorcon has some significant concerns about a few areas listed in Appendix A under “Components and Composition” (section 1.2 and 1.3) where we think there is a need for further clarification concerning exactly what the data requirements may be that are necessary before a company can implement certain types of changes. We believe that the current draft guidance may be unclear on the scientific justification needed to substantiate whether these types of changes may impact drug performance and it may provide too much flexibility in some areas where there could be a higher risk of product impact, especially during the stability period. Colorcon’s experience has shown that making qualitative and quantitative changes to immediate release film coatings as well as making changes in supplier’s of excipients can sometimes have a very significant effect on drug product

quality and stability in certain applications. The guidance needs to include information concerning this for these sections and clearly indicate that a minimum of 3 months accelerated stability on at least one batch for the drug product made using the proposed change be required BEFORE these types of changes are implemented for commercial production, regardless of whether the filing method is to be an annual report or not.

Colorcon has reviewed the draft guidance internally with our technical experts. Based on this review, Colorcon would like to provide the attached specific comments for evaluation when finalizing the guidance document.

This guidance will certainly assist the industry in allowing for easier implementation of the changes listed in Appendix A when manufacturing existing drugs in the United States. However, due to the global nature of the pharmaceutical industry, it will be important for the FDA to work with regulatory agencies in other major regions to gain agreement on a similar approach to handling these types of changes in all regions. Otherwise, it will be difficult for global companies to fully take advantage of the flexibility this guidance provides. Hopefully, through FDA's involvement in ICH and WHO, harmonization of requirements in other regions to match those outlined in this guidance document can be achieved.

Thank you for the opportunity to comment on the guidance document. We look forward to the publication of the final version in the near future.

Sincerely,

David R. Schoneker
Director of Global Regulatory Affairs

Specific Comments - Colorcon

Guidance Line(s)	Comments & Proposed Changes
51-56 (also applies to 85-87 & 96-104)	**Original Text:** For any change, the applicants must assess the effects of the change as they relate to product safety and efficacy and demonstrate those effects through appropriate studies to determine whether it would be more appropriate to submit a supplement. For additional background information regarding the reporting categories for NDAs and ANDAs, see FDA's Guidance for Industry on *Changes to an Approved NDA or ANDA* (April 2004). **Comments:** Although this statement does require a sponsor to run appropriate studies before implementing the change to demonstrate that the change has not significantly impacted drug performance, it refers to the previous guidance on *Changes to an Approved NDA or ANDA* to specify the types of data that may be required to make these changes. This guidance document refers to the SUPAC documents to provide guidance on the data requirements needed to support a change under Components and Composition (see below). **V. COMPONENTS AND COMPOSITION** Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes and should be filed in a prior approval supplement, unless exempted by regulation or guidance (506A(c)(2)(A)). The deletion or reduction of an ingredient intended to affect only the color of a product may be reported in an annual report. Guidance on changes in components and composition that may be filed in a changes being effected supplement or annual report is not included in this document because of the complexity of these recommendations, but may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents). SUPAC's data requirements for annual reportable changes were designed for the types of changes that were specified as Level 1 changes at that time, not for the type of changes being proposed in this new guidance and may not be appropriate for some of the changes in Components and Composition now being allowed as Annual Reportable. This may create confusion in the industry when making these types of changes and some companies may implement IR coating or supplier changes without performing appropriate accelerated stability work which should be done to verify that there are no stability related effects. Note the differences below in the data requirements listed in SUPAC IR for a Level 3 Prior Approval Supplement (PAS) vs. a Level 1 Annual Report (AR) Component and Composition change. There is a significant difference in the stability requirement. The PAS requires 3 month accelerated stability data BEFORE making the change. The AR only requires one batch on long term stability which may not show differences until after the change has been implemented on commercial batches.

PAS Data Required

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and batch records.

Significant body of information available:

One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

Significant body of information not available:

Up to three batches with three months accelerated stability data reported in

supplement; one batch on long-term stability data reported in annual report.

b. Dissolution Documentation

Case B dissolution profile as described in Section III.B.2.b.

c. *In Vivo* Bioequivalence Documentation

Full bioequivalence study. The bioequivalence study may be waived with an acceptable *in vivo/in vitro* correlation has been verified.

AR Data Required

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and stability testing.

Stability testing: one batch on long-term stability data reported in annual report.

b. Dissolution Documentation

None beyond application/compendial requirements.

c. *In Vivo* Bioequivalence Documentation

None.

