**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Division of Pediatric Drug Development
Office of Counter-Terrorism and Pediatrics
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# M E M O R A N D U M

Date: August 16, 2004

From: Solomon Iyasu, M.D., M.P.H. Medical Team Leader
Division of Pediatric Drug Development, Office of Counter Terrorism and Pediatric Drug Development, HFD-960

Through: Shirley Murphy, M.D.
Director, Division of Pediatric Drug Development, Office of Counter Terrorism and Pediatric Drug Development,, HFD-960

To: Dianne Murphy, M.D.
Director, Office of Counter Terrorism and Pediatric Drug Development, HFD-950

Re: Report of the Audit of the Columbia Suicidality Classification Methodology

## Executive Summary

The FDA contracted with Columbia University to perform an independent and blinded review of event narratives for (1) adverse events categorized by various drug company sponsors as "possibly suicide-related," (2) accidental injuries, (3) accidental overdoses, and (4) all other events categorized by sponsors as serious adverse events from 25 pediatric antidepressant trials. Columbia completed its independent review and classification of 423 events and submitted the results to FDA. The FDA conducted an independent internal review of a 15% sample of event narratives (n-64) to assess the robustness and reproducibility of the Columbia suicidality classification scale, methods, and process. Events that were defined as difficult to classify and newly classified events were over-sampled for review. Four FDA clinical reviewers independently reviewed and rated the event narratives in the sample. Similar to the Columbia process, discordant ratings were identified and consensus final ratings arrived at by reviewers. The final FDA audit team ratings were compared to the final Columbia ratings, and the overall concordance rate was 89%. We concluded that the Columbia suicidality classification methodology and process is robust and reproducible.

## Background

In recent years, concern has been raised over a possible link of antidepressant medication and suicidal behavior (suicidal attempts or ideation) in pediatric patients. This concern has focused on the current generation of antidepressant drugs, including, among others, the Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors (SSRIs/SNRIs). These drugs are commonly prescribed off-label to pediatric patients for the treatment of major depression, anxiety, and other psychiatric disorders. The possible association of SSRIs/SNRIs with increased incidents of suicidal behavior was the subject of the Feb 2, 2004 joint meeting of PDAC and Pediatric Sub-committee of the Anti-infective Advisory Committee. Data suggestive of the possible increased risk of suicidal behavior when taking these medications have primarily emerged from 25 completed pediatric antidepressant clinical trials. FDA was concerned that adverse events related to suicidal behavior during the pediatric trials may not have been fully captured, correctly classified, and reported by sponsors in a standardized manner.

The FDA sent a series of letters (7-22-03, 11-24-03, and 12-09-03) to various sponsors and requested more complete adverse event data and event narratives from pediatric trials including all adverse events suggestive of intentional self-injury, suicidal ideation, or suicide attempts; reports of accidental injuries and accidental overdoses; and all reports of serious adverse events. Sponsors were asked to identify all events suggestive of suicidal ideation and/or self-injurious behavior using an FDA specified search strategy and algorithm. The request for data involved 25 placebo-controlled pediatric trials for MDD, OCD, GAD, Social Anxiety/Social Phobia, and ADHD from nine antidepressant drug development programs of eight sponsors. FDA contracted with the Columbia Expert Suicidality Classification Board to independently review and reclassify event narratives received from sponsors in response to the FDA data request.

### The Columbia Expert Suicidality Classification Board

The Columbia Expert Suicidality Classification Board is a joint collaboration of the Departments of Child Psychiatry and Neuroscience at Columbia University. It is composed of experts in pediatric suicidality classification and research. It has over 20 years of experience in suicide research and over 600 publications on the topic of suicidality.

### Charge to Columbia

To conduct an independent, blinded review and classification of all event narratives received from sponsors by a panel of internationally recognized experts in pediatric suicidality.

### Materials reviewed by Columbia

Columbia reviewed narratives for adverse events that occurred during the randomized double-blind phase and/or within 30 days of the last dose of randomized treatment from 25 placebo-controlled antidepressant trials. These narratives included all events suggestive of intentional self-injury, suicidal ideation or suicide attempts, accidental injuries, accidental

overdoses, and all reports of serious adverse events. The narratives are composed of sponsor summaries of information pertinent to these events obtained from case report forms (CRFs) and at times from other sources, e.g., medical charts. The source documentation or CRFs were not made available to Columbia for review. The narratives were blinded with respect to sponsor, trial, and treatment assignment before they were sent to Columbia. Additional blinding to diagnosis was done by Columbia staff before the review and classification of events by a panel of experts external to Columbia University. A total of 423 events (including multiple events for some study participants) were independently rated and classified by this panel.

