May 19, 2010 Wednesday

Today's Intelligence at a Glance

1. Bristol-Myers Squibb: Sprycel May Have Slight Edge Over Tasigna; 55% of Newly Diagnosed CML Patients Will Likely Choose Either Sprycel (30% Share) or Tasigna (25%)
UBS/Goodman, May 18, 2010
HealthACE Abstract *Indication: Hematologic*

2. Bristol-Myers Squibb: Four Factors Separates Ipilimumab (Phase III/Melanoma) from Pfizer's Failed Tremelimumab – Dosage Schedule, Therapy Type, Patients, & Antibody SubType
Goldman Sachs/Rubin, May 17, 2010
HealthACE Abstract *Indication: Skin*

3. Roche: RG7204 (Phase III/Melanoma) Could Be Next-in-Line Behind Ipilimumab; Plans to File for 2nd-Line Use in 2011; 1st-Line Data Expected to Complete in 2012
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4. Oncolytics: Phase I Data for Reolysin Shows Promising Clinical Benefit; Phase II Data in Lung Cancer Expected in 3Q2010, Could Trigger Partnership
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HealthACE Abstract *Indication: Multiple*

5. Cell Therapeutics: Substituting Pixantrone (Phase II/DLBCL) for Doxorubicin in CHOP-R Regimen Shows a Four-Fold Reduction in Severe Cardiac Toxicity
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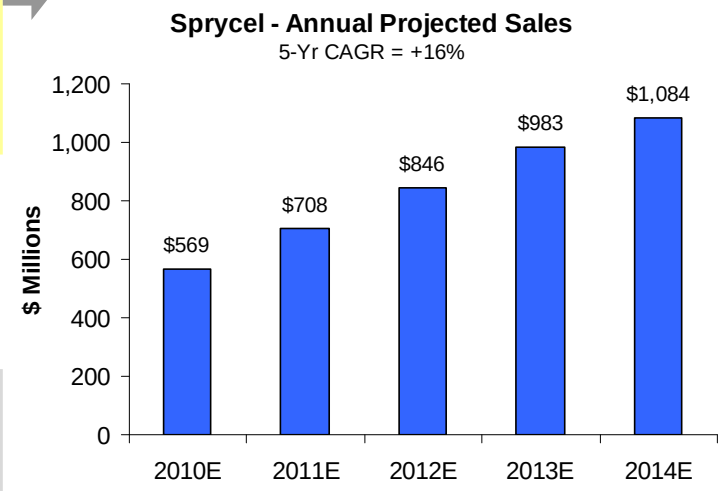
6. Astellas: Estimates OSI Acquisition Will Be Profitable within 3-4 Years After Amortization; Elimination of Overlaps in Cancer Drug Research Could Generate Cost Synergies
JPMorgan/Onozuka, May 18, 2010
HealthACE Abstract *Indication: General*

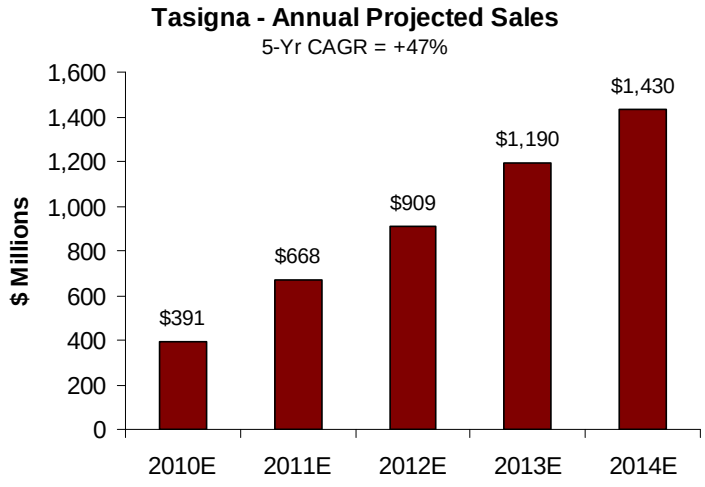
7. Medco: Expands Efforts to Promote Pharmacogenomic Tests; Will Start Offering CML Test to Monitor Gleevec, Sprycel and Tasigna in September
The Wall Street Journal/Mathews, May 19, 2010
HealthACE Abstract *Indication: General*

8. Pharma-US: FDA Transparency Proposal Contains Challenging Measures for Industry, Signals Support for Orphan Drug
Oppenheimer/Newman, May 19, 2010
HealthACE Abstract *Indication: General*

Additional Analysis



Sources: Company Reports; 5+ Brokerage Analyst Reports



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Bristol-Myers Squibb: Sprycel May Have Slight Edge Over Tasigna; 55% of Newly Diagnosed CML Patients Will Likely Choose Either Sprycel (30% Share) or Tasigna (25%)
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While there are several factors working in favor of each drug (Sprycel and Tasigna), we believe Sprycel stands to have an edge over Tasigna for the following reasons.