	Proposed Changes: It is requested that a statement be included in this section of the guidance which specifically would state that 3 month accelerated stability studies must be performed **before** implementing certain types of changes such as the ones specified in the Appendix under Components and Composition to verify that the change does not alter drug product performance throughout the shelf life of the product. Alternatively, this type of statement could be added to the *Changes in an Approved NDA or ANDA* guidance for these types of Component and Composition changes if they are to be categorized as Annual Reportable changes. Further supporting data concerning this issue is included below.
147-149	**Original Text:** 1.2 Change in qualitative and quantitative coating formulation for immediate-release solid dosage forms if the coating material and quantity have been approved in another product and the change in the formulation does not alter release of the drug. **Comments:** These types of changes in the coating formulations for immediate-release solid dosage forms can have a significant impact on the overall stability of the drug product as well as other quality parameters. This text in the Appendix implies that qualitative and quantitative changes in the coating formulation can be made and simply reported in the annual report as long as the change does not alter the release of the drug. As mentioned in the comments above, the data requirements in SUPAC IR which appear to apply, given the way the guidance references back to SUPAC guidances, would only require that one batch be put on long term stability if making this type of change providing that the time zero data did not show a change in the release of the drug. Colorcon is aware of many actual drug examples where the stability and quality of the drug product can be significantly impacted by the specific coating formulation components. Changes in the qualitative or quantitative formulation as well as the suppliers of the components can have a large effect which could potentially be overlooked by drug manufacturers who choose to do the minimum required to meet what is in this guidance before making these types of changes. The attached report titled "**Technical Considerations for Qualitative Changes to Film Coatings on Marketed Products**" by Thomas P. Farrell provides a detailed description of these issues and includes a listing of numerous real-life examples where the stability and quality of various drug products were impacted by the specific formulation components in the film coating. The examples demonstrate a number of problems with all BCS classes of drugs, however there appear to be more problems with BCS II, III and IV class drugs than for BCS class I drugs. These type of qualitative or quantitative changes to the film coating of a drug product have always been considered to be a SUPAC IR Level 3 change in

	the past which required a prior approval supplement. As mentioned in the above comment concerning the PAS Data required for a SUPAC IR Level 3 change, this type of change has normally required that at least one batch be placed on three months accelerated stability if a significant body of information was available OR up to three batches be placed on three months accelerated stability if a significant body of information was not available. This accelerated stability data had to be submitted with the supplement and therefore had to be available BEFORE the drug manufacturer implemented the change in the production of commercial batches. Colorcon's agrees that this is appropriate but is concerned that the draft guidance may be interpreted by some drug manufacturers in a way that is too flexible, given the technical realities of how important each component might be to drug stability and quality. The current wording of this section of the guidance triggers the following questions as well: 1. Changing from one type of IR coating formulation to another would typically involve manufacturing changes to the batch sheet in addition to the change in the coating formulation itself since different formulations may require somewhat different coating process parameters – can this be done as an AR change or does this require a CBE-30 or PAS? 2. Can the weight gain of the IR coating be changed on the dosage form as long as this does not alter the release of the drug? Some companies could interpret that this is simply a quantitative change in the coating formulation. This also involves a change in manufacturing process beyond what is listed in Appendix A. 3. Can the IR coating change involve adding an additional different IR coating as a top coat to an existing IR coating and still be considered an AR change? This could be interpreted as simply a qualitative and quantitative change in the coating since additional coating weight gain of a different formulation would just be added in a separate coating step. This also involves a change in manufacturing process beyond what is listed in Appendix A. 4. Is further clarification needed regarding how to handle an IR coating change on various BCS Class drugs other than BCS Class I – can they still be done as an AR? Is this appropriate for BCS Class II, III and IV drugs? What type of stability data is required before making the change? 5. Can an IR coating be added to an uncoated tablet as an AR change if it doesn't significantly impact the drug release rate (or stability)? This would represent a qualitative and quantitative change of 0 to 100% of the coating. This also involves a change in manufacturing process beyond what is listed in Appendix A.