Columbia suicidality classification scale, methods, and process:

Columbia developed a suicidality classification scale of 12 categories listed below. Nine expert reviewers were trained about the classification scale, methods, and process by Dr. Kelly Posner, Primary Investigator of the Columbia Suicidality Classification Project. Each record was randomly assigned to three of nine expert reviewers to perform a blinded, independent review and classification of event narratives. Ratings for each narrative by each of the three assigned reviewers were reviewed and discordant ratings identified. A consensus meeting facilitated by an expert in pediatric suicidality, not previously involved in the review process, was held. The goal of the meeting was to reach one consensus rating for each event narrative with discordant rating among the three reviewers. Both the individual and the final consensus ratings for all 423 event narratives reviewed by Columbia were sent to the FDA.

**Columbia suicidality classification scale**

1. **Suicide attempt**
2. **Preparatory Actions towards imminent suicidal behavior**
3. **Self-Injurious Behavior, Intent Unknown**
4. **Self-Injurious Behavior, No suicidal Intent, Primarily to affect circumstance**
5. **Self-Injurious Behavior, No suicidal Intent, Primarily to affect internal State**
6. **Suicidal Ideation**
7. **Other: Accident**
8. **Other: Psychiatric**
9. **Other: Medical**
10. **Not enough information**
11. **Self-Injurious Behavior, No Suicidal Intent, Unspecified Type (unsure if 4 or 5)**
12. **Other, Unspecified (unsure if 7, 8, or 9)**

## The FDA Audit of the Columbia Suicidality Classification Project

The FDA is conducting a reanalysis of the pediatric clinical trail data using the newly reclassified events to assess the relationship between antidepressant use in children and suicidal behavior. To assess the robustness of the Columbia suicidality classification scale,

process, and assignments, the FDA conducted an independent internal audit of the classification methodology.

Objectives of the audit

- Review the Columbia suicidality classification scale, methods, and process.
- Assess the reproducibility and reliability of the Columbia Classification scale, methods, and process.

FDA Audit Team

OCTAP was tasked to plan, coordinate, and conduct a collaborative audit process involving DNDP. Input on the plan was obtained from Office of New Drugs. None of the members of the audit team had been involved in reviewing or assessing the pediatric studies under review.

Planning Group

1. Solomon Iyasu , MD, M.P.H, OCTAP, Audit Team Leader
2. Susan Cummins, M.D., M.P.H. OCTAP
3. Thomas Laughren, MD, DNDP
4. Project Managers: Rosemary Addy and Kristin Phucas
5. Armando Oliva, M.D. , OND

Consensus meeting facilitator: Robert Stasko, M.D., DSI

Clinical Reviewers:

1. Cara Alfaro, M.D., DNDP
2. Robert Levin, M.D., DNDP
3. Hari Sachs, M.D., OCTAP/DPDD
4. ShaAvhree Buckman, M.D. OCTAP/DPDD

## FDA Audit methods and process

Sampling strategy and sample size:

The 423 event narratives that were independently reviewed and rated by Columbia were grouped into four predefined strata. A stratified sampling strategy with over-sample of stratum 1, 2, and 3 was employed to select the sample of records for the independent internal FDA audit. The four strata are defined below

- **Stratum 1: Events reclassified by Columbia to non-suicidal events (N=2)**
- **Stratum 2: Events newly identified and classified as possibly suicide related or other categories (N=29)**
- **Stratum 3: Events that were difficult to classify, defined as events with discordant initial independent ratings by Columbia reviewers (N=56)**

- **Stratum 4: Events that are straight forward cases, defined as events with concordant initial ratings by Columbia reviewers (N=336)**

A sample of 64 events were ( 15% sample) selected for review. All event narratives from stratum 1 were included in the sample. Event narratives from stratum 2, 3, and 4 were selected by a simple random sampling technique using a random number table.

- **Stratum 1: All selected ( sample of 2)**
- **Stratum 2: 1/3rd selected (sample of 10)***
- **Stratum 3: 1/3rd selected (sample of 19)**
- **Stratum 4: 1/10th selected (sample of 33)**

***4 of the 10 sampled records were also difficult to classify events**

FDA audit team training

Four FDA clinical reviewers were selected ( 2 from OCTAP and 2 from DNDP) to independently review and classify the 64 sampled event narratives. The review team consisted of two pediatricians, one psychiatrist and one pharmacist.

The FDA audit team received a two-hour training about the Columbia suicidality classification scale, methods, and process conducted by Dr. Kelly Posner of Columbia University. The training was conducted by teleconference and included a review of the classification scale, construct, and examples of event narratives for each of the 12 categories. To test the level of understanding of the classification methods by participants and the success of the training, a test set of event narratives were independently classified by each participant.

Review assignments

Each event narrative selected for the sample was randomly assigned to three of the four FDS reviewers for blinded, independent review and rating. The reviewers were blinded to sponsor, treatment assignments, diagnosis, and the Columbia classification results. Each reviewer was assigned to perform 48 reviews resulting in a total of 192 independent reviews by the four FDA reviewers.

