Colour Management For Formulators
23rd October 2013

Colours in Pharmaceutical Products

Marcel Cimpan
Senior Manager Customer and Technical Services
Agenda

- Uses for colours in the Pharmaceutical industry
  --- Colorcon Brand Enhancement Services
- Pigments available
  --- Oxides
  --- Lakes
  --- Non synthetics
- Global colours
- Regulatory
  --- Quantity restrictions
- Film coat formulation
- Colour measurement and control
- Coating application

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
Uses for colours

- Colouring of coating systems
- Colouring of core tablets
- Colouring of liquid and semi-solid products
- Food and confectionery
Why differentiate at the dosage level?

Do you recognize this drug?

- No trademark protection
- No brand equity
- Increased risk of mix up on the production line and therefore potential product recall
- Increased risk of counterfeiting
- No distinctive shape and color
- No memorable image

Lack of branding does not help patient compliance

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
Disturbing Facts....

Medication errors cause 7,000 deaths each year” (FDA)

At least 1.5 million Americans are sickened, injured or killed each year by errors in prescribing, dispensing and taking medications (Washington Post)

Treating the related injuries cost an estimated $3.5 billion a year (Washington Post)
Guidance for Industry

Safety Considerations for Product Design to Minimize Medication Errors

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER), Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis, Carol Holquist at 301-796-0171.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2012
Drug Safety
FDA Draft Guidance

Different strengths – same look - potential overdose
There is a need to differentiate

- Patients are consumers
- Studies have proven that consumers form an emotional link with colour*
- Examples of drugs where GERX manufacturer used unique shape/color and got higher counting unit sales than others are in the following slides

* (ref: Some aesthetic considerations for over-the-counter (OTC) pharmaceutical products; International Journal of Biotechnology, Volume 11, 2010)
### “Branded” Generics with higher market shares than plain, white tablets

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Generic name/API</th>
<th>Tablet image</th>
<th>Manufacturer</th>
<th>Coated or uncoated</th>
<th>2012 CU (000’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic</td>
<td>Quetiapine 25mg</td>
<td><img src="image" alt="Quetiapine 25mg" /></td>
<td>Teva</td>
<td>Coated</td>
<td>145,656</td>
</tr>
<tr>
<td></td>
<td>Quetiapine 25mg</td>
<td><img src="image" alt="Quetiapine 25mg" /></td>
<td>Lupin</td>
<td>Coated</td>
<td>119,586</td>
</tr>
<tr>
<td></td>
<td>Quetiapine 25mg</td>
<td><img src="image" alt="Quetiapine 25mg" /></td>
<td>Roxane</td>
<td>Uncoated</td>
<td>73,676</td>
</tr>
</tbody>
</table>

* tablets are not to scale so size comparisons should not be made

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
"Branded" Generics with higher market shares than plain, white tablets

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Generic name/API</th>
<th>Tablet image</th>
<th>Manufacturer</th>
<th>Coated or uncoated</th>
<th>2010 CU (000’s)</th>
<th>2011 CU (000’s)</th>
<th>2012 CU (000’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-convulsant</td>
<td>Levetiracetam 750 mg</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Lupin</td>
<td>Coated</td>
<td>133,394</td>
<td>224,581</td>
<td>219,142</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam 750 mg</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Mylan</td>
<td>Coated, white</td>
<td>195,279</td>
<td>185,740</td>
<td>150,016</td>
</tr>
</tbody>
</table>

Interestingly Mylan was the first to file, but after the first year volume dropped to the pigmented Lupin dose

* tablets are not to scale so size comparisons should not be made

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
Brand Enhancement Services

Colorcon can help you differentiate:

<table>
<thead>
<tr>
<th>Therapeutic Category</th>
<th>Color Preference</th>
<th>Tablet Design Session</th>
<th>Mechanical Drawings</th>
<th>Tablet Prototypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td></td>
<td>Stage 2</td>
<td>Stage 3</td>
<td>Stage 4</td>
</tr>
</tbody>
</table>

Improving speed to market from months to weeks

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
Pigments used in film coatings

- Metal Oxides
  - Titanium Dioxide
  - Iron Oxide Red
  - Iron Oxide Yellow
  - Iron Oxide Black
- Aluminium Lakes
- Non synthetics
Types of Pigment

Oxides - Titanium and Iron

- good chemical and light stability
- small particle size
- little batch-to-batch colour variation
- low cost
- excellent opacity
- wide regulatory acceptability
- restricted colour range
- rather dull colours