Factors favoring Sprycel:

- **No black-box warning:** Tasigna's label includes a black-box warning for QT prolongation. It excluded patients with uncontrolled cardiovascular (CV) disease in its Phase III as did Sprycel. Given the exclusion criteria in Phase III for both products, we would not be surprised if their Phase III CV risk profiles look similar; however, given Tasigna's black-box warning, we would expect Sprycel to be viewed more favorably.
- **More convenient dosing:** Sprycel has a clear dose advantage over Tasigna (QD vs. BID). Additionally, Sprycel does not have food restrictions like Tasigna. Patients taking Tasigna are required to avoid food 2 hours before and 1 hour after taking medication.
- **Lower price point:** While both Tasigna ($265/day) and Sprycel ($230/day) are expected to be priced at a premium to Gleevec ($210/day), Sprycel is likely to have some pricing advantage vs. Tasigna.

Factors favoring Tasigna:

- **Potential 6 month head-start:** The PDUFA date for Tasigna's application is in late June, while we assume Bristol will file around mid-2010 and request a priority review status. If it were to get priority review status, we would expect an FDA decision around the end of the year. This scenario would give Tasigna a 6 month head-start over Sprycel.
- **Novartis currently owns the market:** Since Novartis currently owns the 1st line market with Gleevec, we would not be surprised if Novartis has a strategy in place to aggressively convert patients to Tasigna especially since Gleevec is going generic in 2015.

If Data Plays Out, We Believe Sprycel Sales Could Top $2.5B by 2015:

Switch from newly diagnosed patients: From 2011 onwards newly diagnosed, 1st-line CML patients representing about 11% of the total 1st-line population will have a choice among three front line therapies – Gleevec, Tasigna and Sprycel. **We believe that 55% of these newly diagnosed patients will choose either Tasigna or Sprycel due to their more benign side effect profiles. Sprycel could take 30% share and Tasigna to take 25% share.**

Switch from Gleevec maintenance therapy patients: Both Bristol-Myers and Novartis have ongoing studies evaluating the switch of patients that are suboptimally treated with Gleevec. The Novartis studies (LASOR and ENESTcmr) will begin to report data in 2011. Bristol-Myers also has a switch study on which we are waiting for an update from the company. **We estimate that about 20% of the patients on Gleevec maintenance therapy will switch to either Tasigna or Sprycel starting in 2011, with the rate rising to 45% by 2015.** For now we assume that these switch patients will be shared equally by Sprycel and Tasigna until we get more data.

In 2nd-line, we estimate that the ~2:1 market share ratio between Sprycel and Tasigna will decline as Sprycel gains greater share in front-line treatment. In 3rd-line, we estimate Sprycel's market share will somewhat decline (as will Tasigna's share) over time as it gains share in earlier lines of therapy; however, we assume that it will still continue to dominate the market.

Based on these assumptions, **we estimate Sprycel's global sales to grow from about $420M in 2009 to about $2.6B in 2015.**

Source: UBS/Goodman, May 18, 2010
Oncology Indication: Hematologic
Keyword: Market Overview

Bristol-Myers Squibb: Four Factors Separates Ipilimumab (Phase III/Melanoma) from Pfizer's Failed Tremelimumab – Dosage Schedule, Therapy Type, Patients, & Antibody SubType

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Ipilimumab and tremelimumab are both anti-CTLA-4 antibodies with the same biological mechanisms. However, Pfizer discontinued its Phase III melanoma trial for tremelimumab in April 2008 after an interim review showed it would not demonstrate superiority to standard chemotherapy.