Review procedures and instructions

A memo outlining the procedures of the audit was prepared and provided to the audit team (attached in appendix 2). Review team members were allowed no discussion with colleagues or among themselves during the independent review and rating period. A modified rating form (appendix 3) was developed to record the independent ratings/classifications and provided to reviewers. Reviewers were allowed to call Dr. Kelly Posner to obtain clarification about the Columbia classification scale or categories. However, they were specifically instructed not to discuss the specifics of any event narrative under review. Reviewers were asked to indicate on the rating form if they consulted with Columbia before completing their review for any the events they reviewed and rated. Reviewers were

instructed to hand-deliver the completed rating forms in sealed envelopes to Solomon Iyasu, MD, MPH.

The rating forms were checked for completeness and ratings were double-key entered into an Excel database. Accuracy of data entry was checked for errors. Discordant ratings were identified and the event narratives pulled for a consensus meeting discussion similar to that conducted by Columbia. The goal of the consensus meeting was to arrive at a single final consensus rating for each event with discordant ratings among the three reviewers.

The Columbia definition of concordance was used to identify discordant ratings as outlined below:

- **Perfect match for categories 1, 2, 3, 6, or 10**
- **Categories 4, 5 or 11 considered as same rating**
- **Categories 7, 8, 9 or 12 considered as same rating**

The final FDA ratings were compared to the final Columbia ratings of the 64 sampled events using the above criteria. Discordant ratings between the FDA and Columbia were identified and discussed with Dr. Posner during a teleconference. The goal of the discussion was to understand the reasons for the difference between the FDA and the Columbia ratings. Reaching agreement or a consensus rating was not a goal of the teleconference discussion.

Results

Of the 64 event narratives rated , 47 events had concordant initial rating within the FDA audit team. Seventeen of the 64 discordant initial ratings were discussed during a consensus meeting of the audit team and a single final consensus rating was reached for each of the 17 events with discordant initial rating.

A comparison of the final FDA audit team and the Columbia final ratings found concordant ratings for 57 of the 64 events resulting in an 89% agreement rate (kappa=0.84). The narratives for the 7 discordant event ratings were discussed between the FDA audit team and Dr. Kelly Posner of Columbia University. A severity hierarchy (severity hierarchy from higher to lower is 1 or 2 > 6 > 3 > 4 or 5 or 11 >10) was used to evaluate the direction of discordance in ratings between FDA and Columbia and is illustrated in table 1.

Of the seven discordant ratings, six were in the positive direction of the severity hierarchy. In other words, the FDA reviewers were more likely to classify events higher on the severity hierarchy than the Columbia reviewers. Possible reasons for this might be differences in the expertise, experience, and the degree of operationalization of the suicidality scale between the FDA and Columbia reviewers.

Table 1: Discordant ratings between FDA and Columbia and direction of bias

| Event | FDA Rating code | Columbia Rating Code | Direction of Severity bias |
|---|---|---|---|
| 1 | 10=not enough information | 12="other" (unsure if 7, 8, or 9) | positive severity bias |
| 2 | 10=not enough information | 12="other" (unsure if 7, 8, or 9) | positive severity bias |
| 3 | 10=not enough information | 7=other: accident | positive severity bias |
| 4 | 1= Suicide attempt | 3=self-injurious behavior, intent unknown | positive severity bias |
| 5 | 3= self-injurious behavior, intent unknown | 10= not enough information | positive severity bias |
| 6 | 3= self-injurious behavior, intent unknown | 1=suicide attempt | negative severity bias |
| 7 | 6=suicide ideation | 8=other: psychiatric | positive severity bias |

Limitations

Although extent of discordance between the FDA and Columbia final ratings was very small, there are several notable limitations of the FDA audit that may have contributed to this difference.

- Unlike the Columbia reviewers, the FDA audit team's expertise and experience in classifying possible suicidality events was very limited.
- The one-time, two-hour training of the FDA audit team may have been too short to adequately prepare the FDA team for the audit.
- The FDA audit team had a short timeline to review and rate their assigned events (total of 4 working days).

There are other limitations not related to the discordance between the FDA and Columbia ratings that must be stated.

- The FDA audit included neither the evaluation of the quality of the narratives nor the clinical source material or case report forms.
- The audit did not evaluate the validity of the Columbia suicidality scale or compare the results to another classification instrument considered to be a gold standard.

Strengths

Despite the above mentioned limitations and the intentional over-sample of difficult to classify events, the audit achieved a high level of concordance between the two independent reviews.

Conclusion:

The analysis of data from the audit provides evidence that the Columbia suicidality classification scale, methods, and process is robust and reproducible. The demonstration of a high level of concordance even when the scale is applied by a non-expert group on a sample with a proportionally greater representation of difficult to classify events is strong evidence of the robustness of the Columbia methodology.