Advantages

Disadvantages
Types of Pigment

Aluminium lakes

- wide range of bright colours
- brightness retained when mixed together
- low opacity compared with other pigments
- colour depends on particle properties - batch variation
- tendency to form gel structure in liquid products
- some colours show poor stability

Advantages

Disadvantages
Types of Pigment

- Non-synthetic colours
  - natural or nature-identical claim
  - consumer acceptability?
  - low colour strength
  - high cost
  - residual taste and odour
  - restricted colour range
  - batch-to-batch color variation
  - very poor chemical and light stability

Advantages

Disadvantages
Examples of non synthetic colours

Examples of colours exempted from certification

- Annatto extract
- Dehydrated beets (beet powder)
- Caramel
- [beta]-Apo-8'-carotenal
- [beta]-Carotene
- Cochineal extract; carmine
- Toasted partially defatted cooked cottonseed flour
- Grape color extract

Examples of colours approved for ingested drugs

- Paprika
- Paprika oleoresin
- Mica-based pearlescent pigments
- Riboflavin
- Saffron
- Tomato lycopene extract; tomato lycopene concentrate
- Turmeric
- Turmeric oleoresin
Global Acceptable Pharma Colors
US, EU, Japan

- Only a limited number of colors are acceptable for global (US/EU/JP) use:
  - FD&C Blue # 2 (Indigo Carmine)
  - FD&C Blue # 1 (Brilliant Blue)
  - FD&C Yellow # 6 (Sunset Yellow)
  - Titanium Dioxide
  - Iron Oxide Red
  - Iron Oxide Yellow
  - Iron Oxide Black
Regulatory restrictions - summary

- Country specific
- Main regulatory bodies: FDA (USP, GRAS), EU, JP
- All these will list colorants exempted from certification, approved colorants, approved colourants with quantitative limits, banned colouring agents
- In some cases there will be specific regulations or labelling requirements when used in products for children (age specific, eg EU under 36 month)
- Specific labelling requirements when used in food additives or nutritional products
  - Indigo carmine - JP – max 0.1% by w. of color
  - BOx - JP – max 1.539 mg/day oral
    USP – 5mg/day elemental iron
  - ROx - JP – max 95.4 mg/day oral
    USP – 5mg/day elemental iron
  - YOx - JP – max 5.67 mg/day oral
    USP – 5mg/day elemental iron
  - Sunset yellow - JP – max 0.1% by w. of color

Example:
Japanese regulatory only allows 5.67mg of yellow iron oxide per day.
For a 1000mg tablet a 3% weight gain of film is 30mg:
  - one tablet a day could therefore contain a maximum of 5.67mg YOx
  - four tablets a day is 1.4175mg YOx
A pre-dispersed powder containing ....

.... in optimal ratios
Colour measurement

- CIELab
- Measurement
- Factors influencing colour
Representation of CIEL*A*B* Colour Space

Colour space diagram courtesy of Datacolor

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
CIEL\*A\*B\* - Colour Space Diagram

Standard expressed in terms of L, a, b values, e.g. L = 55
a = +14
b = +10

Acceptable colour limit defined as a sphere around the standard point

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
Colour Control - Reflectance Spectrophotometry

Standard white drawdown card  
Liquid dispersion of sample  
Drawdown using standard thickness bar

Measure quantity of light reflected across the visible spectrum

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
Colour Control - Reflectance Spectrophotometry

\[ \lambda, \text{ nm} \]

% light reflected

Blue Red

Standard Production Batch

The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated inappropriately.
Factors Influencing Colour

- Type of light used (metamerism)

- Colour is subjective:

  \textit{COLOUR IS A SENSATION WHICH ONLY EXISTS INSIDE THE BRAIN}

- Tablet shape

- Tablet coating roughness
Coating application
Coating application – spray gun

Manesty ABC
The information contained in this presentation is proprietary to Colorcon and may not be used or disseminated in an appropriate manner.
Coating application – coating system comparison
Evaluation of Tablets

- Color development and uniformity
  - Sampled at 5 minute intervals and compared to the final tablet reference color
  - Target ≤1 DE from reference

![Images of tablets with DE values 10.05 and 0.59]
Coating application – coating system comparison
Final Tablet Appearance

Opadry II PVA

HPMC
Colours are extremely important in pharmaceutical use.

There are many controls and limitations on their use.

Control of batch to batch colour variation is vital.