	Proposed Changes: Colorcon recommends that, due to the many questions resulting from the current wording of section 1.2 of Appendix A, that FDA should either delete this provision from the Appendix and continue treating these changes as a prior approval supplement OR include clarification in the guidance to require that at least one batch be placed on three months accelerated stability BEFORE implementing the change for commercial production and that this data be included in the Annual Report. If this section is going to stay in the guidance the section should possibly be reworded to the following: "1.2 Change in qualitative and quantitative coating formulation for immediate-release solid dosage forms if the coating material and quantity have been approved in another product and the change in the formulation does not alter **the** release **and stability** of the drug **product**. **A minimum of one batch with three months of accelerated stability data is required to be completed prior to implementing the change.**"
151-153	**Original Text:** 1.3 New Supplier of inactive ingredients that have a minimal effect on product performance in the drug product, providing that acceptance criteria remain unchanged **Comments:** Changes in an excipient (inactive ingredient) supplier can many times be a very significant change even when all established acceptance criteria remain unchanged. Excipients produced by different suppliers typically are made using different manufacturing processes and starting materials. This typically results in excipients that have different compositional profiles which may or may not impact product performance, especially stability. Excipients from different suppliers may contain different additives and residual processing aids as well as different impurities which come from the use of different starting materials and manufacturing processes. Typically, the differences that exist from one supplier to another are not things which can be easily characterized by specifications and standard types of functionality related testing. The acceptance criteria used for incoming quality control of an excipient will normally not identify these types of differences. Finished drug product performance testing performed immediately after production may also not show a difference. However, these differences may show up on stability. As mentioned above and in the attached report titled "**Technical Considerations for Qualitative Changes to Film Coatings on Marketed Products**" by Thomas P. Farrell, it is extremely important that changes not be made in a supplier of an excipient without first investigating the stability of the drug product made using the new supplier's material. There are many examples throughout the industry where drug product stability has been impacted after changing to a new supplier of an excipient.

	Due to economic reasons, not all pharmaceutical companies currently perform these type of studies as long as the new supplier's material meets the standard acceptance criteria. This has resulted in many problems over the years and this practice should be discouraged. The wording of this section of the draft guidance may be interpreted by some companies to support an approach simply focused on meeting acceptance criteria rather than emphasizing that the stability of the drug product should typically be assessed whenever making an excipient supplier change unless there are very good reasons why this may not be necessary. The draft guidance discusses the need to meet all cGMP requirements for finished pharmaceuticals and for active pharmaceutical ingredients in line numbers 106 to 113. However, the guidance does not mention anything about making sure that a new supplier of an excipient meets an appropriate level of excipient GMP compliance (such as meeting the IPEC-PQG Excipient GMP guideline). In the current climate, many pharmaceutical companies are trying to source lower cost excipients from overseas suppliers which has resulted in many of the supply chain security issues we have seen over the last few years (ie; DEG in Glycerin, etc.) More detail is needed in the guidance to set an expectation that any new supplier of inactive ingredients must be fully qualified and meet appropriate excipient GMPs . The guidance should not just focus on the drug product and drug substance GMP issues. **Proposed Changes:** This section of the Appendix should provide more information concerning the need for performing appropriate accelerated stability studies on the drug product BEFORE changing the supplier of an excipient and should specify that any new supplier of an excipient must meet appropriate excipient GMPs such as the IPEC-PQG Excipient GMP guideline. The wording of the section should be changed to the following: 1.3 New Supplier of inactive ingredients that have a minimal effect on product performance in the drug product, providing that **the** acceptance criteria remain unchanged **and that the change in the supplier does not alter the release and stability of the drug product. A minimum of one batch with three months of accelerated stability data is required to be completed prior to implementing the change unless a scientifically sound justification can be made to demonstrate that the change is low risk. The new supplier must also be qualified to provide assurance that they meet appropriate excipient GMPs**".

Technical Considerations for Qualitative Changes to Film Coatings on Marketed Products

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September 20, 2010

Oral solid dosage forms have been coated for decades for a variety of reasons including brand identification, anti-counterfeiting, reduction of medication errors, enhanced chemical stability of the active pharmaceutical ingredient (API) and physical stability of the dosage form. While film coatings have been used safely and efficaciously on thousands of drug products globally, their qualification on drug products is not a trivial step. Film coatings comprise multiple excipients, which may potentially interact or react with the API or other excipients formulated with the API in the dosage form. Excipients used in film coatings may also contain impurities that are also potentially reactive. Therefore, qualification of a film coating for use on a drug product must include careful investigation of the stability of the coated dosage form. Such stability studies should specifically examine any effects on the dissolution profile of the drug product and also drug assay over time. Similar considerations must also be taken into account when the film coating of a marketed product is changed, especially if the new film coating is qualitatively different than the currently used film coating, since the introduction of a new component or even a different source of a current component may also introduce new impurities to the dosage form that could potentially react with the API or excipients used in the core formulation.

Film coating compositions may vary widely. In most cases, they contain at least a polymer, a pigment and a plasticizer and often include additional additives such as detackifiers, surfactants and viscosity modifiers. Some commonly used film coating components are summarized in Table 1.

Table 1. Commonly used film coating components.