**Appendices:**

Appendix 1: FDA Audit timeline
Appendix 2: FDA Audit procedures memo
Appendix 3: Modified rating form
Appendix 4: Training Examples of the Definitions for the Columbia Suicidality Classification Scale
Appendix 5: Reliability Case Examples for the Definitions for the Columbia Suicidality Classification Scale
Appendix 6: Background Information on the Suicidality Classification Project posted on the FDA website

Appendix 1

FDA Audit Timeline

- July 20: OCTAP given lead responsibility for audit
- July 21: began planning audit
- July 23: Reviewers selected
- July 26: Reviewer training by Columbia's Kelly Posner (Teleconference)
- July 27: Audit plan and sample selection
- July 28: Reviewer packages distributed
- July 29-Aug 2: set up excel database for data entry, plan data analysis, consensus meeting and identify facilitator
- Aug 3: Completed rating forms returned OCTAP
- Aug 4: Data entered, discordant ratings identified and consensus meeting of FDA reviewers conducted
- Aug 5: Teleconference between the FDA Audit team and Kelly Posner, Columbia to discuss discordant rating scores and understand the reasons for the differences
- Aug 9: CDER briefing of preliminary findings
- Aug 16: Complete written report for inclusion in background package to Advisory Committee members

Appendix 2

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**M E M O R A N D U M**

Date: July 28, 2004

From: Solomon Iyasu, M.D., M.P.H, Medical Team Leader
Susan Cummins, M.D., M.P.H, Medical Team Leader
Division of Pediatric Drug Development, Office of Counter Terrorism and Pediatric Drug Development

To: Hari Sachs, M.D., Medical Officer
ShaAvhree Buckman, M.D., Medical Officer
DPDD, OCTAP, CDER

Robert Levin, M.D., Medical Officer
Cara Alfaro, M.D., Medical Officer
DPNPDP, CDER

Re: Audit of the Columbia Suicidality Classification Project

## Audit of the Columbia Suicidality Classification Project Procedure Memo

The purpose of this memo is to provide a list of procedures to be followed for the independent review and classification of possible suicide attempts within 25 randomized controlled antidepressant clinical trials in pediatric patients. This classification will be performed by CDER medical officers within the Division of Neuropharmacologic Drug Products and the Division of Pediatric Drug Development.

*Process:*

There are 4 reviewers (Hari Sachs, ShaAhvree Buckman, Bob Levin and Cara Alfaro); each participated in a conference call with Kelly Posner on Monday July 26th 2004. During the call Dr. Posner provided training on the suicidality classification scale used by the Columbia reviewers to classify all possible cases.

This scale should be used by the CDER reviewers in the audit. Copies of the background materials are attached, and include: Definitions for the Columbia Suicidality Classification Scale and a Sample Reviewer Rating form.

Each reviewer will be given the narratives and other supporting documents and a form for recording their classification for approximately 48 cases that have been randomly assigned to them. The rater form has been modified from the one originally developed by the Columbia group. Pre-coded ratings have been added to ease key data entry and the numeric ratings correspond with the classification scale on page 2 of this memo, as well as with the classification scheme developed by the Columbia group.

Several of the selected cases had more than one event. The multiple event cases will be labeled as "event <#>" in pencil on the narrative. YOU SHOULD CONSULT SOLOMON IYASU ABOUT EACH OF THESE CASES FOR SPECIFIC INSTRUCTIONS ABOUT HOW TO REVIEW THEM.
SEVERAL OF THESE CASE NARRATIVES HAVE ADDITIONAL HANDWRITTEN NOTES ATTACHED TO THE CASE NARRATIVES WHICH SHOULD BE CONSIDERED IN YOUR REVIEW.

The reviews should be conducted independently; questions about how to interpret the case narratives with respect to the classification scheme for any particular case should be directed to Kelly Posner only (Her Beeper number is xxx-xxxx-xxxx and Cell Phone is xxx-xxx-xxxx). During and after the primary review process, reviewers should refrain from discussing any aspects of their assigned cases or their ratings with each other or with anyone. When you talk with Dr. Posner, please DO NOT GIVE HER THE CASE NUMBER. The narratives and the Reviewer Rating forms should be stored within FDA facilities in a locked file drawer.

We suggest that you skim through all your assigned narratives to determine whether you have a multiple event case first. We also suggest that you set aside the reviews for which you need consultation with Dr. Posner and that you schedule a meeting with her to go over all your questions at one time.

Please fill in your reviewer forms in pen. Do not hesitate to direct any other questions you have about this process to Solomon Iyasu. His direct line is xxx-xxx-xxxx and cell phone xxx-xxx-xxxx.

*The Classification Scale:*

1 = Suicide Attempt
2 = Preparatory actions towards imminent suicidal behavior
3 = self-injurious behavior, intent unknown
4 = self-injurious behavior, no intent, primarily to affect circumstance
5 = self-injurious behavior, no intent, primarily to affect internal state
6 = suicidal ideation
--6a: suicidal ideation, passive
--6b: suicidal ideation, active
--6c: suicidal ideation, active with plan
--6d: suicidal ideation, type unknown
7 = other: accident
8 = other: psychiatric
9 = other: medical
10 = not enough information
11 = self-injurious behavior, no suicide intent (unspecified type, i.e. rater not sure if it is 4 or 5)
12 = "other" ( unsure if rating is "7", "8" or "9")

Definitions for the Scale items are as provided by Dr. Posner. Key points regarding the classification scale are as follows:

- Intent to die is a key construct for the classification of suicide attempts. Intent can be stated or inferred by the rater. Clinical inference is appropriate when the method is clinically impressive (e.g. took 200 pills, set self on fire), and/or if the child believed that the method they used was lethal even if it was not. What matters is whether the child thinks the method used will kill themselves rather than the actual lethality of the attempt.
- Infer intent if the behavior is clinically impressive or there is more than one piece of evidence suggesting suicidal intent.