Early this year, Pfizer entered a co-development agreement with Debiopharm to conduct a Phase III tremelimumab trial in advanced melanoma that will use a biomarker to select patients considered more likely to respond to tremelimumab. This trial has yet to be registered with ClinicalTrials.gov. Pfizer will pay royalties to Bristol-Myers Squibb if tremelimumab comes to market, and **if a successful biomarker is found for tremelimumab, it will likely also work for ipilimumab given the same biological mechanism.**

While we will not know whether ipilimumab will fare a different fate than Pfizer's tremelimumab until the release of Phase III data, there are four important differences that suggest ipilimumab may work whereas tremelimumab did not:

1. **Dosage schedule:** The difference in dosage (10 mg/kg every 3 weeks for ipilimumab in induction phase, 15mg/kg every 3 months for tremelimumab) likely affects the outcome of response as many metastatic melanoma tumors have a doubling time of 30 days, which is far shorter than the dosage period of tremelimumab.
2. **Monotherapy vs. combination with chemotherapy:** The 024 ipilimumab trial studies the effect of ipilimumab with chemotherapy whereas the discontinued tremelimumab trial assessed the efficacy of the drug as a single agent compared with chemotherapy. **Some melanoma doctors believe that CTLA-4 therapy is not likely to be effective as a monotherapy.**
3. **Patient selection criteria:** The 024 ipilimumab trial had no exclusions except for patients with brain metastases while the tremelimumab study excluded patients who had a high lactate dehydrogenase (LDH) level that has been shown to be a negative prognosis factor.
4. **Different antibody subtype:** Both antibodies work by the same mechanism but employ different antibody subtypes. Ipilimumab uses an IgG1 subtype which has been shown to induce stronger antibody-dependent cell-mediated cytotoxicity, a mechanism that could kill cancer cells, compared with IgG2, the tremelimumab antibody subtype.

Phase II ipilimumab data suggests compelling profile. Four Phase II trials have been completed to date and include long-term follow up of patients on-going for more than two years. **All four trials show a durable effect and prolongation of survival with a 25-30% clinical benefit including responses and stable disease.**

Efficacy Phase II data for Ipilumimab in Stage III, IV metastatic melanoma

Study	(-008)	(-022)	(-007)		(-013)		DTIC alone
Phase	II	II	II		II		II
Patient type	previously-treated	previously-treated	previously-treated & naïve		treatment-naïve		treatment-naïve
Arm	ipilumimab	ipilumimab	previously-treated	treatment-naïve	ipilumimab	ipilumimab +DTIC	DTIC
Dose/Regimen	10 mg/kg q3w x4	10 mg/kg q3w x4	10 mg/kg q3w x4		3 mg/kg q3w x4	3 mg/kg q3w x4 + DTIC	standard DTIC dosing
No of patients	155	73	62	53	37	35	383
Overall Response	5.8%	11.0%	15.0%	13.0%	5.0%		7.5%
Complete Response	0.0%	3.0%	n/a	n/a	0%	5.70%	0.8%
Clinical Benefit	27% by WHO criteria, 35% by WHO + irRC	29.2%	35%	31%	22%	37.10%	n/a
Overall Survival	10.2 months	11.4 months	11.6	n/a	11.4 months	14.3 months	7.8 months
1 year survival	47.2%	48.6%	50.0%	69.0%	45.0%	62.0%	n/a
2 year survival	32.8%	29.8%	38% (18 month)	63% (18 month)	21.0%	24.0%	10.0%
>/ Grade 3 toxicity	13.0%	13.0%	50.0%	50.0%	13.0%	23.0%	3.0%

Clinical benefit refers to patients with stable disease or disease response CC

Source: Company data, ASCO abstracts, peer-reviewed scientific journal .

Source: Goldman Sachs/Rubin, May 17, 2010
Oncology Indication: Skin
Keyword: Clinical Trials/Pipeline

Roche: RG7204 (Phase III/Melanoma) Could Be Next-in-Line Behind Ipilimumab; Plans to File for 2nd-Line Use in 2011; 1st-Line Data Expected to Complete in 2012