Film Coating Component	Examples
Polymer/film former	hypromellose (HPMC), hydroxypropyl cellulose (HPC), polyvinyl alcohol (PVA), sodium carboxymethyl cellulose (NaCMC), methacrylic acid copolymers, cellulose acetate and ethyl cellulose
Pigment	titanium dioxide, iron oxides, aluminum lake pigments
Plasticizer	polyethylene glycol (PEG), triethyl citrate, triacetin, medium chain triglycerides, dibutyl sebacate, oleic acid, stearic acid, glycerin
Other additives	maltodextrin, dextrose, polydextrose, lactose, microcrystalline cellulose (MCC), lecithin, silicon dioxide, starches

Film coating components possess functional groups that may be reactive under certain conditions much like excipients used in core formulations.[1] For example, the cellulosic polymers, PVA and PEG possess hydroxyl groups capable of reacting with carboxylic acids or ester groups on drug molecules. On the other hand, methacrylic acid copolymers, stearic acid and oleic acid contain carboxylic acids which may react with hydroxyl or amino groups on drug molecules. Saccharides and polysaccharides such as dextrose, lactose, maltodextrin and MCC are reducing sugars capable of participating in oxidation chemistry including the Maillard reaction.[2] Iron oxides may also catalyze oxidation in some instances.[3] Silicon dioxide can act as Lewis acid and promote hydrolysis, transesterification and oxidation.[1]

Film coating components may also contain impurities that are chemically reactive. For example, peroxides are often found in polyethylene glycols, polyoxyethylene glycol ethers, povidone, hydroxylpropyl cellulose and polysorbate 80.[4,5] Formic acid and formaldehyde are found in numerous excipients including hypromellose, povidone, polyethylene glycol and microcrystalline cellulose.[6] It has also been established that impurities in film coatings can react with APIs. A degradation product was formed during the long-term stability studies of the low dose formulation of Avapro™ film-coated tablet.[7] The degradant was identified as the hydroxymethyl derivative (formaldehyde adduct) of the drug substance, irbesartan, and the authors concluded that the formaldehyde was an impurity found in PEG. The degradant was eliminated by removing PEG from the coating formulation.

Another research group determined that both formic acid and formaldehyde jointly participated in degradation chemistry.[8] Significant degradation of the amine-based smoking cessation drug varenicline tartrate in an early development phase osmotic, controlled-release (CR) formulation yielded predominantly two products: N-methylvarenicline (NMV) and N-formylvarenicline (NFV). NMV was produced by reaction of the amine moiety with both formaldehyde and formic acid in an Eschweiler-Clarke reaction, while NFV was formed by reaction of formic acid alone with varenicline. It was postulated that both formaldehyde and formic acid were formed from oxidative degradation of polyethylene glycol (PEG), which was used in the osmotic coating. The authors also concluded that the degradation chemistry was heavily dependent on the physical state of the PEG. When the concentration of PEG in the coating was sufficiently low, the PEG remained phase compatible with the other component of the coating (cellulose acetate) such that its degradation (and the resulting drug reactivity) was effectively eliminated. To further ensure that PEG oxidation would not occur to any significant extent, oxygen scavengers were added to the product packaging.

Colorcon has also observed chemical and physical instability in coated drug products. Some of these observations are summarized in Table 2. In some cases, specific drug product identification has been omitted, since the information was disclosed under confidentiality agreements with customers. It is clear from these observations that film coatings can adversely impact drug product stability. While PEG has been implicated in adverse findings on multiple occasions, it is by no means the only source of problems. Taken together, the literature on drug-excipient interactions and Colorcon's observations make a compelling case that drug product stability be conducted before any film coating is used on a drug product. This also applies to a film coating change that involves an apparent qualitative match. There are multiple sources of many excipients used in film coating compositions including cellulosic polymers, plasticizers and pigments – each source potentially containing a different array of impurities or additives. For example, some grades of polyethylene glycol contain butylated hydroxytoluene (BHT) as an antioxidant, which may reduce or eliminate degradant formation, while other grades contain no anti-oxidants whatsoever. It has also been reported that one source of HPMC contains 58 ppm of formic acid while another source contains 86 ppm.[6] Therefore, drugs that are prone to oxidation or reaction with formic acid may undergo degradation reactions to a greater or lesser extent depending upon the source of the raw materials selected.

Table 2. Issues observed with select coated drug products.