The definitions of the Classification Scale and the Reviewer Rating form provided by Dr. Posner are on the following pages for reference. Raters will be provided with a separate set of modified Rating form that incorporates the classification scheme on the previous page for completion of their reviews.

*Time Frame for Completion of Work:*

- Wednesday, July 28th—Narratives and Reviewer Rating forms will be distributed to Raters.
- Tuesday, August 3rd—Reviewer Rating Forms should be returned by hand in a sealed envelope (NOT IN THE MAIL, TIME IS OF THE ESSENCE) to Solomon Iyasu by Close of Business (5:00 PM). Reviewers should retain their assigned narratives for the reviewer conference.
- Wednesday, August 4th—Key Data Entry (double entry) to be performed. Cases with conflicting classifications to be identified for consensus conference.

?? Thursday, August 5th—Consensus conference to take place at a time TBD. Hari Sachs has PD that day, so it is likely that this meeting will take place late in the day. We will not know how many cases will have disparate ratings until Wednesday, so it is difficult to estimate how long this meeting will take.

By Tuesday, August 9th, Solomon will have prepared preliminary findings to be presented at the planning group meeting.

Attachments

| Definitions for the Columbia Suicidality Classification Scale | |
|---|---|
| ***Suicide Attempt:*** | ***Self- injurious behavior associated with some intent to die. Intent can be stated or inferred by rater.*** |
| ***Preparatory Acts Towards Imminent Suicidal Behavior*** | Person takes steps to injure self but is stopped by self or other. Intent to die is either stated or inferred. |
| ***Self-Injurious Behavior, Intent Unknown*** | Self- injurious behavior where associated intent to die is unknown and cannot be inferred. |
| ***Self-Injurious Behavior, No Intent, Primarily to Affect Circumstance*** | Self- injurious behavior associated with no intent to die – behavior is intended to effect change in others or the environment. |
| ***Self-Injurious Behavior, No Intent, Primarily to Affect Internal State*** | Self- injurious behavior associated with no intent to die intended to relieve distress. Typical examples are superficial cuts or scratches, hitting/banging, or burns. |
| ***Suicidal Ideation*** | Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior |
| ***Other: Accident*** | Unintentional injury |
| ***Other: Psychiatric**** _____ | Psychiatric symptoms only (when no evidence of any type of suicidality) |
| ***Other: Medical**** _____ | Medical symptoms or procedure only |
| ***Not Enough Information*** | Insufficient information to classify the event |

*** Infer intent if the behavior is clinically impressive or there is more than one piece of evidence suggesting suicidal intent**

**Columbia Suicidality Classification Scale**

*For each event, please mark only one box with an X for the event category and your level of confidence in your rating.*

| Behavior towards Self Injury | Suicidal Thoughts: Intent or Wish to Die | Event category | Rating |
|---|---|---|---|
| ++ | + | ***Suicide Attempt***<br>__ Check if intent is inferred<br>___ Check if "Suicide Attempt" is only information provided | |
| + | + | ***Preparatory Actions Towards Imminent Suicidal Behavior*** | |
| ++ | ? | ***Self-Injurious Behavior, Intent Unknown*** | |
| ++ | - | ***Self-Injurious Behavior, No Suicidal Intent, (To Affect Internal State /Circumstance)*** | |
| | | | |
| - | + | ***Suicidal Ideation***<br>__ passive _____ active<br>__ active w/ plan _____ type unknown | |
| - | - | ***Other: No indication of deliberate self-injury or suicidal behavior or ideation***<br>***Accident*** _____<br>***Medical***_____<br>***Psychiatric***_____ | |
| | | | |
| | | | |
| ? | ? | ***Not Enough Information*** | |

***please specify**

## Appendix 3: Modified rating form

Case Number:_____ Rater Initials:_____ ID#__

**Columbia Suicidality Classification Scale**

*For each event, please circle with pen only one numeric code in the Rating column for the event category that, in your best judgement, most closely matches the case narrative. If you are uncertain, please consult with Kelly Posner. Please circle Yes/No in "Comments" if you needed to consult Dr. Posner to complete your classification.*