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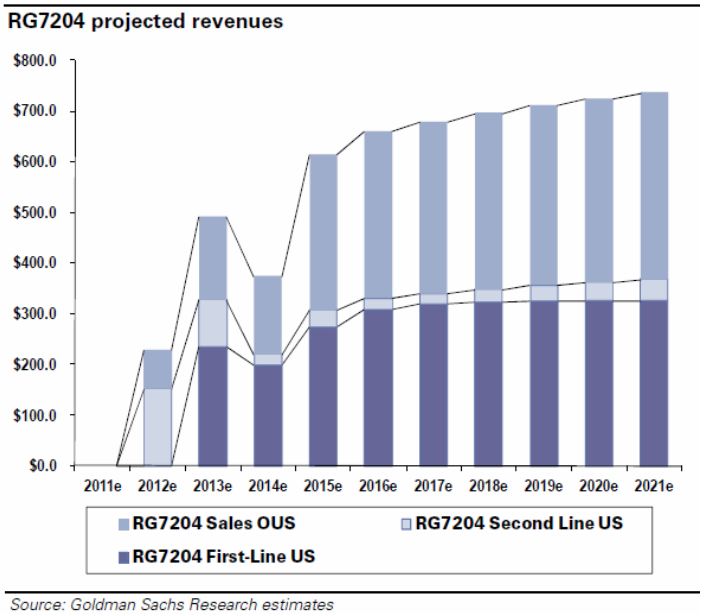
Roche/Plexxikon's RG7204 has the potential to be first- in-class BRAF targeted therapy for metastatic melanoma. RG7204 is currently in Phase II/III development and is **at least 12 months behind ipilimumab**. Melanoma oncologists are all excited about RG7204 because of its rapid response rate, generally low toxicity profile, and oral pill delivery method with no need for hospital visits. The drawback is the almost-inevitable resistance after 6-8 months of treatment.

RG7204 is currently being evaluated as a monotherapy treatment in the second-line setting in a Phase II trial and in Phase III as a first-line treatment. **The Phase II second-line study is expected to be available by the end of 2010 (potentially early 2011), and Roche plans to file for second-line in 2011 based on this Phase II study.** We believe that given the design of the Phase II study (single arm) and for the potential for Ipilimumab to already be on the market, there might be some delay to FDA approval in the second-line setting as the FDA may choose to wait for additional data from the **ongoing Phase III data for first-line metastatic melanoma, which is expected to complete in 2012.**

The BRAF V600E mutation is found in approximately 40-50% of melanoma patients resulting in a clear sub-set of melanoma patients who will benefit from this therapy. Early clinical data indicate that the response rate among V600E-harboring patients is about 80% with a rapid response within weeks of starting treatment. However, currently over 80% of patients will likely develop resistance to the drug within six to eight months and require a different therapy according to our expert calls. Efforts are focusing on other targets in the BRAF pathway to find a suitable treatment to combine with RG7204 to prevent or lower the rate of resistance.

Previous results showed that RG7204 has low toxicity and it is not myelosuppressive (blood cell production inihibitor), a significant positive for a cancer drug. In early trials, adverse events (AEs) were mainly mild rash, joint pain, photosensitivity and fatigue. Notably excisable squamous cell carcinoma (SCC) skin lesions have been observed in 4 (15%) patients. However, the BRAF cell signaling pathway is complex and it may be that its inhibition may reduce melanoma, but may induce other cancer growth, like SCC. The severity of metastatic melanoma greatly outweighs the potential negative side effect of excisable SCC. **If successful, RG7204 could add up to SFr800 to our existing Roche estimates**.



Source: Goldman Sachs Research estimates

$1.00 = SFr1.15

Source: Goldman Sachs/Rubin, May 17, 2010
Oncology Indication: Skin
Keyword: Clinical Trials/Pipeline

Oncolytics: Phase I Data for Reolysin Shows Promising Clinical Benefit; Phase II Data in Lung Cancer Expected in 3Q2010, Could Trigger Partnership

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Oncolytics has announced the publication of Phase I data for Reolysin in the peer-reviewed journal Clinical Cancer Research.

In this study, designed primarily to determine maximum tolerated dose (MTD) in combination with radiotherapy, Reolysin again showed an excellent safety profile and no MTD was reached. Of seven evaluable patients receiving Reolysin with low-dose radiation, two (2/7) showed a partial response (PR) and five (5/7) had stable disease (SD). Of seven evaluable patients receiving high-dose radiation combination, five (5/7) had a PR, while two (2/7) had SD.

Although Phase I results are not usually something that garners much of our attention, the 100% clinical benefit rate seen in this study of patients with advanced cancer receiving palliative therapy appears promising. This is an evidence of the strong potential of Reolysin, and we expect that future studies could show similar promise for the therapy.

The next catalyst for Oncolytics will be the initiation of a Phase III study in head and neck cancer in coming weeks. Additional key milestones in 2010 include the announcement of important data at ASCO in June, and Phase II lung cancer data in Q3 of this year. We believe that the lung cancer data is of particular importance as it may be a trigger for a partnership with big pharma.