Active	BCS Class	Observations	Potential Explanation
aspirin	IV	In 5 cases, release rate retardation was observed during stability studies.	Aspirin may react with PEG to form insoluble PEG acetates. Aspirin or its degradant (salicylic acid) may also complex with aluminum lake pigments.
atazanavir sulfate	II	Coated tablets became insoluble after 6 weeks open dish stability (40°C/75% RH). Attempted dissolution in 0.1 N HCl resulted in pellicle formation.	API is a diester which is capable of reaction with hydroxyl groups on PEG or polymers. The reaction may result in the formation of insoluble products including crosslinked polymeric networks.
clopidogrel besylate and bisulfate	II	In 3 cases, release rate retardation was observed on stability at accelerated conditions.	Clopidogrel may undergo a transesterification via reaction with PEG. The PEG ester may form an insoluble film.
famotidine	IV	Surface discoloration (browning) after open dish exposure at 40/75.	The literature indicates that this drug is very susceptible to hydrolytic degradation, and the degradants may cause the brown color. Use of coatings with lower moisture permeability improves stability.
ibuprofen	II	In 4 cases, the film coatings on ibuprofen products physically changed -blistering, wrinkling and frosting were observed – especially at accelerated stability storage conditions.	Wrinkling and blistering may be due to ibuprofen volatility. A film coating change eliminated the problem. The frosting may have been due to high PEG levels in the coating. When the PEG concentration was reduced, frosting was eliminated.
pseudo-ephedrine	III	In 3 cases, discoloration of coated tablets occurred during accelerated stability studies.	The results are consistent with the PEG mobilization (leading to pigment migration) or PEG autoxidation (leading to pigment fading) at elevated temperature. Problem solved by switching to PEG-free system.
ranitidine	III	Film coatings with PEG show surface yellowing after 3 months at 40/75. A film coating without PEG showed very little yellowing. The uncoated core is much worse - turns brown.	PEG wicks moisture in tablet facilitating the degradation of the active by reaction with water.
sennosides	N/A	In 2 separate cases, dramatic color changes were observed during accelerated stability testing.	Sennosides (anthraquinones) are colored species which may "bleed" through a film of relatively low opacity or which may contain components that solubize antraquinones.
sildenafil citrate	I	Mottling observed after storage at accelerated conditions. Storage in PVC blisters.	Could be due to "de-laking" caused by an acidic species (stearic acid or liberated citric acid).
simvastatin - stabilized with citric and ascorbic acids	II	Pellicle formation on stability.	Crosslinking of PVA by citric acid. Also observed in a hydroxyethyl cellulose (HEC) based film coating at the 2% level in Colorcon development work.
unidentified drug	N/A	After one-month open dish storage at 40/75, dissolution delays were observed vs. T0. Film coating appeared to peel off rather than dissolve. Drug assay was OK suggesting that this was a surface phenomenon.	Active reportedly contains at least one carboxylic acid group and one amino group. PEG could react or interact with carboxylic acid residue to form a relatively insoluble complex at the tablet surface.
unidentified drug	III	In 3 cases, products coated with HPMC-based film coatings had a relatively high level of degradant formation. Use of a PVA-based film coatings resulted in lower levels of degradants.	API s react with formyl equivalents (e.g. formic acid and formaldehyde) to form degradants. HPMC has a higher level of formyl impurities than PVA.
unidentified drug	III	Drug product coated with a NaCMC-maltodextrin based film coating cracks during prolonged storage.	Hygroscopic core absorbs moisture from coating layer thereby reducing Tg of polymeric components in the coating. The coating becomes brittle and cracks under the stress of dimensional swelling.
unidentified drug	II	An amine-containing drug product coated with a dextrose-containing film coating discolored after storage under accelerated stability conditions.	Dextrose is a reducing sugar capable of participating in the Maillard reaction with amines. Degradants formed from this reaction cause discoloration. The problem was solved by removing dextrose from the coating formulation.

N/A = not available.

One must also take into account that film coatings possess functional characteristics – i.e. properties such as water vapor barrier, oxygen barrier and disintegration rate may vary depending on the components in the film coatings. Films comprising PVA are known to be relatively good water vapor and oxygen barriers; whereas, films comprising HPMC are known to be relatively poor.[9] Therefore, during the course of drug product development, a coating may have been selected for its functional characteristics to guard against the deleterious effects of oxygen or water. Any change in the components of the coating after commercialization may also affect the extent to which any degradants are formed during storage. Since the formation of degradants could have implications for drug product efficacy and safety, stability studies should again be conducted before any changes are made to the drug product coating.

Conclusions

Film coatings have been used safely and effectively for decades to improve both the aesthetic and stability characteristics of drug products; however, film coating components could also be sources of API or drug product instability. Therefore, stability studies should be conducted under ICH guidelines before a new product is launched or a coating is changed on a marketed product whether the coating is an apparent qualitative match or not.

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