| *Behavior towards Self Injury* | *Suicidal Thoughts: Intent or Wish to Die* | *Event category* | *Rating* |
|---|---|---|---|
| ++ | + | ***Suicide Attempt***<br>___ Check if intent is inferred<br>___ Check if "Suicide Attempt" is only information provided | **1** |
| + | + | ***Preparatory Actions Towards Imminent Suicidal Behavior*** | **2** |
| ++ | **?** | ***Self-Injurious Behavior, Intent Unknown*** | **3** |
| ++ | - | ***Self-Injurious Behavior, No Suicidal Intent, Primarily to Affect Circumstance*** | **4** |
| ++ | - | ***Self-Injurious Behavior, No Suicidal Intent, Primarily to Affect Internal State*** | **5** |
| - | + | ***Suicidal Ideation***<br>____ 6a: Passive ____ 6b: Active<br>____ 6c: Active w/ plan ____ 6d: Type unknown | **6** |
| - | - | ***Other: Accident*** (No indication of deliberate self-injury or suicidal behavior or ideation) | **7** |
| - | - | ***Other: Psychiatric*** (No indication of deliberate self-injury or suicidal behavior or ideation) | **8** |
| - | - | ***Other: Medical*** (No indication of deliberate self-injury or suicidal behavior or ideation) | **9** |
| **?** | **?** | ***Not Enough Information*** | **10** |
| ++ | - | ***Self-Injurious Behavior, No Suicidal Intent, Unspecified Type*** (unsure if rating "4" or "5") | **11** |
| - | - | ***"other"*** *( unsure if rating is "7", "8" or " 9")* | **12** |

***Comments:*** Please circle "YES or NO" if consultation with Kelly Posner was needed prior to completing the rating: YES || NO

Appendix 4

# *Training Examples of the Definitions for the Columbia Suicidality Classification Scale*

**1. Suicide Attempts**

The patient was angry at her mother after a fight. She took 6-7 unknown tablets and went to bed. She woke up the next morning with ringing in her ears and felt sick and weak. Her mother took her to the pediatrician. No other treatment was needed. The patient denied intent to die, but knew that taking that much medication could hurt her and might kill her.

The patient reported that six days prior to the interview, he tried to take a nap but was unable to sleep off his agitation. He used a razor blade to lacerate his wrists, antecubital fossae, and his back bilaterally. He told his therapist the "the main objective was to stop feeling like that" and he knew he could die but didn't care. According to the patient he also ingested a bottle of rubbing alcohol because he heard in health class "that the medulla will get more suppressed that way," thereby increasing the chances that he would be "successful" and die.

The patient had told his wife and his colleagues at work that he was going out of town on a business trip. He checked into a hotel not far from his home and put the do not disturb sign on the door. Two days later, he was found by the hotel staff who called the ambulance. The ambulance staff noted an empty bottle of diazepam that had just been filled two days prior and a bottle of cognac that was half empty. Upon examination in the emergency room, he stated he was not trying to kill himself but just wanted to get a good night's sleep.

**2. Preparatory Actions Towards Imminent Suicidal Behavior**

Approximately 10 days prior to hospitalization, the patient had run away from home overnight because his father had gone to school and retrieved a recent "bad" report card. The patient was fearful of his father's reaction. Upon the patient's return home, a 5-6 hour argument with his parents ensued and the patient took a vegetable knife and went to his room. He reported putting the knife to his wrist, but never puncturing the skin.

Patient stated he "couldn't stand being depressed anymore" and "wanted to die". He decided to hang himself. He tied a telephone cord to the door knob and placed the cord loosely around his neck. Then, he stopped himself and did not follow through.

At age 11, the patient went to a bridge in the woods near her home, placed a shopping cart full of rocks beneath it, and planned on jumping off the bridge onto

the rocks. She reports that due to “too much preparation,” a friend found her and prevented her from actually jumping.

The patient reported she was sick of having everything go wrong in her life. She felt that the easiest way to kill herself would be to drink some vodka and take all of the medicines in the medicine cabinet. She wrote a note to her husband explaining that she loved him and that his life would be easier without her and all her problems. The patient read the note over and then decided against taking the overdose because of how upset her husband would be.

**3. Self –Injurious Behavior with Unknown Intent**

Patient was angry at her husband. She took 10-15 diazepam tablets and flushed the rest down the toilet. Her husband called the police for help and she was taken to the hospital. She was groggy and stayed overnight in the hospital.

The 9 year old patient had spoken about suicide frequently. After learning that his baseball coach was retiring, he began scratching his arm with a pencil.

**4. Self- Injurious Behavior, No Intent, Primarily to Affect Circumstance**

Patient was feeling ignored. She went into the family kitchen where mother and sister were talking. She took a knife out of the drawer and made a cut on her arm. She denied that she wanted to die at all (“not even a little”) but just wanted them to pay attention to her.

Patient was in class, where a test was about to start, and stabbed himself with a pencil in order to be taken to the nurse’s office.

**5. Self-Injurious Behavior, No Intent, Primarily to Affect Internal State**

A 14 year old girl wrote her name on her arm with a penknife and said she often does so in order to reduce her anxiety.

The patient was noted to have multiple superficial burns on his arms. Upon questioning, he denied trying to kill himself.

**6. Suicidal Ideation**

Active: The patient reported to doctor thinking about hanging himself in the closet. The patient was taken to the hospital and admitted.

Passive: The patient reported ideas about wanting to be dead. Denied acting on these feelings.