Source: Canaccord Genuity/Maruoka, May 19, 2010
Oncology Indication: Multiple
Keyword: Clinical Trials/Pipeline

Cell Therapeutics: Substituting Pixantrone (Phase II/DLBCL) for Doxorubicin in CHOP-R Regimen Shows a Four-Fold Reduction in Severe Cardiac Toxicity

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Cell Therapeutics reported preliminary cardiac safety results from a phase II trial which substituted pixantrone for doxorubicin in the standard CHOP-R regimen. The PIX203 trial compared CPOP-R directly to CHOP-R in the 1st-line treatment of high risk patients with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL, NHL).

While CHOP-R is considered as the standard of care in front-line treatment of DLBCL, exposure to cumulative doses of doxorubicin is associated with increasing incidence of irreversible, severe, and symptomatic cardiac toxicity. This correlation of doxorubicin exposure and increasing incidence of heart damage limits the use of doxorubicin beyond first-line therapy and among patients with pre-existing cardiac disorders. Pixantrone is a potent DNA alkylator which lacks the structural motifs of doxorubicin that are responsible for the formation of toxic drug metal complexes and oxygen free radical generation, the putative mechanisms for anthracycline-related cardiac toxicity.

Preliminary data indicates that patients treated with the CPOP-R regimen experienced significantly less frequent major reductions (>=20%) in cardiac function as determined by serial measurements of left ventricular ejection fraction (LVEF) (2% vs. 13%, pixantrone vs. doxorubicin, respectively), less symptomatic congestive heart failure (CHF) (0% vs. 5%), and less severe grade 3-4 decline in LVEF (2% vs. 10%). Preliminary investigator-determined response rates were also comparable (89% vs. 92%) between the two regimens. Independent radiologic assessment of response and disease progression data is in progress and expected to be presented at national hematology society meetings later this year.

Cell Therapeutics intends to file a marketing authorization application in Europe for pixantrone in the second half of 2010 and these results will be used as supportive data.

Source: PRNewswire-FirstCall, May 18, 2010
Oncology Indication: Hematologic
Keyword: Clinical Trials/Pipeline

Astellas: Estimates OSI Acquisition Will Be Profitable within 3-4 Years After Amortization; Elimination of Overlaps in Cancer Drug Research Could Generate Cost Synergies

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Astellas held a conference call on May 17, saying that it has finalized agreement to buy OSI. The price of $57.50 per share is as we expected because we saw little likelihood of an increase to over $60 for there to be a positive contribution to profits after amortization of intangible assets. OSI management is backing the acquisition, which is now on amicable terms.

Astellas calculates that if the acquisition completes, it will make nine-month contributions to FY2010 consolidated accounts of ¥34 billion in sales, ¥14 billion in operating profit, and an operating loss of ¥17 billion after asset amortization. **It estimates that the acquisition will be profitable within 3-4 years after amortization.**

Our impression is negative because the company (1) calculates annual amortization at around ¥40 billion over several years and (2) seems to be assuming few cost synergies because the deal is a progressive investment aimed at gaining an oncology franchise. J.P. Morgan estimates OSI will make operating profit of $168 million in 2010, $202 million in 2011, and $237 million in 2012 on solid sales of Tarceva. We think some consolidation of U.S. head office functions and elimination of overlaps in basic cancer drug research could generate cost synergies of $50 million in 2011 and $100 million in 2012, bringing the impact on profits in year three (FY2012) to roughly breakeven, assuming annual amortization at ¥30 billion.

Assuming the company's depreciation figures, no synergies and using our OSI forecasts, **we do not see a positive impact on earnings for five years.** The price of $57.50 per share represents a 55% premium to OSI's closing price on February 26 and a total premium of $1.4 billion. The capital outflow of over ¥130 billion could be justified by creation of synergies, but the company did not offer a clear explanation. We can understand the basic strategy of getting on quickly with establishing a business base in oncology as a core therapeutic area, but there are concerns about potential near-term damage to enterprise value from a massive capital outflow.

$1.00 = ¥92.59

Source: JPMorgan/Onozuka, May 18, 2010
Oncology Indication: General
Keyword: Partnerships/Business Developments

Medco: Expands Efforts to Promote Pharmacogenomic Tests; Will Start Offering CML Test to Monitor Gleevec, Sprycel and Tasigna in September

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Medco Health manages pharmaceutical benefits for insurers and employers. Now, the company is pushing to annex a new area: the rapidly growing field of genetic testing. **Medco is expanding its efforts to promote so-called pharmacogenomic tests** – assays that can signal how a person will react to a drug or can help decide what medicine, or what dose, is best.