Pt. hospitalized for worsening of depressive sxs and expressed suicidal thoughts.

**7. Accidental Injury**
11 year-old had scrape on knee

Patient was noted to have a laceration on his neck. He reported he cut himself while shaving.

**8. Psychiatric Symptoms- Only (No type of suicidality)**
Pt. was hospitalized for worsening of depressive symptoms.

Pt. had aggressive outburst, brought to ER.

**9. Medical**
Pt. hospitalized for asthma attack

**10. Not Enough Information**
Patient was noted to have a laceration on his neck

Appendix 5

## *Reliability Case Examples for the Definitions for the Columbia Suicidality Classification Scale*

1. After a fight with her friends at school in which they stopped talking to her, the patient ingested approximately 16 aspirin, and 8 other pills of different types on school grounds. She said she deserved to die and that's why she took the pills. _____

2. The patient reported that he first started thinking about killing himself when he was 12. He thought about how easy it would be to pretend to fall in front of the school bus before it was able to stop so that it would look like an accident. Although he thought about it often, he said he did not have the courage to do it. _____

3. During pill count, the study staff discovered that 6 tablets were missing. Upon questioning, the patient admitted that she was saving them up so she could take them all together at a later time. _____

4. The patient was feeling despondent about her financial situation. Her rent was due and the landlord had threatened to evict her. She went to the bathroom and took a razor from the cabinet. She cut one of her wrists and began bleeding. She bandaged up her wrist herself. During an interview a week later, she stated she had never cut herself before. She was adamant that she did not need to be hospitalized. ____

5. The patient cut her wrists after an argument with her boyfriend. _____

6. The patient wanted to escape from her mother's home. She researched lethal doses of ibuprofen. She took 6 ibuprofen pills and said she felt certain from her research that this amount was not enough to kill her. She stated she did not want to die, only to escape from her mother's home. She was taken to the emergency room where her stomach was pumped and she was admitted to a psychiatric ward. _____

7. The patient stated that she experienced heartbreak over the "loss of a guy" a week before the interview. She stated she impulsively took 4 clonazepam, called a girlfriend, and talked/cried it out while on the phone. She was dismissive of the seriousness of the attempt, but indicated that she wanted to die at the time she took the overdose. _____

8. Patient reported feeling agitated and anxious after a fight with her parents. She went into her room, locked the door and made several superficial cuts on the

inside of her arms. She stated she felt relieved after cutting herself and that she did not want to die. She reported that she had done this before at times of distress, and that it usually helped her feel better. _____

9. The patient's boyfriend called her on the telephone and told her that he was breaking up with her. The patient became enraged. She told him she was going to kill herself and that he would have to live with that for the rest of his life. Then, she hung up the phone. She said she knew that her boyfriend would come over immediately. She went into the kitchen, took a knife from the drawer, and made several cuts on her wrists. She was careful to make sure they would not need stitches and used her blouse to soak up the blood to make the situation appear "more frightening to him." The patient stated she did not want to die, but only to "teach her boyfriend a lesson and make him come back to her." _____

10. Patient described feeling overwhelmed and alone. As she sat in her bedroom smoking a cigarette, she was overcome by the feeling that she was not sure who she was and felt like she was watching a movie of herself. She took the cigarette and burned her forearms with it, twice on each side. She reported that she intended just to feel something real, like pain. _____

11. Several weeks after being informed by her husband that he was having an affair, patient went to Haiti to see him to discuss the situation. She became enraged during their discussion and grabbed his gun with the intention of shooting herself. However, her husband struggled with her, took the gun away before she was able to pull the trigger, and hid it from her. States that she was feeling pain and hurt, and that she was so upset that she wanted to die. _____

12. The patient said that she was feeling depressed about her problems with her boyfriend. She said she wished that one day she would just die in her sleep and not wake up in the morning. _____

Appendix 6

Background Information on the Suicidality Classification Project posted on the FDA website

**What is the Suicidality Classification Project and Why is it Necessary?**

The field of psychiatry has been challenged by a lack of conceptual clarity about suicidal behavior, and a corresponding lack of well-defined terminology. This is reflected in the lack of systematic or standardized language to define suicidal behavior in the original 25 clinical trials of selective serotonin reuptake inhibitors (SSRIs) and other antidepressant drug products in pediatric patients with various psychiatric diagnoses. This lack of standardized terminology for suicidal acts makes it difficult to interpret the meaning of reported adverse events (AEs) that occurred in those studies.

There may be adverse events that were inappropriately classified as suicidal, while other suicidal AEs may have been missed. Illustrative problematic examples include a case classified as a suicide attempt, in which a child slapped herself in the head and a case in which a child stabbed himself in the neck with a pencil, which was classified as an accidental injury.

To avoid unfounded conclusions and misinterpretation, a common set of guidelines must be applied. In order to say with greater confidence whether a behavior is suicidal, *the data need to be examined consistently across trials,* using research-supported definitions that are both valid (relevant features have been shown to be associated with definition) and reliable (clinicians are able to use these definitions in similar ways). Standardized terminology will be agreed upon before interpreting adverse events.