For its employer and insurer clients, Medco also plans new services for genetic tests beyond those just tied to drugs: counseling for members and their doctors, and a consulting service to advise client companies on what genetic tests should be covered. In addition, it's launching a service for health insurers that would administer coverage of high-tech lab tests, which are traditionally handled as a medical benefit by insurers themselves.

Some doctors worry the company is promoting pricey tests that aren't yet ready for widespread use. In addition, Medco's push into lab benefits could eventually put it in competition with the health plans that are also its clients. And some industry critics say pharmacy-benefit managers (PBMs) may have conflicts of interests if they can benefit financially from testing as well as from drugs that may be given based on a lab result.

Medco officials say genetic testing is helping them win more business in the core pharmaceutical-management area, and that their financial interests are closely aligned with clients. "It's a very logical extension and a definite need out there that is not being filled," says David B. Snow Jr., Medco's chief executive.

Currently, Medco's pharmacogenomic program, which covers 220 clients and about 10 million of Medco's 65 million members, includes tests for the blood thinner warfarin and the breast-cancer drug tamoxifen. When one of these drugs is prescribed, the PBM contacts the doctor about the test. If the doctor and patient choose to get it, Medco pays one of its contracted labs to perform the test; the results are sent to the doctor and to Medco.

The new tests this July will be for the widely used anticlotting drug Plavix, as well as two AIDS drugs, abacavir and Selzentry. **In September, Medco will start offering a test for chronic myelogenous leukemia that is used to monitor three drugs, Gleevec, Sprycel and Tasigna.**

Medco says it makes money by charging clients a fee for each pharmacogenomic test. The company says it uses its discounts to offset its margin and administrative costs, so clients pay about the same as they would spend buying independently – about $250 to $1,000 per test.

Medco backs its pharmacogenomic effort with research the company sponsors on the clinical benefits of such tests, and advice from a committee of outside experts. The FDA recently added a "black box" warning on the Plavix label that informs doctors about the genetic test.

Rival CVS has a similar pharmacogenomic program for clients, with a pilot starting in July and a full rollout early next year. **Pharmacogenomic tests "are the next frontier" to improve drug benefits**, says Per Lofberg, president of the Caremark PBM. Other big pharmacy-benefit firm, Express Scripts, says it won't contract with labs to provide drug-linked tests, though its pharmacy-benefit system does support them.

Medco says its broader lab-testing efforts will complement the work of health plans, not compete with them. It will integrate offerings from DNA Direct, which Medco acquired in February, to administer coverage of lab tests. This work would use the insurer's contracted network of labs, not one provided by Medco.

Source: The Wall Street Journal/Mathews, May 19, 2010
Oncology Indication: General
Keyword: Management/Strategy/Financials

Pharma-US: FDA Transparency Proposal Contains Challenging Measures for Industry, Signals Support for Orphan Drug

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The FDA Transparency Task Force released 21 draft proposals to increase transparency today (5/19) for public comment. Although all proposals may not be enacted, we believe implementation would provide a more challenging environment for industry. We summarize the key points below.

The FDA may disclose Complete Response Letters: We believe public disclosure of Complete Response letters would improve visibility for investors and the efficiency by which drug stocks trade (Draft Proposal 13). Full disclosure of Complete Response letters would clearly state FDA's reasons for not approving an application, and importantly, reveal whether additional clinical studies were requested. However, we believe the industry will strongly oppose this measure.

Agency proposes more detail on plant inspections: The FDA has proposed expanding the scope and level of detail for inspection reports, including clinical trial investigators, institutional review boards, and manufacturing facilities, raising the bar for drug development/manufacturing (Draft Proposals 6,7). The FDA proposes differentiating between Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI), which would give investors higher visibility into a drug's development and manufacture, but increase pressure on the industry.

Orphan Drug Proposal signals continued positive bias from the FDA: We are encouraged by the FDA's proposal to endorse Orphan drug applications that are abandoned, withdrawn, or terminated if the drugs could represent a significant advance (Draft proposal 12).

Releasing safety information from ongoing trials a tough pill for the industry: The FDA Task Force has proposed a summary of safety and efficacy information for ongoing trials, which seems a tough pill to swallow for companies involved in drug development (Draft proposal 16). Specifically, the Task Force believes summary disclosure may be appropriate when the information is necessary to protect the public health.

Source: Oppenheimer/Newman, May 19, 2010
Oncology Indication: General
Keyword: FDA/Regulatory Issues