**The Classification Procedure**

***The Panel***

To address this problem, an independent panel of internationally-recognized experts in suicide assessment and adolescent suicide research will be convened to classify data from the pediatric depression trials. This distinguished panel is independent, in that no member has had any involvement in the drug treatment trials in question.

National and international panel members will include but are not limited to:

- David Brent, M.D., University of Pittsburgh, an expert in suicide risk factors and assessment and management of adolescent suicidal behavior (with a particular expertise in psychotherapeutic interventions);
- Anthony Spirito, Ph.D., ABPP, Brown University, who studies adolescent suicide attempters, with a particular focus on psychotherapy intervention;
- Peter Marzuk, M.D., Weill Medical College of Cornell University, who studies assessment/classification, epidemiology, and variables associated to suicide (aggression and violence, drug-abuse);

?? Patrick O'Carroll, M.D., M.P.H., who is the Regional Health Administrator for U.S. Department of Health and Human Services; previously with the Center for Disease Control and Prevention. He led all of CDC's epidemiologic research and prevention efforts related to attempted and completed suicide, particularly focusing on suicide classification issues;

?? Greg Brown, Ph.D., University of Pennsylvania, who has studied the assessment of suicidal behavior and the development of practice guidelines for management of adolescent and adult suicidal patients in primary care and behavioral health settings, as well as in psychotherapy interventions for individuals at high risk for suicide;

?? Annette Beautrais, Ph.D., who conducts the Canterbury Suicide Project, Department of Psychological Medicine, Christchurch School of Medicine, New Zealand. She has systematically collected data on suicide identification, monitoring, and epidemiology of secular trends in completed suicide in adolescents.

?? Cheryl King, Ph.D., ABPP, University of Michigan, an expert on adolescent suicidal behavior, who is conducting research on psychosocial interventions for suicidal adolescents. She is past President of the American Association of Suicidology.

***The Procedure***

Kelly Posner, Ph.D., Maria A. Oquendo, M.D., Madelyn Gould, Ph.D., M.P.H., and other research scientists at Columbia University with expertise in suicide classification, assessment techniques, and genetic and treatment research will be responsible for convening the expert panel, as well as for the design, implementation, and oversight of the classification methodology and its application to the FDA data. The project will involve reviewing clinical descriptions of events and rating whether a particular event can be classified as suicidal. The procedures to accomplish this are based on the Columbia team's experience with training of others in suicide assessment, development of measures and manuals to aid assessment of suicide, and use of suicide event consensus conference procedures.

Research-based definitions, established before the data are reviewed, will be systematically applied to case descriptions. The documents that will be circulated for review will include information that was deemed to be relevant pursuant to requests from the FDA. All narratives will have been de-identified of information on the patients, the pharmaceutical company, and the drug being studied, prior to the panel's receiving them and before expert review. Panel members will initially participate in a training session and pre-reliability study, to ensure that application of research-supported definitions will be conducted in a consistent way. The expert panel will then systematically review over 400 case descriptions from the 25 pediatric trials, including events that were originally described as possibly suicidal, all events coded as accidental injuries, and all serious adverse events. The review of the additional events that were not originally indicated as possibly suicidal renders the process more meaningful by allowing for a more objective

review (i.e., reviewers, in addition to not knowing what treatment the subject received, also will not know the initial classification of any cases). Furthermore, the review of the additional cases will allow for the possibility of the identification of missed suicidal cases, since as mentioned previously, there may be some cases among the accidental injuries that were not classified appropriately. The approximately 400 cases will be randomly assigned to panel members in such a manner that each case will be independently reviewed by multiple raters. If there is non-agreement on any particular event, the case will be reviewed in a consensus procedure. If consensus still cannot be reached, the case will be classified as "indeterminate."

The panel's task will be to rate whether a described event belongs in a particular behavioral classification. Classifications will include: suicidal events (suicide attempts, aborted attempts [for example, a child/adolescent changed his/her mind before starting the potentially self-injurious act], and interrupted attempts [for example, someone stopped the child/adolescent before potential injury began], and suicidal ideation-related events); non-suicidal events (self-injury or mutilation without suicidal intent, events attributable to other psychiatric symptoms, medical or accidental injuries); and indeterminate events (non-consensus or unable to classify due to limited data). Of note, the panel will also provide confidence assessments for each classification, indicating how certain they feel about a particular classification, based on the information provided.

Classification determinations will then be provided to the FDA. *Neither the expert panel nor Columbia University will be responsible for interpretation or analysis of the panel's ratings of events.* The suicidality classification project is solely responsible for the methodology that will produce expert classification ratings.

***Future Directions***

Guidelines that will foster better ascertainment of suicide-related information and adverse event determination are warranted. The Suicidality Classification Project will inform researchers from Columbia in the development of such guidelines, enabling appropriate classification and identification of suicidality-related events and behavior. This may lead to a greater consistency of categorization of what does and does not constitute a suicidal event and improve suicide identification and surveillance.